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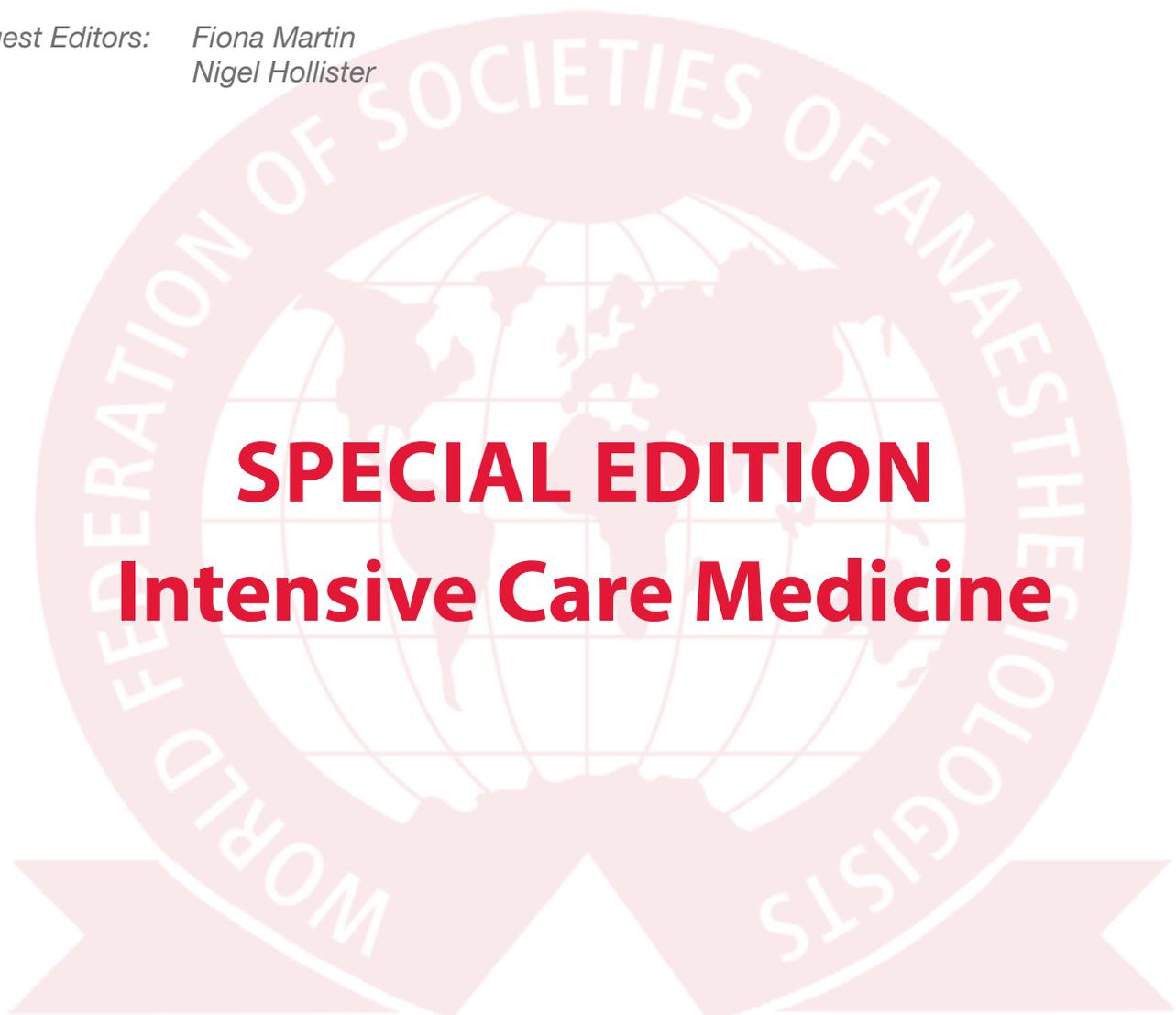
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Guest editorial

The Global Sepsis Alliance – fighting a global disease

Only in the past thirty years has sepsis been recognized as a very common disease of global proportions and impact. Initially underdiagnosed and unrecognized, it is now accepted that sepsis, a clinical syndrome defined by the presence of both infection and a systemic inflammatory response,¹ is most probably one of the leading causes of death in the world.² 727,000 patients were hospitalized with a primary diagnosis of septicæmia or sepsis in the United States in 2008, more than double the number of patients documented in 2000.³ In-hospital deaths were more than eight times more likely in patients with a diagnosis of septicæmia or sepsis compared to other diagnoses.³ These estimates concern an environment of a developed, modern intensive care setting. There is very little data available for the developing world, where the majority of worldwide deaths related to sepsis are to be expected due to the prevalence of HIV/AIDS, malaria and maternal sepsis. It has been proven that the introduction of evidence-based guidelines focussing on early recognition, emergent antibiotic treatment and application of fluids and vasopressors can reduce sepsis-related mortality.⁴ It is unclear to what extent these interventions can be translated to a developing world setting.⁵

A multitude of local, national and international organisations and societies dedicated to sepsis have developed over the past years. The Global Sepsis Alliance (GSA) was launched in September 2010 as part of a Merinoff Symposium of the Feinstein Institute for Medical Research on Long Island, to take on sepsis as a global problem. The GSA was founded by the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM), the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS), the International Sepsis Forum (ISF), the Sepsis Alliance USA (SA) and the World Federation of Critical Care Nurses (WFCCM) to coordinate global efforts against sepsis and to speak with one voice. In the meantime, the member organisations of the GSA represent over 600,000 health care professionals from more than 70 countries (Table 1). The GSA has set out to “Speak in One Voice” offering consistent, easily understood messaging to governments, philanthropies and the public.

The GSA has set goals to provide opportunities supportive of global interaction and defined output. As a first step, the GSA has developed a definition of sepsis that facilitates communication with the lay public:

Sepsis is a life threatening condition that arises when the body's response to an infection injures its own tissues and organs. Sepsis may lead to shock, multiple organ failure, and death, especially if not recognized early and treated promptly. Sepsis remains the primary cause of death from infection despite advances in modern medicine, including vaccines, antibiotics, and acute care. Millions of people die of sepsis every year worldwide.

Large scale studies are necessary to find out more about possible interventions to reduce sepsis-related morbidity and mortality. A major goal of the GSA is to assist societies and initiatives in the process of developing proposals for experiments, trials, projects and programs in support of researchers, caregivers and the public, especially in securing funding to implement such efforts. The GSA is to be empowered to easily identify and access resources and people of common purpose and intent within and without the scientific community.

The 2005 World Health Organisation Health global report on global child death considers that 80% of global child deaths are related to severe infections associated with pneumonia, malaria, measles, neonatal sepsis, and diarrhoea.⁶ One exemplary project supported by the GSA is the development and implementation of sepsis demonstration projects in the poor districts of Ugandan, both urban and rural, in collaboration with the Ministry of Health, Makerere University College of Health Sciences, Mbarara University of Science and Technology and the Centre for International Child Health, University of British Columbia. The GSA will employ its contacts to regionally and globally disseminate the initiative's experiences, findings and lessons learned. The GSA will focus on addressing with equal commitment and vigour the needs of both adults and children in the developed and developing world.

The GSA urges the medical community to recognize sepsis as a medical emergency, requiring the administration of fluids, antibiotics and other appropriate treatments of infection within one hour of first suspecting a case of sepsis. This is also possible in regions without modern intensive care units, using a less sophisticated approach.⁷

In conclusion, the global burden of sepsis is high and is increasing, especially in the developing world. The

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Table 1. Membership of the Global Sepsis Alliance.

Membership of the Global Sepsis Alliance

Founding organizations

International Sepsis Forum (ISF)
Sepsis Alliance (SA)
World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS)
World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM)
World Federation of Critical Care Nurses (WFCCN)

Committed organizations

American Thoracic Society (ATS)
Australia and New Zealand Intensive Care Society (ANZICS)
Belize Medical and Dental Association
Centre for International Child Health
Chilean Society of Critical Care
Chinese Society of Critical Care Medicine
Dutch Meningitis Initiative
Emirates Intensive Care Society
German Sepsis Society and German Sepsis Aid
Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva (GiViTi)
Hellenic Sepsis Study Group
International Forum for Acute Care Trialists (InFACT)
International Pan Arab Critical Care Medicine Society
Latin American Sepsis Institute
Maventy Health International
Society of Critical Care Medicine
Spanish Edusepsis Network
Surgical Infection Society (SIS)
Survive Sepsis
United Kingdom Sepsis Trust

use of current evidence-based knowledge must be applied to reduce the worldwide high sepsis mortality rate. Healthcare professionals and laypersons must be taught that sepsis is an emergency requiring urgent treatment. The GSA will focus on programs to better understand that sepsis is an emergency and to foster a greater understanding of the medical burden of sepsis among the public and is planning a World Sepsis Day for 2012. The GSA encourages all concerned groups and societies to learn from each other and to join forces in the fight against sepsis at a global level and to become a member of the GSA. More information is available on the GSA website at www.globalsepsisalliance.com.

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Editor's notes

Dear Readers,

Welcome to this Special Edition of *Update in Anaesthesia*, which focuses on Intensive Care Medicine. This specialty has developed greatly over the last 30 years, however development of dedicated intensive care units (ICUs) in more poorly resourced countries has only come about in the last few years. We think of an ICU as a location in the hospital where the sickest patients are admitted for more invasive monitoring and more aggressive organ support and therapy. Inherently these monitors and treatments incur far higher costs than standard ward care, making them unachievable in many settings.

However, equipment is not the major factor that sets the ICU or high dependency unit (HDU) apart from the other wards of a hospital; it is the expertise and numbers of the ICU staff that confers the most dramatic advantage in providing effective care for the critically ill. Nursing staff numbers, and therefore the nurse to patient ratio, vary starkly between the general wards (around one to sixty in the description of a Ugandan ICU by Towey and Anyai, on page 16 of this edition of *Update*) and the ICU (ideally 1:1, but commonly 1:4 or 1:6). In addition it is the quality of training and experience of these nursing staff that has a major impact on patient care, particularly where staff morale allows good retention of staff and longevity of careers in the ICU.

In addition to good nursing care, close attention to the detail of basic good medical care by trained and experienced clinical officers and doctors, probably has a far greater impact on patient outcome than use of expensive, invasive equipment. In fact there are few interventions in ICU for which the evidence remains relatively unequivocal, examples being nursing patients in the semi-recumbent position (30 degrees head up) to decrease the incidence of ventilator associated pneumonia and administration of antibiotics to patients with sepsis within one hour of presentation. Therapies such as steroids and activated protein C for septic shock, despite encouraging early randomised control studies, have now been proven to be ineffective or harmful. Many of the more technical strategies for providing advanced respiratory support to patients with intractable hypoxia, such as extra-corporeal membrane oxygenation and high frequency oscillation ventilation, have very little supporting evidence.

So we are left in a situation where timely basic interventions are likely to bring about the greatest improvements in mortality and morbidity of critically ill patients, manoeuvres such as effective airway management and haemodynamic resuscitation in trauma, early antibiotics and surgical source control in sepsis. These strategies are available in most healthcare settings around the world.

This edition of *Update in Anaesthesia* attempts to provide an overview of the essential aspects of care of the critically ill and critically injured, with particular focus on practices that are most relevant and achievable in poor resource settings. For most topics in our speciality we have tried to achieve a balance between making the text relevant to workers where 'high-tech' equipment is not available and achieving

appropriate coverage of the topic for areas where some level of more advanced equipment may be available. In many parts of the world, health centres that are geographically close to each other may vary greatly in their resources, due largely to the influence of alternative funding streams from non-government organisations.

I hope that this edition is useful. I would appreciate your feedback at bruce.mccormick@nhs.net. The articles do not cover this subject fully and suggestions for further ICM topics would be welcomed. This edition is available, along with the full back catalogue of *Update in Anaesthesia* at <http://update.anaesthesiologists.org>

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Intensive care medicine in resource-limited settings: a general overview

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WHAT IS INTENSIVE CARE MEDICINE?

Intensive or critical care medicine refers to the medical specialty which focuses on the management of critically ill patients. Critical illness describes a general state which may arise from various medical pathologies (e.g. trauma, infection, acute coronary syndrome, stroke etc.) and leads to the impairment of vital (consciousness, circulation or respiration) or single organ functions (e.g. kidney or liver function). Furthermore, intensive care includes the care of patients after major surgery or the observation of patients in whom critical illness may rapidly occur.

INTENSIVE CARE MEDICINE IN RESOURCE-POOR SETTINGS

In Western countries, the first intensive care units (dedicated hospital wards where intensive care medicine is practiced and critically ill patients are cared for) were established in the 1950s and 1960s following the last European polio epidemics.¹ Since then the number of intensive care units (ICUs) has grown steadily and intensive care medicine has gained importance as a medical specialty in its own right. The majority of acute care hospitals in high-income countries now run one or more ICUs. The most frequent pathologies leading to ICU admission in Western countries are cardiovascular diseases, major surgery, sepsis and respiratory failure.

Although the first ICUs were introduced to select resource-poor settings shortly after intensive care medicine started to develop, the majority of critically ill patients in less developed countries, harboring around two thirds of the world population, still do not have access to intensive care.² Few data exist on the current state of intensive care medicine in less developed countries, but there seems to be wide variability in the availability of ICUs in these countries, ranging from non-existent to sophisticated centres in selected private hospitals catering for a few privileged patients. Recent data from the Republic of Zambia revealed that only 29 ICU beds exist for the entire country of 12.9 million people and only 7% of hospitals providing surgical services run an ICU. Even in those hospitals with ICUs, basic equipment is lacking and an oxygen supply is only inconsistently available.³ Similar data were reported from other African or Asian regions.

In countries like Bangladesh, India and Nepal, there has recently been an important increase in the availability of intensive care units, although shortage in staffing, lack of basic equipment, poor maintenance of equipment and interrupted supplies often pose major challenges. In addition, the medical profession in less developed countries is, in general, not set up to provide formal training in intensive care medicine. Knowledge about important recent progress in the field is frequently absent. These factors inevitably result in a lack of recognition of intensive care medicine as a medical specialty in resource-poor settings. As a consequence, disproportionately high mortality rates have been reported for selected critical illnesses in developing countries.⁴

DIFFERENCES IN INTENSIVE CARE MEDICINE BETWEEN HIGH INCOME AND RESOURCE-POOR SETTINGS

Intensive care medicine between Western and less developed countries not only differs in equipment and material availability, but also in the patient populations treated in the ICU.⁵ In less developed countries critically ill patients admitted to the ICU are characteristically younger, suffering from less premorbid conditions. The underlying diseases leading to ICU admission in resource-poor areas differ geographically from those seen in high income countries. While in Northern developing countries (e.g. central Asian countries) ICU admission diagnoses are similar to those reported from high income countries, tropical and infectious diseases are among the leading causes of critical illness in developing countries in South Asia, South America and Africa. Trauma and sepsis are far more common in ICUs of developing than Western countries. Disease severity at ICU admission is typically higher in resource-poor settings, while the number of interventions and procedures performed is smaller compared to critically ill patients admitted to ICUs in high income countries. Irrespective of the ICU admission diagnosis, mortality rates of critically ill patients are consistently higher in less developed than in high income countries.⁵

ICU STAFFING

An ICU needs the presence of well trained and

Summary

This introductory article gives an overview of intensive care medicine in developing countries and contrasts its development with high-income countries. The second part of this manuscript aims to give the reader a general overview of the basic aspects and requirements of ICUs and intensive care medicine in resource-poor settings.

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experienced ICU workers 24-hours-a-day, 7-days-a-week. An ideal ICU team consists of nurses, specially trained in intensive care medicine, one or more intensivists (physicians specialized in providing intensive care medicine) and a variable number of nurse assistants, technicians and cleaners. In many resource-poor settings, the role of the intensivist is taken over by a nurse anaesthetist or an anaesthetic clinical officer. This is a practicable and legitimate policy since maintenance and restoration of vital functions is one of the key fields of anaesthesia. If the intensivist is not a medical doctor, it is advisable that a physician is available to assist in the care of the critically ill patient's underlying disease. Ideally, the intensivist in charge should be a physician specially trained in intensive care medicine. In some Western countries (e.g. the United Kingdom), specialized postgraduate training programs for intensive care medicine exist. In addition, diplomas in intensive care medicine can be taken from international intensive care societies (e.g. the European Society of Intensive Care Medicine).

Due to the wide-ranging lack of health care personnel and qualified staff in many resource-poor settings, the anaesthetist/physician caring for the ICU often has to fulfill additional medical duties in the operation theatre or hospital, particularly at night and during weekends. This frequently leaves the ICU unattended by an intensivist and places more responsibility on the ICU nurses, making them the key players of the ICU team. Trust and good communication with the intensivist in charge, as well as continuous education, adequate training and a strong team spirit, are of outstanding importance for ICU nurses in resource-poor settings.

ORGANIZATIONAL ASPECTS OF AN ICU

An ICU can be organized in different ways. Larger hospitals in particular often run specialized ICUs caring for critically ill patients with selected diseases; for example surgical, pediatric, neurosurgical, cardiac, medical or burns ICUs. Although this may have some benefits for certain patient populations, recent data indicate that multidisciplinary ICUs caring for patients with different pathologies may result in better care. In any case, it is important to understand that caring for a critically ill patient, irrespective of the underlying disease, must include an interdisciplinary approach, involving integration of physicians from other medical specialties such as neurologists, surgeons or pediatricians. Mutual respect is a prerequisite for fruitful interdisciplinary communication.

In a *closed ICU* one or more intensivist is principally responsible for the care of all patients admitted to the ICU. This organizational structure is in contrast to the *open ICU* where different physicians, who are not continuously present in the ICU, care for single critically ill patients. Organization of ICUs as closed units, including the presence of a an intensivist, has been shown to result in lower mortality, less complications, a reduced length of ICU stay and lower costs, when compared to open ICUs.⁶ If hospitals are too small to implement a 24-hour intensivist service, telemedical assistance by external intensivists may be used to support decision making and patient care.⁷ Although most reports on intensive care telemedicine originate from high-income countries (the United States and Australia), personal experience of the author suggests that regular (e.g. weekly) telemedical counseling by experienced intensivists can be a valuable tool to improve patient care in ICUs in resource-limited areas.

CONSTRUCTIONAL ASPECTS OF AN ICU

Even though intensive care medicine can be supplied under several circumstances and at various locations, an ICU in a resource-poor setting has certain constructional requirements. Non-leaking roofs, closable windows/doors, solid walls and, whenever necessary, a functional heating system must be available to protect patients and staff from adverse climate influences. Floors and walls should be easily washable to allow effective cleaning. Light and a stable electricity supply are further indispensable prerequisites to run an ICU. Stable electricity supply, on the one hand, includes the availability of a power generator (e.g. driven by gasoline or diesel), providing electricity in case of power cuts. On the other hand, in many resource-poor settings, voltage stabilizers need to be placed in the main electrical line supplying the ICU, in order to prevent voltage peaks that may damage delicate medical apparatus such as mechanical ventilators or patient monitors.



Figure 1. Intensive care unit in a rural African hospital - 1, patient monitor; 2, suction machine; 3, oxygen concentrator; 4, mechanical ventilator; 5, mosquito net.

Running water with a constant supply of soap is essential to reduce cross-infection between critically ill patients. In areas where malaria and other insect-transmitted infectious diseases are endemic, mosquito nets should be available for each ICU bed to protect patients from insect bites during evening and night times (Figure 1). Air filtering and room climatization are not essential, but can greatly help to maintain clean air and adjust room temperatures and air pressure to patient needs. Although no scientific data have so far proven that isolation of patients with resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*, can reduce transmission of these bacteria to other patients, an ICU should include a room to isolate patients. For certain infectious diseases, such as open pulmonary tuberculosis or certain viral haemorrhagic fevers, isolation is obligatory. When spatial isolation is required, the patient should not be in isolation from medical and nursing care. The nurse base, an integral part of the ICU, should be placed centrally and allow full sight on as many ICU beds as possible (Figure 2).

OXYGEN, PRESSURIZED AIR AND SUCTION

One of the most important drugs required in the ICU is oxygen. Oxygen can be stored and supplied in various ways. Oxygen



Figure 2. View from the nurse base of a Mongolian ICU.

concentrators provide 90-100% oxygen but rely on a constant electricity supply and usually do not provide oxygen flows higher than $4-6L \cdot min^{-1}$. While this is sufficient to treat neonates and infants with respiratory insufficiency, in many cases it is inadequate to oxygenate larger children or adults with respiratory failure. In contrast, oxygen cylinders can provide pure oxygen at high flow rates and are independent of electricity supply, but need to be replenished at regular intervals. This must be addressed in advance before the last cylinder has emptied, leaving the patient with respiratory distress without oxygen. Central oxygen systems are the most efficient and convenient way to store and supply ICUs with oxygen. The source of oxygen of a central oxygen system can either be a special oxygen tank storing oxygen at low temperatures, or a bank of oxygen cylinders. Both of these require regular maintenance and replenishment. The tubing of the pressurized oxygen system must consist of a non-oxidizing material, typically copper. In countries where no professional companies offer installation of medical air systems, refrigeration engineers usually have sufficient experience in installing copper/pressurized gas lines.

Pressurized air, used to run mechanical ventilators, can similarly be administered either by direct connection of a compressor to the mechanical ventilator or preferably by connecting a compressor to a central air system, providing pressurized air through single outlets at each ICU bed. Although specific medical air compressors exist, oil-free industrial compressors, with a pressure regulator as well as additional air filters, provide comparable air qualities. These are more easily affordable in resource-poor settings (Figure 3). Where oil-free compressors are available air filters need to be placed in the air lines and before air enters the ventilator. Although oil spilling into the patient's respiratory system is the by far most relevant danger, more frequent complications are acute blockade of line or air filters in the ventilators. Central suction units may be connected to the pressurized air system, but usually depend on special suction generators, which can be cumbersome to find and install in resource-limited areas.

BASIC RESOURCE REQUIREMENTS OF AN ICU

Although intensive care medicine, above most other medical specialties, relies on technical devices and material resources, it is



Figure 3. Air compressor supplying the pressurized air system of a Mongolian ICU, with the pressure regulator indicated by the white arrow.

crucial to consider that no apparatus can replace an alert ICU worker at the bedside. Nonetheless, certain technical devices are required to support the work of the ICU staff. These typically include patient monitors, suction machines and mechanical ventilators. While patient monitors measuring ECG, respiratory rate, arterial blood pressure and oxygen saturation should be available at each bed, suction machines and mechanical ventilators can be used specifically for patients in need of these devices. The technical aspects of mechanical ventilators must be considered, because the majority of available ventilators depend on a dual supply of pressurized oxygen and air. In ICUs where neither pressurized air nor adequate stores of pressurized oxygen are available, only ventilators with internal air compressors together with an external oxygen source (e.g. from an oxygen concentrator or an oxygen cylinder) can be used.

Infusion and syringe pumps allow drugs and fluids to be administered at exact rates and dosages, but, in the clinical practice of resource-poor settings, may well be replaced by mechanical drop regulators or close clinical surveillance by a nurse. Any device not depending on electricity increases patient safety during power cuts, particularly when vital drugs (e.g. catecholamines) are infused. Despite being a life-saving intervention, renal replacement therapy in patients with acute kidney failure is usually unavailable in resource-poor settings. Given that neither intermittent hemodialysis nor continuous hemofiltration is superior in terms of patient survival, and that hemofiltration is more time and resource-consuming, intermittent hemodialysis is the technique of choice to treat patients with acute kidney failure in resource-poor settings. Although data on the use of peritoneal dialysis in critically ill patients with acute kidney failure are conflicting, peritoneal dialysis may be an option if local experience is available.

Similarly, a basic set of essential disposable materials, drugs and laboratory tests need to be available to adequately and safely care for critically ill patients. These sets usually do not need to include high-end materials or a large variety of drugs or tests, but should focus on the basic needs of critically ill patients treated in the respective ICU. Furthermore, small numbers of essential materials, drugs and tests warrants expert use by the ICU staff and facilitates stock maintenance.

THE ICU'S PLACE IN A RESOURCE-POOR HOSPITAL

Intensive care medicine is an integrative medical specialty, requiring close cooperation with several other medical disciplines and technical services (e.g. laboratory services, blood bank etc.) in the hospital. Therefore, to assure adequate and efficient care of critically ill patients, other medical departments and hospital services need to be prepared and trained to manage the needs of critically ill patients.^{2,4}

Since ICUs in resource-poor settings are either non-existent or have only recently been established, acceptance of ICU services among colleagues from other medical specialties (who have so far cared for critically ill patients on the hospital ward) is a frequent problem. After establishing an ICU in a resource-poor hospital, referral and admission rates are often low. If patients are admitted this typically occurs at a pre-terminal stage, where ICU interventions may fail to save the patient's life. This can lead to a perception amongst ward staff and relatives that patients are transferred to the ICU to die. Integration of ward physicians into ICU care (e.g. during daily rounds or regular discussions at the bedside), together with education of the hospital staff about when to admit patients to the ICU are ways to increase acceptance of newly established ICU services in resource-poor hospitals.

When ICU services are well-established and accepted, unavailability of ICU beds is a far greater problem. ICU bed capacities need to be coordinated with the emergency department and the operation theatre at regular intervals each day. From a practical standpoint, ICUs should always have the capacity to admit unplanned critically ill patients. This can be organized by leaving one ICU bed in the hospital unoccupied or having the facility to discharge one patient rapidly to an appropriate hospital ward.

INTENSIVE CARE MEDICINE 'WITHOUT WALLS'

Provision of intensive care medicine is not only restricted to the ICU. In order to prevent patients being admitted too late, after they have developed irreversible shock or organ failure, the intensivist can play a valuable role in assessing patients before ICU admission (e.g. in the operation theatre or the emergency department) or after ICU discharge (post-ICU review). In several hospitals, intensivists play a key role in resuscitation teams or medical emergency teams. The function of these teams within a hospital is described in a later article. Implementation of medical emergency teams in hospitals of high-income countries reduced the rates of unexpected cardiac arrests on non-ICU wards.⁸ In addition to providing resuscitation and emergency care, intensivists may further assist physicians from other medical specialties with certain clinical problems (e.g. prescription of parenteral/enteral nutrition, provision of palliative care, cannulation of central vessels or assessment of surgical and anaesthetic risks).

CONCLUSION

Intensive care medicine is a comparatively young medical specialty which has grown rapidly to become an essential component of modern hospitals. Many hospitals in resource-poor settings do not run ICUs and critically ill patients frequently receive suboptimal care with unacceptable levels of mortality. When implementing intensive care medicine in resource-poor settings several staff, constructional, organizational and resource aspects need to be considered.

Table 1. Ten basic principles of intensive care medicine.

- 1 No medical apparatus can replace the presence of an ICU worker at the bedside.
- 2 No diagnostic test can replace a thorough patient history, chart review or systematic clinical examination.
- 3 Supportive therapy is life-saving, challenging and may distract the intensivist's attention from searching for the underlying cause of critical illness. Always try to identify why a critically ill patient is sick and do everything to treat this condition.
- 4 Always ask why a patient is deteriorating or fails to improve. Never accept or explain treatment failures simply by disease severity.
- 5 Do not over-sedate. Only sedate agitated patients or those with certain diseases (intracranial hypertension, acute lung or circulatory failure).
- 6 Do not overhydrate patients. Although fluid resuscitation can save lives in the acute phase, indiscriminate infusion of fluids at later stages leads to complications (e.g. sepsis), prolongs ICU stay and increases mortality.
- 7 Do no harm! Be aware that every intervention and drug applied in the ICU carries the potential to harm the patient.
- 8 As soon as the patient has stabilized do everything to reduce invasive support.
- 9 Always consider the therapeutic consequence before performing diagnostic tests (e.g. imaging studies).
- 10 Do not indiscriminately order laboratory tests but only measure these values where relevant and pathologic information can be expected.

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Systematic assessment of an ICU patient

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INTRODUCTION

The Surviving Sepsis Campaign¹ and World Health Organisation surgical checklist² have demonstrated that use of a systematic review and checklist approach, to optimise patient management and safety, improves outcome. Reducing surgical mortality is dependent upon the ability to recognise and 'rescue' patients who develop complications.^{3,4} Improved survival of patients treated in critical care has been attributed to improvements in the processes of care, rather than the introduction of individual therapies or diagnostic modalities.⁵ Furthermore, the strict implementation of dedicated processes of care, often called *care bundles*, improves ICU and hospital mortality.⁶ In this article, we describe a head-to-toe assessment and treatment strategy to guide the daily or night review of intensive care patients. This systematic assessment incorporates the current evidence and care bundles that contribute to improve outcome.

HISTORY

If the patient is awake, introduce yourself and explain who you are and what you intend to do. Whether they are awake or asleep, try to avoid focusing intently on the monitors and charts, thereby ignoring the patient. Although we have more monitoring and tests available to us, the focus of our attention should always be the patient, their symptoms and clinical signs.

The patient's presenting complaint (e.g. pneumonia) will usually be the primary focus of your assessment, but after the first few days of admission the emphasis may shift to other priorities; a patient may recover from intra-abdominal sepsis but be left with respiratory failure due to acute respiratory distress syndrome (ARDS) or underlying airways disease. Details of the past medical history and the presentation of the primary pathology may be difficult to obtain, but information should be sought from relatives, the ambulance crew, referring hospitals and general practitioners or hospital specialists caring for the patient's chronic medical conditions.

When you encounter a patient for the first time, it is worth sitting down to read the current and old hospital notes in full (including specialists letters and old

investigations), in order to form a complete picture of the patient's medical history. The physician's traditional wisdom that 90% of the diagnosis is in the history is equally applicable to patients on the intensive care unit. Some patients will only be able to answer your questions for a short period before clinical deterioration or sedation prevents this. The information that you obtain from them may be vital, for example sudden onset of chest and abdominal pain whilst vomiting in a septic patient, suggests a perforated oesophagus, a diagnosis that can easily be missed without a suggestive history. If a patient's response to treatment is not as predicted, review the presentation and consider whether the working diagnosis is correct.

Decisions made regarding admission to ICU, require some knowledge of patient's physiological reserve, their quality of life and their own attitude to such treatments. These decisions should be made and documented preemptively rather than when a catastrophic deterioration occurs.

Patients may remain in the ICU for some weeks. Experienced intensivists are able to plot the next few days of a patient's ICU stay, allowing goals to be set for certain aspects of the patient's illness. In spite of this, unexpected events occur relatively frequently and it is important have flexibility to focus on whatever issues arise.

EXAMINATION

Physical examination of the patient and their observations can often occur together. A systematic approach must be used and a 'head-to-toe' system is appropriate. Each section focuses on history, clinical examination and observations. Even though this approach is 'labour-intensive' it is this type of attention to detail that may make a difference in a patient's progress in ICU. For example, identifying and removing a cannula that has been in for 5 days, is not being used and shows erythema around it, may prevent an episode of *Staphylococcal* bacteraemia.

Try to avoid making assumptions about other what other medical staff have done; if a trauma patient has been moved rapidly from the emergency department to theatre for abdominal bleeding, when they arrive

Summary

- A structured approach to assessment and management improves outcome.
- Management should incorporate best evidence and current care 'bundles'.
- Checklists, such as FASTHUG, can aid the complete assessment of the ICU patient's needs.
- Good documentation and communication between health professionals, the patient and family are vital parts of a daily review.
- Many of the disease processes and therapies described are discussed in more detail in later articles in this edition.

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in the ICU and there is no documentation that a secondary trauma survey was completed, then the ICU team must take responsibility to perform it. Most would choose to assess the primary organ failure first, so in a head-injured patient, start with the central nervous system.

Head/central nervous system

General considerations

If the patient's primary pathology is a head injury, cranial surgery or a cerebral event then your assessment should be adjusted accordingly. The patient's Glasgow Coma Score (GCS) should be recorded - for head-injured patients this is most usefully done when sedation has been stopped. If a painful stimulus is applied to assess the motor response, avoid repeating this procedure by different clinicians more than once a day. A full cranial and peripheral nerve examination should be performed daily where indicated - for example in those with fluctuating neurology due to a cerebral abscess or Guillain-Barré syndrome. Note the pupil size and reaction.

Over-sedation is undesirable for a number of reasons and performing daily sedation breaks reduces length of stay on ICU.⁷ A sedation score such as the Richmond Agitation-Sedation Scale (RASS) may be used to monitor and titrate sedation appropriately.⁸ Delirium occurs in 15-80% of critical care patients. It increases mortality and causes cognitive decline in the long-term.⁹ Delirium should be regularly sought and quantified using the CAM-ICU score and management steps, such as treatment with haloperidol, applied if appropriate.^{10,11}

Despite the availability of adequate methods of analgesia and appropriate monitoring, pain control can be poor in ICU. Pain scores should be recorded and analgesia reviewed daily, particularly in postoperative patients. Most of the techniques that are applicable for postoperative patients on the surgical ward can be used in ICU and it is useful for intensivists to learn regional techniques such as rectus sheath and epidural insertion. Simple analgesics such as paracetamol should be prescribed routinely, although non-steroidal anti-inflammatory drugs are usually avoided in the critically ill.

Patients with intracranial pathology

Patients at risk of raised intracranial pressure should ideally be treated at centres with specialist input and, where available, intracranial pressure (ICP) monitoring should be considered for those requiring sedation and at risk of high ICP. Local policies targeting cerebral perfusion pressure (CPP, usually >60mmHg) should be followed when the ICP is greater than 20-25mmHg or when there is clinical or radiological evidence of a raised ICP.

Standard neuro-protection includes treating patients head-up 30 degrees with the endotracheal tube taped rather than tied (to minimise obstruction to cerebral venous drainage), ventilation to a PaCO₂ of 4.5-5kPa and the maintenance of a PaO₂ greater than 8kPa. Glucose should be in the normal range and steps should be taken to avoid hyperthermia. Disorders of sodium metabolism are common in brain injury. Serum sodium should be maintained at the upper normal range. Ensure adequate sedation, analgesia and muscle relaxation.

Seizures need prompt treatment and phenytoin is the preventative anti-epileptic of choice. The administration of mannitol and hypertonic

saline is controversial, but they are often reserved for use in patients with high ICP or suggestive physical signs, for example a blown (fixed, dilated) pupil.¹⁶ Hyperventilation is a short-term measure to reduce critically high ICP before surgical intervention, but should be considered a rescue therapy only.

In many centres around the world, ICP monitoring is not available, so patients with severe head injury are sedated and managed as above for 48 to 72 hours. After this time, daily sedation breaks allow assessment of their underlying condition.

Respiratory and ventilation

General considerations

A past medical history of respiratory disease, including lung function tests, and current respiratory issues should be noted. The patient's airway and respiratory system should be examined. If an endotracheal tube is in place, note that the length at the teeth is as documented at insertion and check its position is correct on the most recent chest Xray. Often it is only possible to auscultate the chest anteriorly and in the axillae. The ventilator settings should be inspected and the measured tidal volume, minute volume, peak and plateau pressures noted. Note whether the patient appears comfortable on these ventilator settings, in particular whether they are 'fighting' (co-ordinating poorly with) the ventilator or display an increased work of breathing. The patient's saturations and, where available, arterial blood gases should be inspected and trends noted. Regular arterial gas measurements of PaO₂ and PaCO₂, assessment of the PaO₂:FiO₂ ratio and pH are useful in guiding your ventilation strategy.

If the clinical appearance, oxygenation or blood gases are not satisfactory, then you must address this by altering the ventilator mode, settings or level of sedation to improve the situation. Set targets for gas exchange; these should be specific to each patient, so that a patient with severe COPD may have a target SaO₂ of 88% or above.

Acute respiratory distress syndrome (ARDS)

ARDS occurs in up to 14% of ventilated patients, and carries a mortality of 40-60%.¹² It arises as a complication in both pulmonary and non-pulmonary conditions and is diagnosed according to specific criteria (see Box 1).

Low tidal volume ventilation of 6ml.kg⁻¹ and a conservative fluid management strategy should be used in patients with ARDS.^{13,14} Aim for plateau pressures below 30cmH₂O, allowing hypercapnia if necessary.¹⁵ High PEEP has been shown to be beneficial for patients with confirmed ARDS (PaO₂/FiO₂ < 200mmHg),¹⁶ and in severe left ventricular failure. Early paralysis with neuromuscular blocking agents may improve outcome in patients with ARDS with a PaO₂/FiO₂ ratio < 150mmHg.¹⁷

Weaning

The ICU clinician should implement a strategy for gradual weaning of ventilation, from mandatory positive pressure ventilation to a progressive reduction in pressure support, to levels that simply compensate for the resistance of the endotracheal tube and the circuit. Tracheostomy is often used in the ICU to aid weaning from ventilation, and most are now placed using a percutaneous dilational

Box 1. Proposed new definition of ARDS (European working group and awaiting formal publication).

	Mild ARDS	Moderate ARDS	Severe ARDS
Timing	Acute onset within 1 week of a known clinical insult or new/worsening respiratory symptoms		
Hypoxaemia	PaO ₂ /FiO ₂ 201-300mmHg with PEEP/CPAP ≥ 5cmH ₂ O	PaO ₂ /FiO ₂ ≤ 200mmHg with PEEP ≥ 5cmH ₂ O	PaO ₂ /FiO ₂ ≤ 100mmHg with PEEP ≥ 10cmH ₂ O
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload		
Radiological abnormalities	Bilateral opacities	Bilateral opacities	Opacities involving at least 3 quadrants
Additional Physiological Derangement	N/A	N/A	Minute volume >10L.min ⁻¹ or compliance < 40ml.cmH ₂ O ⁻¹

technique. The strength of a patient's cough, their secretion load and swallow function should be assessed. In patients with a tracheostomy, the ability of the patient to tolerate deflation of the cuff and use of the speaking valve are important indicators of weaning progression. Where available, extubation to non-invasive ventilation may reduce the risk of reintubation in patients with COPD.¹⁸

Circulation

A comprehensive examination of the cardiovascular system should be performed daily. This should include auscultation of the heart sounds and lung bases. Peripheral perfusion, pulses and the presence of peripheral oedema should be noted. Oedema will be present in the lower back and sacrum of a patient that has been supine for a prolonged period and this is a common finding in those who have been critically ill. Spontaneous clearance of oedema, with an accompanying diuresis, is usually a sign that an acute episode of sepsis is resolving.

It is useful to chart observations of heart rate, blood pressure, capillary refill and interventions, such as fluid and inotrope administration, graphically, in order to identify trends. Baseline and serial ECGs are important in patients with ischaemic heart disease, to assess for ischemic changes associated with acute deterioration of the patient. Where available, transthoracic (TTE) or transoesophageal (TOE) echocardiography are useful in evaluation of the structure and function of the right and left ventricles and heart valves.

The use of goal-directed fluid therapy, guided by cardiac output monitoring is controversial but may be of benefit in early sepsis,¹⁹ however many units lack the required equipment for this. The clinical response to fluid administration and, where available, central venous oxygen saturations (ScvO₂) may be employed to guide the use of fluids, inotropes and vasopressors (See Box 3).¹⁹ The use of steroids should be reserved for refractory shock.⁵

Abdomen and nutrition

The abdomen should be fully examined at least daily, as it is a concealed source of infection and subsequent driver of inflammation in critical illness. The presence of any surgical drains should be noted and the trends of collection volumes noted to see if further surgery is required, or whether the drain can be removed. Abdominal

pressure measurements may be required if abdominal compartment syndrome is suspected on examination. Where available the serum lactate provides a non-specific indicator of pathologies such as bowel ischaemia, that are difficult to detect clinically. Nasogastric (NG) tube placement should be confirmed on a daily basis by pH testing or chest Xray if being used for feeding. The NG tube should be removed as soon as it is no longer needed.

The patient's daily weights should be recorded as a basic nutritional assessment. The typical critical care patient's energy needs are approximately 25kcal per kg per day.²⁰ This may be doubled in severe sepsis, trauma and burns. Oral intake, NG feeding and any gastric residual volume should be used to calculate energy intake. If available, dietician support and the use of feeding guidelines,²¹ will aid adequate calorie, protein, fat, essential amino-acid and mineral input. If NG feeding fails, consider the use of post-pyloric feeding via a tube inserted through the stomach into the proximal small bowel. The potential for re-feeding syndrome should be considered in patients with poor dietary input prior to their ICU admission.

Bowel output should be recorded, and diarrhoea noted and tested for infectious organisms such as *Clostridium difficile* that causes pseudomembranous colitis. Other causes of diarrhoea such as overflow, drugs, high-osmolar feed and intestinal ischaemia should be considered. Delayed gastric emptying is indicated by large aspirates from the NG tube. This is relatively common in critically ill patients and early administration of prokinetics, such as metoclopramide or low-dose erythromycin, is often required. Aperients may be required for constipation.

Early enteral nutrition, is recommended to prevent stress ulceration of the stomach²² and to preserve mucosal integrity. Ranitidine or a proton pump inhibitor, such as omeprazole, should be given to ventilated patients who are not yet established on enteral feeding.^{22,23} Parenteral nutrition (PN) should be reserved for those patients in whom enteral feeding is contraindicated or failing.²⁴

Renal, fluids and electrolytes

The urine output should be charted every hour where appropriate. Most urinary catheters are colonised with bacteria, but these are usually not clinically significant. However, catheters should be removed if not

SURVIVING SEPSIS CARE BUNDLE (ABBREVIATED)¹

Initial resuscitation (first 6 hours)

1. *Begin resuscitation immediately if hypotensive or lactate > 4mmol.L⁻¹. Targets are:*
 - a. CVP 8-12mmHg
 - b. MAP ≥ 65mmHg - norepinephrine or dopamine are first-line vasopressors. Use epinephrine as second-line in norepinephrine/dopamine refractory shock. If possible use an arterial catheter to guide vasopressor infusions.
 - c. Urine output ≥ 0.5ml.kg⁻¹.h⁻¹. Do not use low-dose dopamine infusions for renal protection.
 - d. Central venous O₂ saturations ≥ 70% or mixed venous ≥ 65%.
 - e. If venous saturation target missed:
 - i. Consider further fluid,
 - ii. Transfuse packed red cells to a haematocrit of ≥ 30% and/or,
 - iii. Start dobutamine infusion 5-20mcg.kg⁻¹.h⁻¹. Do not increase cardiac index to supranormal levels.
2. *Ventilation*
 - a. 6ml.kg⁻¹ tidal volumes. Aim for plateau pressure ≤ 30cmH₂O.
 - b. Permissive hypercapnia may be required to minimize plateau pressures, except in patients with intracranial hypertension.
3. *Diagnosis*
 - a. Obtain appropriate cultures as long as this does not significantly delay antibiotic administration. Two or more blood cultures (one percutaneous culture and cultures from each vascular access device in place > 48hours).
 - b. Perform imaging studies promptly to confirm and sample any source if safe to do so.
4. *Antibiotic Therapy*
 - a. Begin broad-spectrum antibiotics with good penetration to presumed source and active against likely pathogens as soon as possible, but at least within 1 hour of recognizing sepsis or septic shock.
 - b. Combination therapy should be considered for *Pseudomonas* infection or in neutropaenic patients, until culture susceptibilities are available.
 - c. Stop antibiotic therapy if the cause is found to be non-infectious.
5. *Steroids*
 - a. Hydrocortisone < 300mg per day in divided doses can be considered for fluid and vasopressor-refractory shock.

required or in patients who are anuric due to renal failure. The trends in renal function and electrolytes should be examined frequently and correlated with the patient's progress as a whole.

The patient's fluid administration should be reviewed and the daily and cumulative fluid balances noted. The use of crystalloid versus colloid fluid is still debated. The use of starch-based colloids does not improve survival and may cause renal impairment.^{25,26} The SAFE study showed no benefit of albumin over saline in all ICU patients and subgroup analysis suggested albumin may reduce mortality in sepsis, but increase it in traumatic brain injury.²⁷

Dialysis or renal replacement therapy (RRT) may be required in hyperkalaemia, fluid overload, uraemia, acidosis, or poisoning due to a filterable toxin. There is no difference between intermittent

haemodialysis (IHD) or continuous veno-venous haemodiafiltration (CVVHD) in outcome, but CVVHD may be better tolerated in patients who are cardiovascularly unstable.²⁸ Thrombocytopenia is a common complication of renal replacement therapy and is usually due to consumption by the extracorporeal circuit, but other causes such as heparin induced thrombocytopenia (HIT) should be considered.

BLOOD TESTS

All of the patient's blood tests should be reviewed and trends noted - this is most easily viewed when plotted on a chart. Where available, ICU patients require daily measurement of renal function, electrolytes and haematology indices. Magnesium and calcium levels, clotting function and blood grouping for transfusion are frequently required. Low levels of magnesium (<0.7mmol.L⁻¹) and phosphate should be treated by intravenous supplementation.

A conservative transfusion strategy is usually recommended in 'stable' critically ill patients; aim for a haemoglobin level above 7g.dL⁻¹,^{29,30} although a higher haemoglobin concentration may be targeted in patients with ischaemic heart disease and septic shock.¹⁹ Transfusion practice is greatly affected by local availability of donor blood and by the prevalence of diseases such as malaria within the population.

Where available, platelet transfusion is usually guided by consultation with a haematologist, but should always be considered when:

- the platelet count is <5 x10⁹.L⁻¹ regardless of bleeding,
- 5-30 x10⁹.L⁻¹ in active bleeding, or
- <50 x10⁹.L⁻¹ when surgery or invasive procedures are planned.

Some neurosurgery centres may aim for a platelet count of >100 x10⁹.L⁻¹ in cases of intracranial haemorrhage.

Blood glucose control has been controversial, with a major recent study demonstrating that tight glucose control worsens outcome.³¹ Use an intravenous infusion of short-acting insulin or regular injections of subcutaneous insulin to keep blood sugar levels between 5 and 8mmol.L⁻¹.

MICROBIOLOGY

Sepsis can begin insidiously and may be difficult to recognise, but should be suspected if the patient is not progressing as expected. Many patients are relatively immunocompromised in response to their primary illness, and tend to develop secondary episodes of sepsis several days after admission. A thorough CNS, respiratory, cardiac and abdominal examination, looking for stigmata of infection, should be completed to identify the likely sources of infection. Management should follow the surviving sepsis bundle (see Box 2). Blood cultures and other microbiology samples should be taken and appropriate antibiotics administered within 1 hour.¹ Each hour that appropriate antibiotic administration is delayed increases mortality by 8%.³²

Microbiology input should be sought and antibiotics tailored to local pathogens and their known sensitivities. Antibiotics should be reviewed on a daily basis and stopped after an appropriate response and duration.

RADIOLOGY

Current and past imaging should be reviewed as required. A competent person should check every diagnostic test and document the results, to ensure that relevant information is not missed and that patients do not undergo unnecessary harmful procedures involving exposure to Xrays. There is no evidence that routine daily chest radiography is superior to clinically indicated studies.

MEDICATIONS

Scrutinise the patient's medication chart on every ward round, stopping any unnecessary drugs and antibiotics. If the patient has impaired renal or hepatic function, special consideration should be made for the risks of each medication administered and the remaining medication should be dose-adjusted. Levels may be required for certain medications, such as digoxin and phenytoin. Each medication should be reviewed in light of the current diagnosis and issues affecting the

patient, for example the presence of ACE inhibitors or non-steroidal anti-inflammatory drugs in acute kidney injury.

Ensure that, when appropriate, the patient's usual drugs are restarted (e.g. antihypertensive drugs after an episode of sepsis).

VASCULAR ACCESS

Routinely check any vascular access catheters for each patient. Your unit should have robust system for documenting the insertion date of each of these. If sepsis develops and no other source is evident, replace all venous and arterial catheters. There is no evidence to support routine replacement of venous catheters after a certain number of days, but suspicion of infection should increase the longer a cannula is in situ, particularly if there are local signs of infection (erythema, pus).

FASTHUG

The application of a final series of checks helps to ensure that all elements of good supportive care are in place. The FASTHUG assessment is one such system in common use (see Box 3).³³ This simple assessment covers many aspects of important ICU care, that are often neglected, but will reduce the incidence of ventilator associated pneumonia (VAP), deep vein thrombosis (DVT), stress ulcers and malnutrition.

Box 3. FASTHUG mnemonic³³

FASTHUG

- F Feeding** - Ensure nutrition has been assessed and that the patient's nutrition needs are being met.
- A Analgesia** - Pain should be assessed and pain relief given for the patient's disease process and medical interventions (including as part of sedation strategy).
- S Sedation** - Sedation should be assessed and patients not over-sedated. Daily sedation breaks should be considered.
- T Thromboprophylaxis** - All patients should receive prophylactic dose subcutaneous low molecular weight heparin unless contraindicated. TED stockings or calf/foot pumps should be applied.
- H Head-up** - The head of the bed should be elevated to 30 - 45 degrees to reduce gastro-oesophageal reflux and nosocomial pneumonia in ventilated patients.
- U Ulcer prophylaxis** - Ranitidine should be prescribed for ventilated patients, not established on enteral feeding. Once enteral feeding is established, it should be discontinued.
- G Glucose control** - Aim to keep glucose levels ≤150mg.dL⁻¹ (8mmol.L⁻¹) using a validated protocol.

DOCUMENTATION

Document all of your findings in a systematic way. Always clearly date and time your assessment of the patient. Make a clear *problem list*, followed by a *plan* for the day that relates to the problem list. It is useful to tick off the items on the plan as they are completed.

FAMILY/NEXT OF KIN

Ask who the immediate family are and whether they have had any discussion with members of the nursing or medical staff. Should someone speak to them today to keep them up-to-date with changes in the patient's condition? Document any discussions that you do have.

OTHER POINTS

- Discuss the resuscitation status of the patient and check that any decisions about the levels of care offered in the case of clinical deterioration have been documented.
- Ask the nurse looking after that patient whether they have any other issues that have not been resolved in your assessment.
- Ask any other members of the team whether they have anything else to add.
- Explain your main findings and plans to the patient, in as much detail as appropriate.

SUMMARY

This system will guide you to perform a comprehensive assessment of your patient. In ICU rigorous attention to detail can make the difference between survival and death. Combine clinical skills with knowledge of current evidence to reach a diagnosis and guide your management of each patient you encounter.

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Intensive care medicine in rural sub-Saharan Africa - who to admit?

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INTRODUCTION

St.Mary's Hospital Lacor is a not-for-profit, church hospital situated in northern Uganda. It is in a rural area which, until recently, has suffered considerable insecurity and is in one of the poorest areas of rural sub-Saharan Africa.¹ The hospital has significant overseas support and patient care is subsidised in order to fulfil its mission of serving the poorest patients to the highest standards possible. There are approximately 500 hospital beds and 5000 operations are performed in the theatre block per year. Since July 2005 we have prospectively collected data on outcomes of all patients admitted to the ICU. The data of over 2000 patients is stored on an Access® database.

ICU STAFFING AND INFRASTRUCTURE

The eight-bed ICU has 8 trained nurses and 4 assistant nurses. There is one anaesthetic officer assigned to the ICU who also covers the emergency theatres in the night, with one nurse anaesthetist. One overseas anaesthesiologist, has been attached to the ICU for the last 9 years and he is the only physician with a clinical responsibility totally to the ICU. All patients are admitted under the care of the admitting physicians,

who also have duties in the main wards, labour ward, outpatients and theatre. There are no other dedicated ICU medical staff.

The majority of the nurses on the ICU are not rotated around the main wards, as is often the custom in other institutions, so that a core of locally trained specialised ICU nurses has been retained.

The ICU has no capacity for peritoneal dialysis or haemodialysis. There are no infusion pumps or blood gas analysis and it is only occasionally possible to estimate serum electrolytes. There are currently three Glostavent ventilators (Diamedica, UK) in ICU with a fourth in theatre and an adequate number of pulse oximeters and non-invasive blood pressure machines. The ratio of trained nurses to patients varies from 1 to 4 to 1 to 8. The ICU is a large open-planned area with two cubicle spaces, situated close to theatre (Figure 1).² With a physical capacity of eight beds, and with the added possibility of admitting more patients on trolleys if required, the ICU is rarely physically short of beds to accept referrals from the hospital clinicians. However the nursing staff number is fixed so in busy times the ratio of nurses to patients suffers.

Summary

This article describes some of the factors to be weighed up when considering which patients are appropriate for admission to an intensive care unit in a country with limited resources. The authors describe their experience running an ICU in a rural part of Uganda, and use the audited outcomes of a cohort of 2,202 patients admitted over a six-year period.

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Figure 1. The intensive care unit at St Mary's Hospital Lacor, Uganda.

ADMISSIONS POLICY

Admission of patients to the ICU is open to any clinician, with no strict policy to guide this. Clinicians have discovered by a process of clinical experience how best the ICU could serve their patients and inappropriate admissions have been identified by ward round feedback on a daily basis.

The difficulty of deciding who to admit to the ICU has both ethical and clinical factors. The concept of futility remains an issue no matter what resources are available and it remains an issue of continuous discussion in many guises. If ICU admission is refused then the patient will receive the level of care that is offered on the general wards, and so this must also be evaluated in order to compare that offered in the ICU.

General ward care

The patient ratio on the wards may range from one trained nurse to 30 patients to one trained nurse to 60 patients, with the night shifts often the most stretched. Any critically ill and unstable patient who is denied access to the ICU will then be admitted to the ward, where both the nurse to patient ratio, and the experience of the individual nurses to deal with these patients, is far less favourable than in ICU. However, we do not have data from ward patients for direct comparison to the ICU patient population.

The issue of who to admit to the ICU and also who to discharge back to the ward is, in practice, an ongoing discussion between the ICU and ward-based clinicians. ICU ward rounds are conducted three times per day and the suitability of each patient for discharge back to the wards is discussed, in light of new referrals and the need to maintain a good nurse to patient ratio.

ANALYSIS OF ADMISSIONS TO ICU

The annual rate of admissions to ICU has grown over the last 5 years, from 264 patients in 2006 to 449 patients in 2010. The ICU mortality has remained at a steady level, ranging between 26 to 36% (Figure 2).

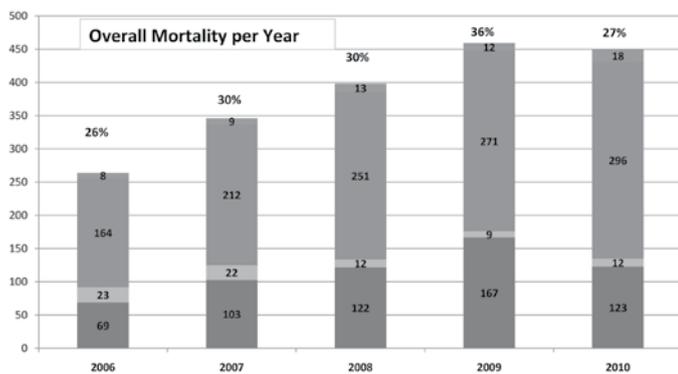


Figure 2. Analysis of admission to ICU at St Mary's Hospital Lacor, with mortality data. Upper section of bar = number referred; second section from top = number discharged to ward; third section from top = number discharged home; bottom section = number died

The work of Fenton and colleagues, assessing the mortality of Caesarean sections in Malawi, demonstrated that 80% of deaths occur in the postoperative period.³ It is likely that general surgical deaths have a similar postoperative emphasis in Africa. Figure 3 shows our outcomes in 2202 patients over the last 6 years, shown according to their admission specialty.

Thirteen arbitrary diagnostic groups were used. The development of our ICU has largely been driven by a need to meet the demands of the surgical, obstetric and gynaecological services. Medical admissions comprise 7% of admissions with a mortality of 47%. We have encouraged the development of a high dependency area within the general medical ward, containing oxygen concentrators and pulse oximeters, so that rational oxygen therapy can be administered without the need for ICU admission for this reason alone.

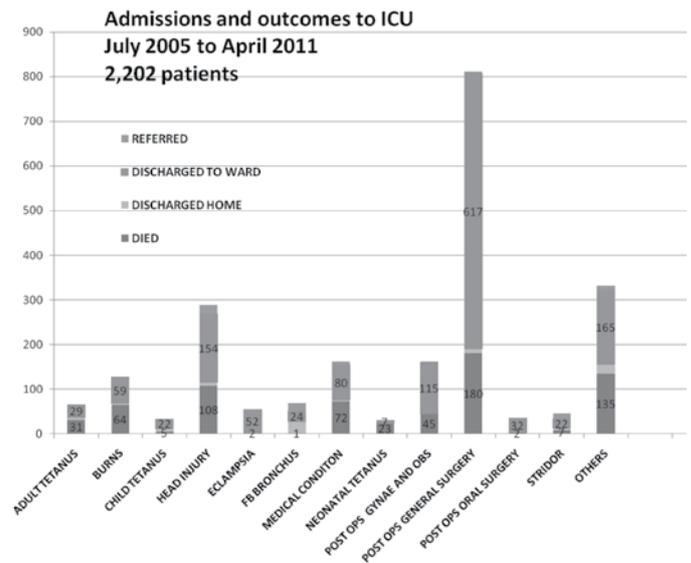


Figure 3. Outcomes in 2202 patients over the last 6 years, shown according to their admission specialty. 'Referred' means admitted to the ICU but later referred to another hospital, usually the teaching hospital in Kampala.

Head injured patients, judged clinically to be unsuitable for ward management are admitted to the ICU, but our policy has always been not to undertake advanced respiratory support, with intubation and ventilation, in these patients. The limited number of nurses and ventilators, along with the expectation of poor outcomes, even with prolonged ventilation, has ensured that this policy persists today. On rare occasions intubation and ventilation has been commenced, when sputum retention is considered to be a major factor in deteriorating coma or when early referral to an urban area is an option. Of 282 head-injured patients admitted, 108 died, 154 were discharged to the ward and 20 were referred on to Mulago Hospital, Kampala for further care. Overall mortality for head injured patients admitted to ICU was 37%.

All patients undergoing thyroidectomy are admitted to the ICU postoperatively for at least one night, as our experience is that a small number of patients develop airway problems postoperatively on the main ward. These are not reliably recognised and effectively managed on the general ward.

Figure 3 shows that postoperative general surgical patients form the largest diagnostic group in our ICU patient population. The mortality for this group is 22%, perhaps reflecting that our non-physician anaesthetists recognise the importance of adequate preoperative resuscitation. During the intraoperative period active resuscitation, cardiorespiratory monitoring and respiratory support is continuous.

We now view the postoperative period as the time of greatest risk to the patients - the general wards have a poor nurse to patient ratio, limited monitoring and limited senior staff available ward, meaning that monitoring of hypoxia and adequate blood and fluid replacement is difficult to establish. The non-physician anaesthetist assigned to the ICU is ideally situated, equipped and trained to identify high-risk postoperative patients needing blood, fluid and/or oxygen therapy, as well as pain relief.

Ventilation in ICU

Among the general surgical patients, 181 (23%) were also given intermittent positive pressure ventilation (IPPV) and the overall mortality of this sub-group was 52% (Figure 4).

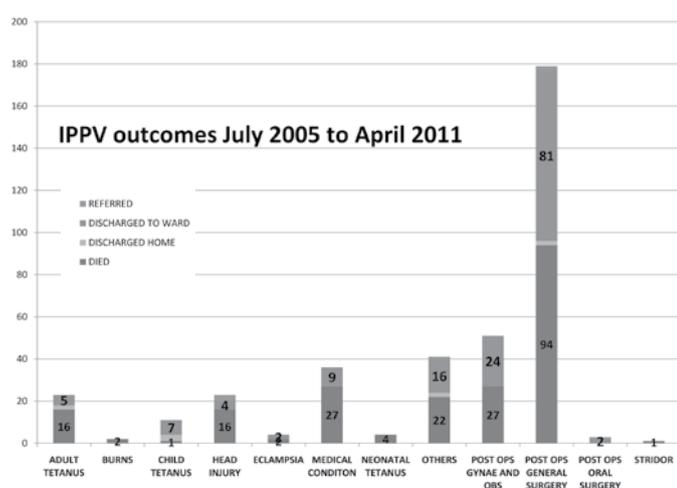


Figure 4. Outcomes of ventilated patients by diagnostic group.

Postoperative IPPV is the main invasive ICU intervention that we can offer. Our theatre anaesthetist is trained to identify patients with cardiorespiratory instability during surgery or in the immediate postoperative period, that may benefit from postoperative IPPV. These patients are transferred to ICU for ventilation. We use the same type of ventilator/anaesthesia machine (the Glostavent) in theatre and in ICU, and this has made this process of postoperative IPPV much easier to manage and teach.

Among the postoperative surgical patients who received IPPV, 83 (47%) survived. It is our view that the majority would have died if managed on the general ward without the facility for IPPV. A similar experience of postoperative support is seen with the 162 obstetric and gynaecological patients, in whom the overall mortality was 26%. Within this group 51 patients were given IPPV with a mortality of 53%, with 24 survivors. Again we believe that the majority would have died if they had received only ward care.

Figure 5 shows that in the 378 patients from all diagnostic groups, who received IPPV, the mortality was 56%, with 150 survivors. Eight patients suffered snakebite with a neurotoxic venom, where muscle fasciculation and respiratory distress required IPPV. Six of these patients were among the survivors. Six patients were admitted with some form of poisoning, often a pesticide (organophosphate) compound with five, all of whom received IPPV, surviving. Although

they represent a small subgroup, patients suffering respiratory failure following snakebite and poisoning have a good outcome in our practice. Similarly, patients who developed acute pulmonary oedema occurring under general anaesthesia formed a small group with very good outcomes when treated with postoperatively ventilation. The majority of these patients had longstanding anaemia exacerbated by acute haemorrhage, predisposing to development of pulmonary oedema.

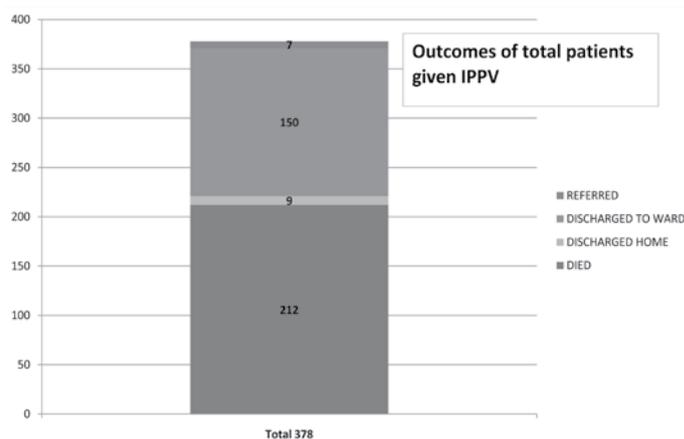


Figure 5. Outcomes of all ICU patients treated with IPPV.

Tetanus

Tetanus is a disease category which requires special consideration as its treatment lends itself particularly to the skills of anaesthetists and intensivists. We have classified tetanus into neonatal, child and adult. In our experience neonatal tetanus outcomes have been very poor, with a mortality of 77% in 30 neonates admitted. Four patients were given IPPV and all died. We no longer offer IPPV for neonatal tetanus.

The introduction of magnesium sulphate therapy for adult and child tetanus has, in our view, contributed to a major improvement in our outcomes, in comparison with the care previously offered in the general ward. Our protocols have been published in a previous edition of *Update in Anaesthesia*⁴ and follow the advice of anaesthetists in Sri Lanka.⁵ The mortality in 65 adults with tetanus receiving ICU management was 48% and in local conditions we consider this a remarkably good outcome, giving 34 survivors. In 23 of these patients tetanus was so severe that, despite large doses of magnesium sulphate, the spasms could not be controlled and so they were sedated, paralysed, ventilated and subsequently tracheostomy performed. There were 7 survivors in this group (mortality 80%).

In our experience tetanus in children has a much better prognosis with an overall mortality of 15% from 33 children. In 11 children the spasms were so severe that they were sedated, paralysed, ventilated and received tracheostomy, yet only one of these children died (mortality 9%). The management of severe tetanus in children and adults is very demanding on the ICU nurses and anaesthetists, as it may require IPPV for up to 4 weeks, but is one of the most rewarding conditions to treat. Venous access is a challenging problem in these long stay patients and femoral and internal jugular lines are usually required.

Severe burn patients are managed in the ICU and our mortality is 50%.

CONCLUSION

The majority of patients admitted to our ICU in rural sub-Saharan Africa were postoperative surgical patients. The nurse to patient ratio, close supervision and assessment by anaesthetists and basic 'ABC' interventions is superior to that available on the general wards. We believe that this has produced better outcomes for many diagnostic groups and consequently admissions rates have rapidly increased over that last six years, although we recognise that comparative data for patients receiving ward-based care is not available. The main sustainable and inexpensive invasive intervention offered in our ICU is postoperative IPPV. This is indicated in patients with reversible respiratory insufficiency and/or haemodynamic instability - conditions that would likely lead to death on the general wards.

The most dramatic effective intervention for medical patients was IPPV for poisoning by pesticides. General medical patients remain a very small percentage of our admissions over the 6 years of data collection. Tetanus patients had good outcomes compared with ward care and very early in our experience all tetanus patients were treated in the ICU. Snake bite patients with neurotoxic paralysis also did well with

IPPV. Rational use of oxygen with oximetry monitoring and oxygen therapy using oxygen concentrators has proved to be a sustainable inexpensive and effective treatment for hypoxia from whatever cause. We continue to train the general ward clinicians and nurses on basic principles of rational oxygen therapy so that ICU admissions for this sole reason are reduced.

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Identifying critically ill patients: Triage, Early Warning Scores and Rapid Response Teams

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*Correspondence Email: timothy.baker@karolinska.se**Summary**

This article describes the principles of triage of newly admitted patients and those who deteriorate on the ward.

The existing systems are explained and the authors suggest those that are best suited to practice in a low-resource setting.

INTRODUCTION

One of the most important tasks in a hospital is prioritising which patients to treat first. This is known as triage and should involve the quick and accurate detection of life threatening or serious illness. Triage facilitates timely clinical care and prioritises the use of the hospital's resources according to clinical need. The patients at highest risk can be cared for in emergency rooms or intensive care units, so that equipment and human resources can be concentrated at the point of greatest need.

In emergency departments in high income countries, formal triage systems are ubiquitous. In low income countries, triage is often absent or of insufficient quality and may be one of the weakest parts of the health system. Queue-based systems are common, without effective mechanisms to prioritise the critically ill.

Further identification of critical illness also takes place after admission to hospital. Such ward-based triage involves the regular assessment of clinical needs in order to detect the deteriorating in-patient.¹ Rapid Response Teams, that may include staff from the intensive care unit, are called to provide emergency and critical care for ward patients identified by triggers in ward-based triage. Ward-based triage and Rapid Response Teams are relatively new and are becoming increasingly utilised in high income countries, but remain in their infancy in low income countries.

In this article we describe the available methods for triage and make recommendations for triage-on-arrival, ward-based triage and Rapid Response Teams that are realistic and feasible for use in hospitals in low-resource settings.

FORMS OF TRIAGE

The methods for prioritising patients, including their advantages and disadvantages, are summarised in Table 1. Some of the methods such as vital signs and danger signs are suitable for prioritising according to clinical need and will be described in detail below. Others, such as prioritising by ability to pay, or unselective queue systems are in common use but do not help in identifying the critically ill.

Patient report

The patients themselves provide the first source of triage information. However, assessing a patient's illness severity through self-report is confounded by problems of both under reporting due to a lack of recognition and by over reporting in order to gain quicker medical attention.

Nurse or clinician intuition

Utilising the intuition of experienced clinical staff is quick and simple and many critically ill patients will be correctly identified in this way. However, such a subjective assessment is prone to considerable bias if used alone. Intuition has been adopted into most triage systems in high-income countries as an additional criterion for increasing sensitivity.

Ability to walk

Patients who are unable to walk by themselves are often critically ill. Noting the inability of a patient to walk is almost instantaneous and in a number of studies inability to walk has correlated with outcome.² It is likely that this is a proxy measurement for a number of abnormalities, including reduced conscious level.

Vital signs

Abnormal vital signs (heart rate, respiratory rate, systolic blood pressure, conscious level, body temperature, oxygen saturation) have been shown to predict mortality in a low-income setting. In a Single Parameter Score (SPS) system, triggers are defined for each vital sign and any patient with one or more observation falling beyond these triggers is categorised as an emergency (see Table 2). The sensitivity and specificity of SPS depends on the defined triggers, and one limitation is that some seriously ill patients will be missed. SPS is well suited to inpatient use where time or resources are limited because of its simplicity, particularly when combined with a nurse's intuition.

Heart rate

Heart rate at either extreme is associated with increased mortality; bradycardia is often a pre-terminal event and tachycardia a common finding in critical illness. Co-interpretation of heart rate and blood pressure abnormalities can be particularly useful.

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Table 1. Methods for prioritising patients.

Method	Advantages	Disadvantages
<i>Patient report</i> Incorporated into most triage systems (patient history)	Quick and simple	Liable to distortion, or difficult to interpret
<i>Intuition</i> The intuition of an experienced health staff	Quick and simple. May incorporate considerable clinical information	Medical professionals may not accurately identify patients at risk
<i>Ability to walk</i>	Quick and simple Proxy measurement for a number of abnormalities	If used alone will miss some critically ill patients and include some stable patients
<i>Vital signs</i> Single Parameter Score (SPS)	Quick and simple. Uses routinely collected medical data. Well validated in high-income countries	May miss some critically ill patients
<i>Compound physiological abnormalities</i> Early warning Scores	Scoring systems are well validated in high-income settings	Time-consuming Minimum information available on the performance of the scores in resource limited settings
<i>Danger signs</i> ETAT ³ World Health Organisation quick check	Incorporates early emergency management with triage. System shown to be beneficial when non-skilled staff provide healthcare (for example in children using IMCI)	May be time-consuming Emergency treatments may delay the triage of other patients.
<i>Complex triage systems</i> SATS ⁴ Manchester Triage System	Sophisticated, likely to have good sensitivity and specificity SATS validated in South Africa	Complex, requires training. Not validated in low-income setting
<i>Specialty</i> e.g. Pregnant women redirected to the obstetrician. Trauma teams represent a hybrid system with multiple specialties involved	Rapid directed care by specialist	Minimal use of severity markers; may delay the point at which action is taken
<i>Queuing</i> First-come-first-served	Simple. Requires minimal oversight therefore personnel concentrate on healthcare delivery	Doesn't prioritise according to clinical need
<i>Means to pay</i> Direct admission to a fee-paying ward		Ethically difficult to defend Does not promote equity of access to healthcare.

ETAT=Emergency Triage and Treatment; IMCI=Integrated Management of Childhood Illness; SATS= South African Triage Score

Table 2. Single parameter score.

	Adult normal range	Critical illness triggers
Heart rate	50-90	<40min ⁻¹ >130min ⁻¹
Respiratory rate	10-20	<8min ⁻¹ >30min ⁻¹
Systolic BP	100-140	<90mmHg
Conscious level	Awake, alert	Any sudden deterioration Responds only to Pain or Unresponsive
Temperature	36°C - 37.5°C	>39°C
Oxygen saturation	≥95%	<90%

Respiratory rate

Respiratory rate is one of the most sensitive single physiological parameters in prediction of mortality. However, medical staff are often reluctant to count respiratory rate due to perceived time pressure and it is unfortunately often omitted.

Systolic blood pressure

Hypotension is a good marker of severe disease and can reflect diverse pathologies such as depleted intravascular volume, loss of vascular tone in septic shock, poisonings or cardiac failure. Although both systolic and diastolic values are relevant, for simplicity in triage, the systolic alone can be used.

Conscious level

Reduced conscious level is a common finding in critically ill patients. The simple AVPU scale of conscious level (A = Awake; V = responds to Voice; P = responds to Pain; U = Unresponsive) allows conscious level to be objectively measured and documented, and deterioration identified. The Glasgow Coma Scale is good for predicting prognosis, but may be overly complex for triage.

Body temperature

Abnormal temperature can indicate severe illness. However, temperature has relatively less value where febrile illness may be trivial but common, for example adult malaria in endemic regions.

Oxygen saturation

The World Health Organization recommends the use of oxygen for patients with raised respiratory rate or oxygen saturations less than 90%. Where pulse oximeters and oxygen concentrators or other delivery devices are available, using hypoxaemia as a marker of critical illness is reasonable. Research is required in low-income country settings to identify which patients would benefit most from oxygen therapy.

Compound scores of physiological abnormality - Early Warning Scores (EWS)

Combining several vital signs may improve the accuracy of triage decisions. Compound scores encompass multiple measurements, each of which may be graded according to the degree of derangement. An aggregated score summarises all of this data into a single number (see Table 3). With increasing score the risk of mortality rises.² A threshold can be chosen above which the patient is labelled as critically ill or an action is taken. For example a healthy person with all measurements within the normal range has an EWS of 0, whereas a critically ill patient has been defined as anyone with a score of 5 or more.

Table 3. Early Warning Scores.

	3	2	1	0	1	2	3
Commonly used EWS							
Respiratory Rate		<9		9-14	15-20	21-29	>29
Heart rate		<41	41-50	51-100	101-110	111-129	>129
Systolic BP	<71	71-80	81-100	101-199		>199	
Temperature		<35		35-38.4		≥38.5	
Conscious level (AVPU)				Alert	Reacts to voice	Reacts to Pain	Unresponsive
The South African Triage Score (SATS) adds the following							
Trauma				No	Yes		
Mobility				Waking	with help	stretcher/ immobile	

Note: EWS= Early Warning Score; BP= Blood Pressure; the threshold for critical illness is ≥5 for EWS or ≥7 for SATS

Example: A patient with a respiratory rate of 32 (3 points), heart rate 120 (2 points), systolic BP 110 (0 points), temperature 37 (0 points) and conscious level V (1 point) has an EWS of 6 points and is therefore critically ill.

Early Warning Scores give a fuller picture of physiological derangement than single parameter scores and are generally more sensitive, but less specific, depending on the chosen threshold. In other words most patients who are critically ill will be identified using an EWS, however in addition some stable patients will be mistakenly labelled 'critically ill'. Scoring systems have been further refined by the addition of other factors, for example taking into account age as part of a modified EWS, age specific values to improve paediatric use, or the presence of trauma (South African Triage Score, see Table 3). A recently proposed score from the UK includes the electrocardiogram (ECG) as a parameter, further improving sensitivity, but increasing complexity.⁵

Early Warning Scores have been devised from data from well resourced settings with relatively low rates of HIV. In other areas, such as in sub-Saharan Africa, the limited evidence available suggests that EWS perform less well. Differences in study endpoints, however, have made comparisons difficult and the impact of the higher prevalence of HIV is not well known. Such limitations require that EWS systems are properly validated in the setting in which they will be used.

Danger signs

Danger signs are physiological findings or conditions that indicate that the patient is critically ill. This is the basis for the Paediatric Emergency Triage and Treatment (ETAT) guidelines that have been developed by the World Health Organization.³ The danger signs form a checklist that is simple to follow, standardizes the triage process and allows coupling of triage to early life saving interventions. A patient with any danger sign is classified as an emergency and the checklist indicates which investigations or treatments should be initiated. For example a patient showing the danger sign 'reduced conscious level' is an emergency, hypoglycaemia should be suspected and the airway should be kept clear. The introduction of ETAT in resource limited settings has been shown to reduce mortality, but adult guidelines have been harder to draft.

Complex triage systems

In high-income countries, triage systems based on algorithms involving diagnosis and physiological parameters are most commonly used. Examples are the Manchester Triage System and the Australian Triage Scale. The validity of these systems in low-income countries has not been determined, they are time consuming and their implementation requires extensive training. The triage system with most relevance to low-income countries is the South African Triage Scale (SATS).⁴

SATS (previously called the Cape Triage Score) is a nationwide triage system in South Africa established in 2006.⁴ It is based on a modified EWS using physiological signs (see Table 3) and adds in several diagnoses and clinical signs termed 'discriminators', such as pain, hypoglycaemia, seizures and nurse's intuition, that can modify the triage category. Each patient is given one of four categories: red (immediate), orange (very urgent – see within 10 minutes), yellow (urgent – see within 60 minutes) and green (delayed priority). SATS assessment takes 2–4 minutes. It has been validated in South Africa, and is increasingly promoted in similar settings in other countries.

Combining triage and treatment

Many triage systems categorise patients into three levels of urgency:

Emergency; Priority; Non-urgent. Clear documentation of the triage findings and the patient's category of urgency can be done with a stamp on the patient's notes, or colour coding stickers, such as red for emergency, yellow for priority and green for routine.

Integrating the triage system with the provision of clinical care allows rapid action to be taken.⁶ Emergency patients can be transferred to a resuscitation room, a senior clinician can be called and emergency treatments can be given. Where danger signs are used, emergency treatments can be recommended for each finding. However, with increasing complexity of intervention, the system becomes less of a triage tool and more a management guide. Provision of clinical care may delay the triage of subsequent patients.

Ward-based triage and Rapid Response Teams

Physiological derangement amongst in-patients is a precursor to adverse events such as cardiac arrest and death. This observation has led to the development of systems for early recognition and treatment of such individuals, and the advent of Rapid Response Teams (RRT), also known as Medical Emergency Teams (MET). Regular and systematic ward-based triage can be used for all patients based on single parameter or compound scores. Where ward staff recognise abnormalities beyond a predefined trigger level, they call for medical support. The RRT may consist of physicians, specialist nurses, anaesthetists or others with specific skills in acute medical care. Some are combined with ICU outreach services, whilst others are independent. Such heterogeneity of structure and service makes generalisation of their impact difficult. Before-and-after studies in single centres have shown reduced cardiac arrest rates and even reduced hospital mortality by approximately 20% in high-income countries.⁷ These findings have been confirmed by a recent meta-analysis.⁸

RRTs are uncommon and have not been formally studied in low-income countries. While the model is attractive, significant alterations may be necessary depending on the available facilities. Research should be directed at identifying areas of maximum impact.

RECOMMENDATIONS

The following are the authors' recommendations for triage in a hospital with limited resources. Suggested audit criteria for triage-on-arrival are presented in Table 4.

Triage on arrival to hospital

Every hospital should have a formal triage system for new patients. It is important to consider when and where triage should be done, who should do it and how it should be done.

When and where

Triage should precede registration processes and payment for services, where these are demanded. Emergency patients should be triaged and treated irrespective of ability-to-pay. The triage area should be close to the hospital entrance and should provide privacy. A resuscitation or emergency room should be situated nearby for the immediate treatment of the critically ill.

Who

As triage has the potential to save lives and reduce costs, it should

be a prioritized activity and senior staff should be appointed where possible. This is often a skilled nurse with specific training. However, where resources are limited, triage can be performed by any staff member – doctor, nurse, auxiliary nurse, porter, gateman, record clerk, cleaner – as long as they understand the principles of triage and have been trained in recognising the emergency patient.

Table 4. Suggested audit criteria for triage-on-arrival.

Triage initiated	<ul style="list-style-type: none"> • Patients arriving to hospital should be given a triage category • There should be sufficient documented evidence to support this decision
Triage action appropriate	<ul style="list-style-type: none"> • There should be documentation of all vital signs: walking status, airway patency, HR, RR, SBP, conscious level, temperature and, where available, oxygen saturation • A patient with reduced conscious level should have their blood glucose checked or sugar given, within 5 minutes • A patient with any overt bleeding should have immediate measures to prevent further blood loss • A patient with respiratory distress (RR >30min⁻¹ or oxygen saturation <90%) should be given oxygen within 5 minutes
Triage decision implemented	<ul style="list-style-type: none"> • Emergency patients should be seen by a clinician within 10 minutes • Urgent patients should be seen by a clinician within 60 minutes
Triage categories reasonable	<ul style="list-style-type: none"> • Patients who die within 48 hours of admission should have been classified as emergency

HR= Heart Rate; RR= Respiratory Rate; SBP= Systolic Blood Pressure

How

Triage must be quick and simple. After a triage decision has been made, patients should be moved quickly to appropriate areas in order to decongest the assessment area. The choice of triage system should depend on the available human and physical resources. Whichever is used, it should be fairly and consistently applied. The most useful methods of triage are likely to be the vital signs, ability to walk, the triage nurse's intuition and the danger signs described above.

Ward based triage

Staff shortages often preclude regular full reassessment in resource-poor settings. Identifying the deteriorating inpatient is however necessary for reducing mortality and all hospitals should have at least a basic

ward-based triage system. Vital signs should be checked regularly and we recommend the use of the Single Parameter Score system with the triggers in Table 2. An EWS could also be used but it is more complex and time-consuming and may be difficult to implement. The intuition of the ward nurse is a valid additional criterion.

Rapid Response Teams

Where patient deterioration has been identified, an immediate response should follow. Interventions can include emergency 'ABC' treatments such as freeing a blocked airway, providing oxygen, or intravenous fluids, or calling senior staff and ensuring that the patient is seen first on the ward round. Staff should be trained in the acute management of the critically ill patient and there should be clear guidelines for the most common emergencies. Rapid response teams should be considered where resources allow, but may only be useful where intensive care facilities are present.

CONCLUSION

Although seen as a vital part of hospital systems in much of the world, triage in low-income countries has been neglected. Introducing simple and realistic triage for patients on arrival and on the wards prioritises resources, based on clinical need, and has the potential to reduce mortality.⁶ Research is required into the optimal methods of triage when resources are limited; which triggers should be used for instituting medical care and which treatments are appropriate; the effects of HIV status on triage scores; and the cost-effectiveness of Early Warning Scores and Rapid Response Teams.

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Critical care where there is no ICU: Basic management of critically ill patients in a low-income country

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INTRODUCTION

Critical care can be defined as all care given in hospital to patients with serious and reversible disease. The burden of critical illness is especially high in developing countries.¹ Over 90% of maternal deaths, child deaths, deaths from sepsis and deaths from trauma occur in developing countries.² 50% of child deaths in hospitals occur within 24 hours of arriving at the hospital. One survey from South Africa found that as many as one in four of medical admissions is critically ill.³

High-income countries can afford resource-intensive and sophisticated services for managing critical illness. In countries with much lower healthcare spending, there is a need for inexpensive critical care, but there are many barriers to its provision. Processes for prioritising and caring for critically unwell patients are not routinely implemented. Life saving drugs and equipment are not immediately available. Medical guidelines often lack relevance and treatments may not be evidence-based for resource-poor settings. Staff training in the management of critical illness is uncommon, and intensive care units (ICUs) are rare. Critical care has not been promoted as it cuts across traditional disciplines and lacks advocates.

Critical care need not be expensive. Cheap treatments such as adequate fluid resuscitation to children with diarrhoea and intravenous dextrose for hypoglycaemia can be life saving. Emergency triage and treatment for children in a hospital in Malawi costs only US\$1.75 per patient and has reduced hospital mortality by 50%.⁴ Oxygen therapy can cost between one and six US dollars per day (WHO figures).

In this article we describe critical care services which are feasible in a district hospital in a low-income country. We focus on the hospital structure, routines and basic clinical management and do not discuss advanced interventions such as mechanical ventilation and dialysis, or care within specialist intensive care units.

THE HOSPITAL STRUCTURE

Critically ill patients arriving at hospital require early identification and treatment. An appropriate physical environment can facilitate this. Formal triage systems at the entrance to hospital should divide the patients

into urgent and routine cases, and direct the urgent cases to a resuscitation room or emergency department. Dividing the patients in this way can be both clinically and cost effective, as resources can be focused on those who have the most pressing clinical needs.

The emergency department should be adjacent to the hospital entrance and have facilities designed for managing emergency patients. There should be resuscitation bays or rooms for immediate treatments, with emergency drugs and equipment always at hand. Medical staff should be present or on-call 24 hours-a-day and have senior staff who can be called quickly for complicated or serious cases. Treatment rooms should be spacious to allow a team of several health professionals to work efficiently together and communication between practitioners must be prioritised; a quiet place with good access to radiology, laboratory and surgical provision is ideal.

Within the hospital, at least 1-2% of beds should be assigned for the critically ill.⁵ This means at least 4-8 beds in a 400-bed hospital. An ICU can concentrate expertise and resources and provide good critical care. Staff can receive directed training in managing the critically ill, effective routines can be set up and emergency drugs and equipment can be kept near the patients who need them most. However, there is a risk that an ICU could divert already scarce resources from the rest of the hospital: it should provide treatments and facilities consistent with the rest of the healthcare system. Where a separate ICU is not possible, designating beds on a general ward as 'critical care' or 'high dependency' beds improves medical oversight.

Where resources allow, hospitals can introduce a 'Rapid Response Team'. This is a team of hospital staff trained in critical care who may be summoned to support the care of seriously ill patients on a general ward. Rapid Response Teams can improve communication between the wards and the ICU. They can provide critical care treatments outside the designated ICU and provide 'on the job' critical care training to general staff.

IDENTIFYING THE RIGHT PATIENTS

Triage is the quick and accurate detection of patients with life threatening illness. Formal triage systems are

Summary

Many of the life saving therapies delivered in an ICU can be delivered in the most resource-poor settings. This article describes how infrastructure, personnel and clinical care may be designed to deliver effective care for all critically ill patients.

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ubiquitous in hospitals in many parts of the world, but in low-income countries triage is often absent or of poor quality. Queue-based systems are common and can result in delays for the critically ill patients and less rational prioritisation of the hospital's resources.

Every hospital should have a formal triage system for new patients. Triage should precede registration processes and payment for services. The triage area should be close to the hospital entrance and be near to (or part of) the emergency department. As triage has the potential to save lives and reduce costs, it should be a prioritised activity, with senior staff appointed where possible.

Triage must be quick and simple. The choice of triage system depends on the available human and physical resources. Most triage systems involve vital signs, early warning scores or danger signs.

Vital signs

Abnormal vital signs (heart rate, respiratory rate, systolic blood pressure, conscious level, body temperature, oxygen saturation) have been shown to predict mortality in a low-income setting. Limits or 'triggers' can be defined for each vital sign and any patient with one or more observations falling beyond these triggers is categorised as critically ill (see Table 2 in previous article).

Early warning scores

Combining several vital signs may improve the accuracy of triage decisions. Compound scores or 'Early warning scores' encompass multiple physiological measurements, each of which may be graded according to the degree of derangement.⁶ An aggregated score summarises all of this data into a single number. With increasing score the risk of mortality rises. A threshold can be chosen above which the patient is labelled as critically ill or an action is taken.

Danger signs

Danger signs are physiological findings or conditions that indicate that the patient is critically ill. The danger signs form a checklist that is simple to follow, standardises the triage and allows for the coupling of triage to early life saving interventions. A patient with any danger sign (for example 'reduced conscious level') is classified as an emergency, and the checklist indicates which investigations or treatments should be initiated.

Ward-based triage

Further identification of critical illness also takes place after admission to hospital. Such ward-based triage involves the regular assessment of clinical status in order to detect the deteriorating inpatient. Vital signs should be checked regularly and the triggers used for defining critical illness. The intuition of the ward nurse is a valid additional criterion.

Postoperative critical care

Postoperative patients can leave theatre in a critical state, due to the effects of the surgery and anaesthesia. Many of these patients have a good prognosis if they receive adequate critical care for a limited period of time. Indeed, many ICUs have begun as postoperative units. Hospitals with ICUs should have the capacity to manage the critically ill postoperative patient. Hospitals without an ICU should have a recovery room, where the patients can be cared for directly after the

operation, and critical care or observation beds on the general ward.

An initiative for predicting postoperative risk, the Surgical Apgar Score, has recently been developed.⁷ Based on three intra-operative parameters: estimated blood loss, lowest heart rate and lowest mean arterial pressure, it has been shown to provide an objective indication of risk and could be used for post-operative triage in hospitals in low-income countries (see Appendix 1).

Criteria for admission to ICU

An ICU should have well defined admission criteria. These criteria depend on the facilities and expertise available but should be based on the hospital's triage systems. The goal is to admit the patients to the ICU who could most benefit from the critical care, i.e. those who have life threatening conditions and have a reasonable chance of recovery. Equally important are discharge criteria. Those patients who have sufficiently improved and no longer require critical care, or those who are judged to be too severely ill to benefit from the available care should be discharged from the ICU to free up beds for other critically ill patients.

SIMPLE ROUTINES

Although hard evidence of effective critical care interventions is lacking, it is clear that earlier treatment, more intensive monitoring and more goal-based systems have been beneficial. Increasing staff to patient ratios improves all of these and may be the single most important factor for successful critical care. Regular physiological observations can identify deterioration early and monitor the success of interventions. Frequent assessment by medical staff is similarly important – twice daily ward-rounds of critically unwell patients and 24 hour access to a clinician should be routine.

The most effective interventions for the critically unwell patient are simple, but need to be carried out quickly. Emergency drugs and equipment such as diazepam, oropharyngeal airways, oxygen delivery equipment, intravenous fluids and giving sets should be kept on the ward and always be available. A full list of emergency drugs and equipment is in Appendix 2. Keeping these well stocked is challenging: supplies may be erratic, used items may not be replaced and equipment may be 'borrowed' for use elsewhere. For an efficient emergency service, these disruptions must be minimised. A list should be kept on the ward and daily stock-taking and equipment testing by designated 'in charge' clinical staff should be carried out. Critically ill patients should not be required to pay before they have access to life-saving therapies and relatives and staff should not need to leave the ward to find or purchase the treatments.

The patient's observations, received treatments and fluid balances should be regularly documented. This enables early recognition of the deteriorating patient, monitors the success of the care and reduces errors in drugs prescription and dispensing. Documentation can also be useful for quality control and audit. Basic hygiene routines including hand washing before and after patient contact and use of disposable gloves should be rigorously followed to reduce nosocomial infections.

CLINICAL MANAGEMENT

Effective clinical management of the critically ill patient involves concentrating on the common and easily preventable causes of

mortality. These are often described with the ‘ABCDE’ acronym. The clinician should begin by assessing the Airway, treat any abnormality found, then successively assess and treat the Breathing, Circulation and Disability (neurological dysfunction) before moving on to Everything Else. This approach is used in emergency and critical care training all over the world and has been found to be effective and easy to remember, even in stressful circumstances. The details of clinical management are covered in detail in several other articles in this edition of *Update*.

IMPROVING QUALITY OF CARE

Staff should be adequately trained in caring for critically ill patients. Training includes both ‘pre-service’ in colleges and universities, and ‘in-service’ through courses and seminars. Evaluation and feedback from external senior critical care specialists can be valuable. National and local guidelines and standards for managing the critically ill are rare and should be developed to encourage improved care.

All hospitals should have a system of audit for evaluating the care they are providing. Additionally, specific case discussion as part of mortality and morbidity meetings (M and M) is useful. This evaluates the strengths and weaknesses in the medical care of fatal cases. It is fundamental to their success that blame attribution is not pursued, but sensitive discussions may identify specific areas for improvement.

ETHICAL ISSUES

Critical care brings with it several specific ethical issues. These issues are extremely important and health staff should have an understanding of them. Critically ill patients and their relatives should be treated sensitively and with respect. Decisions are frequently made that have a huge impact on the patients’ lives and sometimes the patient is incompetent to make decisions themselves due to their illness.

End-of-life care has great social, cultural and religious, as well as medical, importance. Continued active treatment of a patient, who will not benefit from it, should be avoided. Palliative care services and adequate pain-relief can improve support for patients and their carers at the end of life. The point at which treatment becomes palliative rather than ‘active’ depends on the wishes of the patient, informed by senior medical opinion and may often be affected by cultural norms.

CONCLUSION

The requirements for a simple critical care service are summarised in Table 4. In order to ensure such services are routinely available, critical care needs to be moved up the policy agenda. Strong advocacy is required, even if hampered by the lack of critical care specialists. Training in critical care is crucial and should be aimed at both newly trained and professionally established healthcare workers. While there remain so few critical care physicians, other clinicians must be trained in providing effective care to critically unwell patients. Increasingly, hospitals in less developed settings are developing links with those from high-income countries.

This has the potential to improve training, and act as a catalyst for improvement in care. However, care should be taken that such initiatives are truly collaborative and well grounded within the existing hospital systems. Research is required to give a better understanding of critical care in low-income settings, to evaluate the clinical effectiveness of critical care interventions and to establish their cost effectiveness. The WHO recently began promoting surgical services as a way to reduce mortality and morbidity. Critical care should be next in line.

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Table 1. Requirements for a simple critical care service.

Hospital structure	Emergency department ICU or critical care beds on a ward
Identifying the right patients	Triage on admission Triage on wards
Routines for Critical Care	Increased nurse:patient ratio Regular observations Regular ward rounds Senior medical review Emergency drugs and equipment to hand, restocked, no need to pay Documentation
Clinical management	ABCDE approach Supportive care
Improving the quality of care	Training and supervision Guidelines Audit and clinical governance

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APPENDIX 1. *The 10-point Surgical Apgar Score⁷*

	0 point	1 point	2 points	3 points	4 points
Estimated blood loss (ml)	>1000	601-1000	101-600	≤100	
Lowest mean arterial pressure (mmHg)	<40	40-54	55-69	≥70	
Lowest heart rate (beats per min)	≥85*	76-85	66-75	56-65	≤55*

*Occurrence of pathologic bradyarrhythmia, including sinus arrest, atrioventricular block or dissociation, junctional or ventricular escape rhythms, and asystole also receive 0 points for lowest heart rate. The Surgical Apgar Score is calculated at the end of any operation, from the estimated blood loss, lowest mean arterial pressure and lowest heart rate entered in the anaesthesia record during the operation. The score is the sum of the points from each category.

APPENDIX 2. *Emergency equipment and drugs for use in Critical Care. This is a generic list and should be modified according to local and national resources, pathologies and formularies. Modified from: WHO Essential Trauma Care Guidelines; WHO Generic Essential Emergency Equipment List; Baker et al "Standards for Good Quality Emergency and Critical Care in Low Income Countries" (unpublished).*

Equipment

Clock with second hand
Gloves - clean
Gloves - sterile
Sharps disposal
Running water
Soap
Oropharyngeal airway (adult and paediatric sizes)
Suction machine (foot powered or electric)
Suction catheters - size 16FG
Laryngoscope (working and spare batteries)
Endotracheal tubes – adult and paediatric sizes
Rigid neck collar
Sandbags/towel rolls and head restraints
Chest tube & underwater seal (or equivalent)
Sterilised surgical set for small procedures
Oxygen concentrator/cylinder with face masks or nasal prongs and tubing
Pulse oximeter
Resuscitator bag and mask (Ambu bag)
Stethoscope
Foetal stethoscope
Blood pressure monitoring equipment
IV cannulae – adult size (e.g. 18G)
IV cannulae – paediatric size (e.g. 22G, 24G)
IV giving sets
Needles
Syringes – at least 2ml, 5ml
Lumbar puncture needles
Urine catheters & bags
Gauze and bandages
Skin disinfectant
Torch (and spare batteries)
Electricity 24hours/day
Telephone or other emergency communication system
Light suitable for clinical examination
Bedside blood glucose testing device and strips
Thermometer
Refrigerator
Weighing scales – adult and paediatric
Nasogastric tubes
Spacer device for inhaled salbutamol

Drugs

Oral rehydration solution
IV glucose 5%
IV glucose 50% (or other concentration $\geq 10\%$)
IV crystalloid (Normal saline or Ringers lactate)
Diazepam
Paracetamol
Parenteral penicillin (or equivalent)
Parenteral gentamycin (or equivalent)
Parenteral quinine (or equivalent)
Ketamine
Lignocaine for local anaesthesia
Epinephrine (adrenaline)
Atropine
Frusemide
Nifedipine or other anti-hypertensive
Aminophylline
Salbutamol (for inhaler or nebuliser)
Hydrocortisone
Insulin
IV/IM opioids e.g. morphine
Naloxone
Thiopentone
Succinylcholine
Non-depolarising muscle relaxant
Oxytocin/ergotamine
Magnesium sulphate
Phenobarbital/phenytoin

Monitoring in ICU - ECG, pulse oximetry and capnography

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Summary

Monitoring serves an important role in ICU as an adjunct to clinical evaluation.

It is important that all staff are familiar with their equipment in order to use it safely and to the maximum benefit of the patient. In particular, the settings of the alarms must be tailored to each patient, with consideration to their age, weight and pathology.

INTRODUCTION

In the intensive care unit (ICU), monitoring a patient's physiological parameters is an important part of their overall care package. Monitoring alerts you to any deterioration in a patient's condition and also helps you to assess their response to treatment. In this article we will consider three of the most commonly used electronic monitoring systems - electrocardiogram (ECG), pulse oximetry (SaO₂) and capnography. While these monitoring systems are important and useful, it should be remembered that they are always an addition to, rather than a replacement for, good clinical monitoring of heart rate, blood pressure, capillary refill time, respiratory rate, neurological status and urine output.

WHAT ARE THE BENEFITS OF MONITORING?

ECG, SaO₂ and CO₂ monitoring systems require a source of power and usually additional 'consumables' such as the pulse oximetry probe or the D-fend water trap of the capnograph. They also require technical expertise for maintenance and repair. These aspects all make them potentially problematic in a low resource environment.

However the benefits include:

- **Additional clinical information.** ECG, SaO₂ and CO₂ give very useful information about your patient's cardiorespiratory function. This information is continuous and in 'real time' and so is especially useful in critically ill patients.
- **Non-invasive.** These monitors are non-invasive, and so are well tolerated.
- **Early warning system.** The monitor's alarm systems can be adjusted to detect deviation of parameters from acceptable levels, thus providing a prompt warning of any change in the patient's condition. Careful attention to the trends of these deviations will alert you to early signs of clinical deterioration.

The following section considers each monitoring system in turn, assessing what it can, and what it can't, tell you. The physics behind each type of monitor is not

described, but can be found in previous editions of *Update in Anaesthesia*.¹⁻⁴

PULSE OXIMETRY (SaO₂)

If allowed only one form of monitoring, many anaesthetists would choose a pulse oximeter, reflecting how useful and informative this equipment can be. Most pulse oximeters are stand-alone units, usually battery-powered, but it may also be incorporated as part of a larger multipurpose monitor. It consists of a sensor probe, usually placed on the patient's finger, and a screen to display measured values.

What can it tell you?

The most important information available from this monitor is the arterial blood oxygen saturation (SaO₂), which is given as a percentage. In a normal person breathing air, a value of 96-100% is normal. Note that in smokers and those with chronic lung disease the value is likely to be slightly lower, around 92-95%. Critically ill patients, particularly with a primary (e.g. pneumonia) or secondary (e.g. acute respiratory distress syndrome) lung disease will have impaired gas exchange and low oxygen saturations. The target level of saturation, achieved by administration of oxygen and ventilation, should be set with reference to their usual respiratory status. For example it is reasonable to aim for an SaO₂ of 88% in a patient with underlying chronic lung disease with an intercurrent infection.

Most SaO₂ monitors display a value for the heart rate and emit an audible tone in time with the heart beat. The pitch of the pulse tone varies as the SaO₂ level changes; it is difficult to guess the SaO₂ when you hear the tone in isolation, but a change in the pitch of the tone alerts you to look at the monitor. A pulse waveform is also included on the screen of some monitors - this gives information about the quality of the signal and indicates whether a low recording is likely to be genuine. In general, if a good signal is received, this indicates that perfusion to the patient's extremities is good. This also has specific role where the perfusion of a limb is at risk, for example following trauma or vascular surgery. A weak or absent signal, should alert you to assess the patient's perfusion and blood pressure. Be aware that the signal will transiently disappear if the blood pressure cuff inflates on that arm.

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What can't it tell you?

The SaO₂ only tells you part of the picture regarding oxygen delivery to the tissues, as this is also dictated by the haemoglobin level and the cardiac output. A patient with a hemoglobin level of 3.5g.dL⁻¹ may have a SaO₂ of 100%, but have poor oxygen content in their blood and therefore low oxygen delivery to the tissues.

The SaO₂ value is determined by the effectiveness of both ventilation (i.e. the pump function of the lungs) and gas exchange across the alveolar-capillary membrane. However ineffective ventilation (for example, due to airway obstruction, opioid excess or neuromuscular weakness), causes type 2 respiratory failure, in which CO₂ accumulates. Pulse oximetry gives no indication of the arterial CO₂ level - a drowsy patient may have a reassuringly normal SaO₂ level if oxygen is being administered, but may have severe respiratory acidosis with a PaCO₂ over 10kPa and be close to cardiovascular collapse.

Tips for successful use

Bright or fluorescent ambient light causes interference with signal detection, as can bright sunshine. The effects of external light can be minimized by covering the hand and probe with a dark material.

Patient movement can lead to artifact on the trace and inaccurate measurements - this is a particular problem with combative or agitated patients. If transferring a patient on an uneven road, taping the probe to the finger so that it moves 'with the limb' may help.

Different types of probe are available and if you have a choice, use one that is appropriate for your circumstances. All probes work in the same way; they are just designed to fit different sized patients and different parts of the body. Smaller ear probes are available as well as special probes for children. If no paediatric probe is available, an adult finger probe can be placed around a small child's hand or foot. Paediatric probes often come as single use stickers designed to go around a baby's hand or foot - when supplies are short these can be re-used after wiping gently with a cleaning swab, as long as they are not soiled. These probes will also fit well onto an adult's finger and do not fall off during transfers.

In a cold or shocked patient try placing the probe on a more central site. A finger probe can be clipped inside the patient's mouth to detect through their cheek. Alternatives are the nose or earlobe. A small ear probe can also be placed onto the cheek, the lip or onto a nostril.

ELECTROCARDIOGRAM (ECG) MONITORING

ECG monitoring in ICU usually involves display of one lead - lead 2 - and measures the electrical activity of the heart along its long axis from right to left. Three electrodes are required for this - one on the right shoulder (usually red), one on the left shoulder (usually yellow) and one placed on the left side of the chest (usually green). Lead 2 is felt to detect most arrhythmias, which is the main role of ECG monitoring in the ICU setting.

What can it tell you?

The heart rate is calculated by the monitor by averaging the number of complexes over a set period of time. If the patient has an irregular rhythm such as atrial fibrillation the rate is calculated most accurately if the calculation period is set at the longest available.

Arrhythmias are usually diagnosed by setting the alarm limits at a high and low limit, to detect tachy- and bradyarrhythmias. The default alarm settings are usually appropriate for a healthy adult undergoing anaesthesia, but may be inappropriate for critically ill adults or for young children. An adult with sepsis may have a heart rate of 120 per minute, which will be continuously above the default 'high heart rate' setting. The alarms can be adjusted manually to levels that would represent a clinically significant deviation from their current reading. Some monitors allow you to set the upper and lower alarm limits at 10% above and below the current measured value.

Some more advanced modules are able to recognize patterns and diagnose arrhythmias, however it is often down to the clinician to identify the nature of the arrhythmia (artifact due to movement or shivering is commonly interpreted as ventricular fibrillation). It is useful to use ECG and pulse oximetry in conjunction; onset of a broad complex tachycardia with loss of the pulse oximetry waveform indicates pulseless ventricular tachycardia (VT), a medical emergency.

It is often useful to print a rhythm strip on a piece of paper in order to study the rhythm more closely (e.g. looking for P-waves). It is also usually possible to 'pause' the screen to allow further analysis.

Be aware that some ECG signals are misread by the monitor, for example large T-waves may be counted as separate QRS complexes, doubling the measured rate. Again this can be resolved by comparing to the waveform and heart rate of the pulse oximeter. Multi-channel monitors that combine ECG, pulse oximetry (and invasive arterial blood pressure) usually default to show the heart rate from the ECG reading, but this can be changed to read from a different channel.

What can't it tell you?

When a patient develops myocardial ischaemia, a single lead ECG may show morphology changes if the ischaemia happens to be in the area of the heart that corresponds to the single lead position. Otherwise it will be missed. You should request a full 12-lead ECG to assess all areas of the myocardium if you suspect myocardial ischaemia. A normal ECG trace does not always indicate a well patient; in the case of a pulseless electrical activity (PEA, formerly electro-mechanical dissociation) cardiac arrest, the patient has no cardiac output despite the fact that the ECG may be displaying normal sinus rhythm. Always check that what the monitor tells you corresponds with your patient's clinical appearance.

Tips for successful use

Poor quality ECG monitoring can be due to poor contact between the electrodes and sweaty or dirty skin. Clean the skin thoroughly and allow it to dry completely before applying electrodes. If a patient is shivering or moving around then interference on the screen may give the appearance of an arrhythmia.

If you do not have any ECG sticker type electrodes, you can improvise by using a small piece of saline soaked gauze to couple the ECG lead to the skin.

CAPNOGRAPHY (CO₂) MONITORING

There are various types of CO₂ monitoring available but most systems consist of a connector, placed in series with the patient's breathing



Figure 1. Monitoring screens for a patient who has sinus beats followed by couplets and triplets of pulseless ectopic beats. In (a) the heart rate source (circled) is the pulse oximeter, correctly reading the effective pulse as 40bpm. In (b) the ECG has been selected as the heart rate source, recording a rate of 188 per minute (square), that corresponds to the number of ECG complexes, whether they generate an effective cardiac output or not. Either of these selections can be misleading if the ECG or pulse oximetry monitoring is viewed in isolation.

system that is attached, via a sampling line, to a monitor. The monitor analyses the gas and the values are displayed on a screen. To get the most accurate reading, the connector in the breathing system should be placed as close as possible to the patient's mouth. If it is placed distant from the patient's mouth, falsely low readings result, as alveolar gas is diluted with fresh gas from the circuit tubing.

What can it tell you?

CO₂ monitoring systems can tell you three important things:

1. Whether CO₂ is being detected in the patient's expired gas or not,
2. The partial pressure of CO₂ (capnometry),
3. It provides a continuous CO₂ waveform plotted against time (capnography).

More basic systems do not give a waveform but are nonetheless very useful.

Is CO₂ present in the patient's expired gas?

This information alerts you to a serious problem with the patient. If there is no CO₂ detected, either:

- the patient is not being ventilated e.g. displaced endotracheal tube, circuit disconnection, or
- no CO₂ is being delivered to the lungs because circulation has ceased (cardiac arrest).

Both of these situations obviously need urgent attention.

Where available it is mandatory to have capnography present during induction and intubation of the critically ill, in order to rapidly confirm tracheal intubation, or to identify incorrect placement.

How much CO₂ is present?

The CO₂ reading at end-expiration (end-tidal, ET-CO₂) most accurately represents the PaCO₂, but note that the ET-CO₂ level is generally 0.5kPa lower than the PaCO₂. However this difference is not predictable in all patients, particularly those with major mismatches between perfusion and ventilation of their lungs. For some conditions, such as acute head injury, the PaCO₂ level is critical and so, where available, arterial sampling is useful. Even if performed very irregularly, it can be used to quantify the end-tidal:arterial CO₂ difference, so that capnography can be used more effectively to alter the patient's ventilator settings.

CO₂ output from the lungs is dictated by:

1. The rate at which CO₂ is produced and transported to the lungs (i.e. the patient's metabolic rate and cardiac output).
2. The patient's minute ventilation (MV) - this is the volume of gas moving into the lungs per minute and is the product of respiratory rate and tidal volume. The relationship is inverse, i.e. if the MV rises the PaCO₂ falls.

The monitor will give you a number in mmHg, kPa or percentage, with the percentage very close numerically to the kPa value, since atmospheric pressure is 101kPa. As a guide, 4-6kPa or 35-45mmHg are normal values in healthy non-smokers. Often the trend in CO₂ and the rate of rise or fall is more important than the actual value. For example, a rising CO₂ in a ventilated patient could indicate that their lungs are becoming less compliant, as they develop ARDS, or that their metabolic rate has increased, as they develop sepsis.

The capnography waveform

In order to recognize abnormal waveform patterns a normal waveform for a circle system is shown in Figure 2.

What can't it tell you?

All of the scenarios described above are guides to be assessed in line with clinical review of the patient. Sudden loss of the capnograph trace may represent equipment failure or blockage of the sample tubing with water vapour. For this reason the sample tubing should always be on the ventilator side of a heat and moisture exchanger.

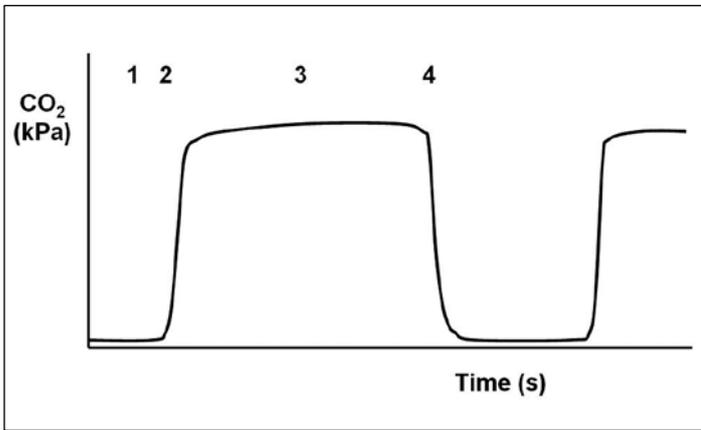


Figure 2. Normal capnography trace; Phase 4 corresponds to the onset of inspiration, Phase 1 corresponds to inspiration. During this phase the waveform should return to zero. If it doesn't, this indicates an element of rebreathing; Phase 2 corresponds to the onset of expiration. As alveolar gas containing CO₂ mixes with dead space gas the level of CO₂ in the breathing circuit rises. Phase 3 is the plateau phase and corresponds to expiration of pure alveolar gas. The CO₂ value at the end of this phase is the end tidal CO₂ (ET-CO₂) and is the value displayed by the monitor. It is normal to have a very slight upslope during the plateau phase. The level of CO₂ detected in the circuit drops as fresh gas is inspired.

The following are examples of abnormal traces that you might see on the ICU:

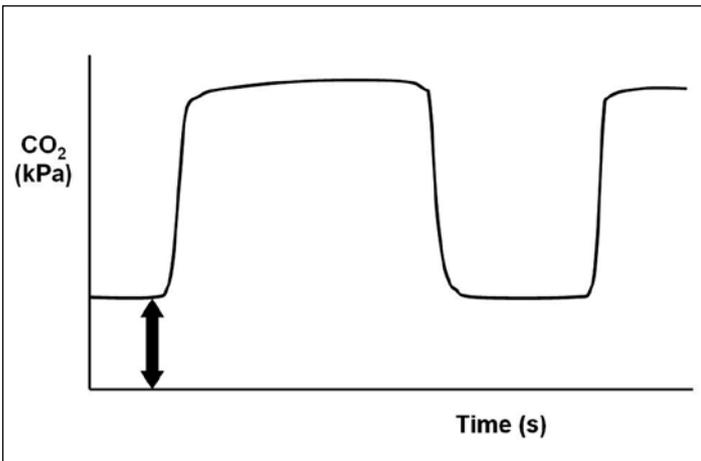


Figure 3. Rebreathing - the baseline does not return to zero (arrow) and may increase over time. This is commonly caused by exhausted soda lime or in inadequate gas flows for the breathing circuit in use.

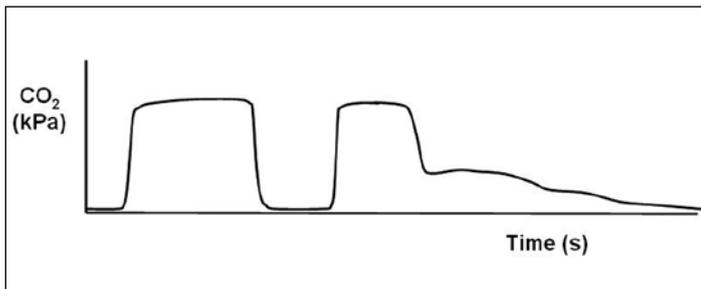


Figure 4. Sudden decrease in CO₂ waveform. This may represent an interruption in ventilation e.g. breathing circuit disconnection or a sudden decrease in cardiac output e.g. cardiac arrest.

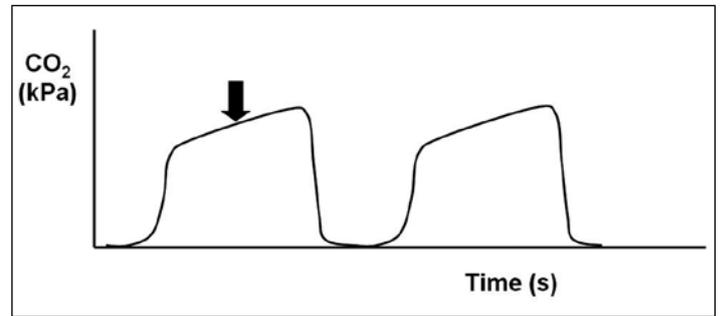


Figure 5. Up-sloping phase 3. An up-slope to the phase 3 plateau (arrow) is often seen in patients with a prolonged expiratory time e.g. in lung disease such as chronic obstructive pulmonary disease (COPD). A longer time for expiration may be required if the patient is being mechanically ventilated.

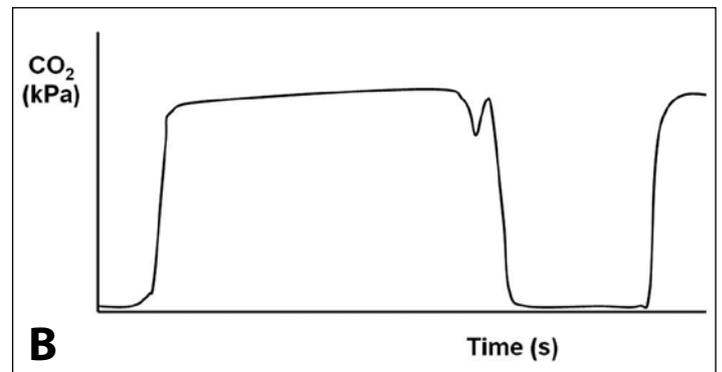
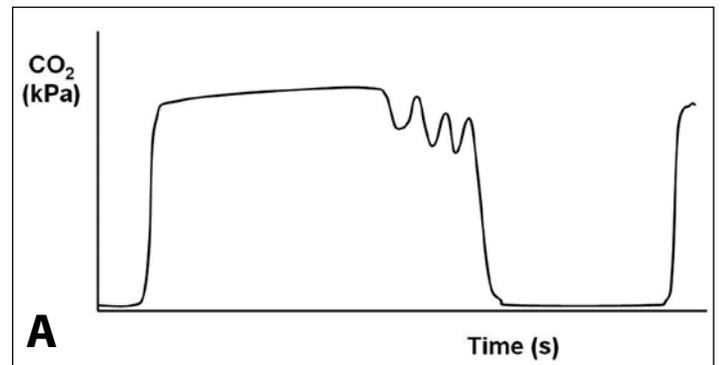


Figure 6. Superimposed waveform. Sometimes you might see smaller waves or oscillations on the normal CO₂ waveform. This might represent cardiac oscillations whereby a pressure wave from the heart is transmitted to the airway (A). Alternatively it might represent regular attempts by a patient to breathe over the top of mechanical ventilation (B) - as a 'clef' in the CO₂ waveform.

SETTING ALARMS

A major factor in the effective use of monitors to alert nurses and clinicians to a change in the status of the patient, is the sensible use of the machine's alarm systems. Most monitors come with pre-programmed alarm settings, set by the manufacturer for an average adult patient. Typical settings are as follows (but may differ between manufacturers):

- SaO₂: Will alarm if less than or equal to 94%
- ET-CO₂: Will alarm if less than 4kPa or greater than 6kPa

- ECG: Will alarm if heart rate less than 60 or greater than 100 beat per minute. Some monitors will detect arrhythmias.

As you become more familiar with the patient you are treating you may decide to alter the alarm settings. For example, a fit young patient may have a normal heart rate of 40-50 and you will want to alter your alarm settings accordingly. If you do not do this, then the alarm will sound continuously, be repeatedly silenced and will lose its power to alert you to clinically important changes. As evidence of this, you may notice that the 'silence' or 'suspend' buttons on your monitors wear out well before the other buttons!

Beware of relying completely on the monitor alarms - someone may have re-set them to limits that are not appropriate to your patient, or even turned the alarm system off altogether.

CONCLUSION

Using capnography, pulse oximetry and ECG monitoring can be an invaluable addition to treating a patient in the ICU setting, increasing safety and optimising treatment. Remember that all monitors are only

as good as the person using them - think about what you are measuring, set your alarms appropriately and always use them in conjunction with clinical examination.

FURTHER READING

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Invasive blood pressure monitoring

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INTRODUCTION

Invasive (intra-arterial) blood pressure (IBP) monitoring is a commonly used technique in the Intensive Care Unit (ICU) and is also often used in the operating theatre. The technique involves the insertion of a catheter into a suitable artery and then displaying the measured pressure wave on a monitor. The most common reason for using intra-arterial blood pressure monitoring is to gain a 'beat-to-beat' record of a patient's blood pressure.

ADVANTAGES OF IBP MONITORING

- Continuous 'beat-to-beat' blood pressure monitoring is useful in patients who are likely to display sudden changes in blood pressure (e.g. vascular surgery), in whom close control of blood pressure is required (e.g. head injured patients), or in patients receiving drugs to maintain the blood pressure (e.g. patients receiving inotropes such as adrenaline).
- The technique allows accurate blood pressure readings at low pressures, for example in shocked patients.
- The trauma of repeated cuff inflations is avoided in patients who are likely to need close blood pressure monitoring for a long period of time e.g. ICU patients.
- Intravascular volume status can be estimated from the shape of the arterial pressure trace, either by eye or by waveform analysis by a specific device e.g. a pulse contour analysis system.
- IBP measurement allows accurate assessment of blood pressure in certain patients not suitable for non-invasive blood pressure monitoring, e.g. patients with gross peripheral oedema in ICU or morbidly obese patients.
- The indwelling arterial cannula is convenient for repeated arterial blood sampling, for instance for arterial blood gases. This is not usually the sole reason for insertion of an indwelling arterial catheter.

DISADVANTAGES OF IBP MONITORING

- The arterial cannula is a potential focus of infection, although arterial lines become infected far less frequently than venous lines, especially central venous lines.
- The arterial catheter can lead to local thrombosis which may result in emboli travelling down the limb or occasionally arterial occlusion – this is rare if the catheter is kept flushed with saline and an appropriate vessel is chosen. The radial, femoral and axillary arteries may be used, as may the arteries of the foot, the posterior tibial and dorsalis pedis arteries. Where possible, the brachial artery should be avoided as this is an end artery and has no collateral supply – occlusion of the brachial artery will result in loss of blood supply to the lower arm.
- Any drug inadvertently administered into the arterial line may form crystals and cause catastrophic ischaemia of the limb. Examples of drugs with which this has been reported are thiopentone and antibiotics. All arterial lines should be clearly labelled and the tubing colour coded (usually with a red stripe) to avoid confusion. Drugs should never be administered via the arterial line.
- The insertion of an intra-arterial blood pressure monitoring system can be difficult and time consuming, especially in shocked patients. This can potentially distract from other problems that need more urgent attention.
- The monitoring equipment, spare parts and cannulae are expensive when compared to non-invasive methods of blood pressure monitoring.
- The arterial monitor requires an electrical supply which will limit its usefulness in some settings.

COMPONENTS AND PRINCIPLES OF IBP MONITORING

The components of an intra-arterial monitoring system can be considered in three main parts (see Figure 1):

1. the measuring apparatus,
2. the transducer,
3. the monitor.

Summary

Where the facilities exist, invasive blood pressure monitoring provides continuous monitoring of changes in blood pressure in unstable patients with critical illness. It allows also frequent assessment of arterial blood gases and lactate, in order to gauge progression of disease and the response to therapies. This article describes the theory of the technique in order that inaccuracy in measurement can be minimised. We also provide practical tips for insertion of appropriate catheters. Arterial pulse contour analysis for estimation of cardiac output is described in more detail in a later article in this section.

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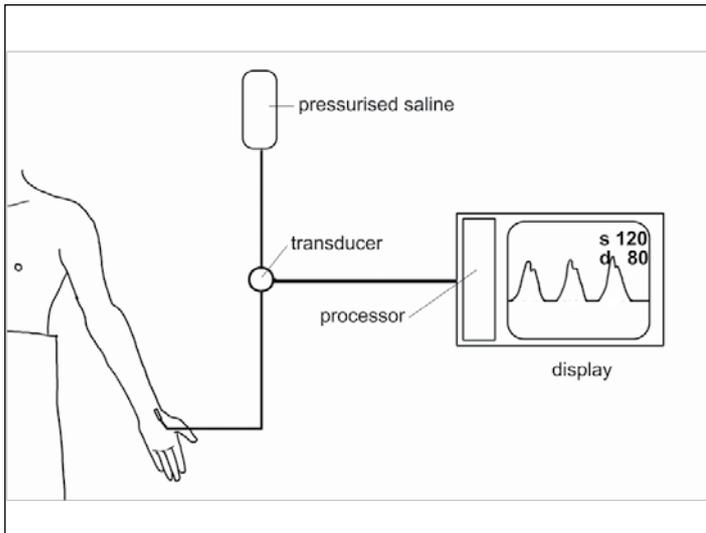


Figure 1. Components of an arterial monitoring system.

The measuring apparatus

The measuring apparatus consists of an arterial cannula (20G in adults and 22G in children) connected to tubing containing a continuous column of saline which conducts the pressure wave to the transducer. The arterial line is also connected to a flushing system consisting of a 500ml bag of saline pressurised to 300mmHg via a flushing device. Formerly 500IU heparin was added to this fluid, but many centres now consider this to be unnecessary. The flush system provides a slow but continual flushing of the system at a rate of approximately 4-5ml per hour. A rapid flush can be delivered by manually opening the flush valve. There is also usually a 3-way tap to allow for arterial blood sampling and the ejection of air from the system if necessary. The three-way tap must also be clearly labelled as arterial, to minimise the risk of inadvertent intra-arterial injection of drugs. For small children a smaller volume of flush is administered via a syringe driver, so that it is not possible to over-administer fluid by repeated flushing of the arterial cannula.

The transducer

A transducer is any device that converts one form of energy to another – for example, the larynx is a type of physiological transducer (air flow converted to sound). The output of transducers is usually in the form of electrical energy. In the case of intra-arterial monitoring the transducer usually consists of a flexible diaphragm with an electric current applied across it. As pressure is applied to the diaphragm it stretches and its resistance changes, altering the electrical output from the system. The transducers used are differential pressure transducers and so must be calibrated relative to atmospheric pressure before use.

The monitor

It is not necessary for the anaesthetist to have an in-depth understanding of the internal workings of the monitor. Modern monitors amplify the input signal; amplification makes the signal stronger. They also filter the ‘noise’ from the signal – unwanted background signal is removed with an electronic filter - and display the arterial waveform in ‘real time’ on a screen. They also give a digital display of systolic, diastolic and mean blood pressure. Most monitors incorporate various

safety features such as high and low mean blood pressure alarms and tachycardia and bradycardia alerts.

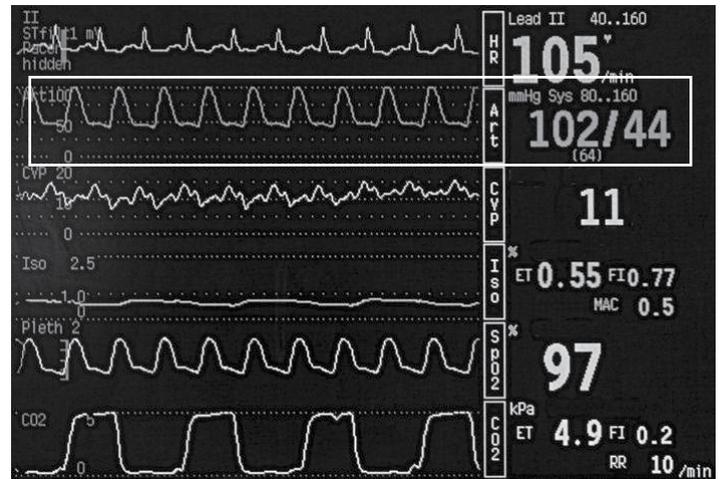


Figure 2. Invasive blood pressure monitoring (boxed). The waveforms are usually colour coded (red for the arterial trace) and the monitor displays the systolic/diastolic BP, with the mean arterial BP in brackets below.

ACCURACY OF IBP MONITORING

The accuracy of intra-arterial monitoring is affected by several important physical principles - the oscillation, natural frequency, damping and resonance of the system

Oscillation

A swinging pendulum is an example of a system that oscillates. When a pendulum is pushed (energy is put into the system), it moves away from its resting position, then returns to it. The resting position for a pendulum is at the bottom of its arc of swing and is dictated by gravity. However, the pendulum doesn't usually just return to the resting position, but tends to overshoot, swinging past the resting point in the opposite direction to the original push. This cycle continues until all the energy put into the system has been dissipated. The tendency of a system to move either side of set point is referred to as its tendency to oscillate.

Damping

Imagine you have two identical pendulums. One has recently been well greased at its point of rotation (fulcrum) and the other is stiff from rust. When an equal sized force is applied to each, the well greased one will oscillate freely around the set point but the old rusty pendulum may barely move. This is because much of the energy put into the system will be used up or damped in overcoming the frictional force of the rusty axis. The rusty pendulum will tend to oscillate at smaller amplitude (i.e. smaller swings) and for a shorter period of time than the well greased one. How freely a system oscillates following an input of energy is dependant on the degree of damping in the system.

A ‘well damped’ system tends not to oscillate freely whereas a ‘poorly damped’ system may oscillate wildly. The amount of damping inherent in a system can be described by the damping coefficient (D) which usually lies between 0 and 1 (but can be greater than 1). A system with a D value greater than 1 describes a system that is over-damped, will

not oscillate freely and takes a long time to initially move away from and to return to its resting point (a high friction pendulum). A D value less than 1 and approaching 0 describes a system that is under-damped, that oscillates freely, moving rapidly away from its resting point and back again, but tends to overshoot and then oscillate around the resting point (a low friction pendulum). A D value of exactly 1 is known as critical damping.

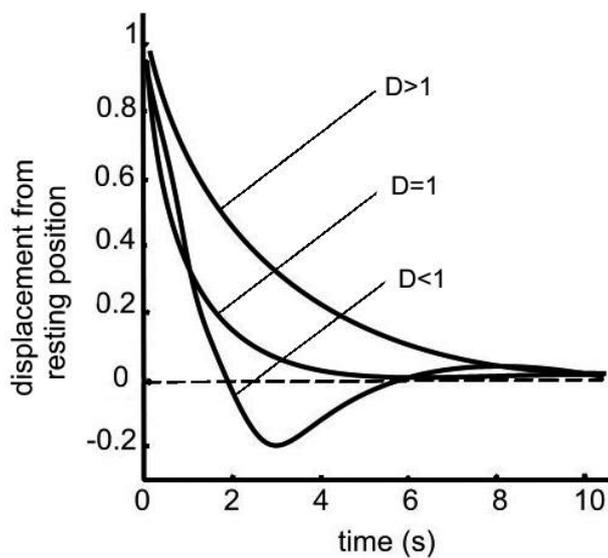


Figure 3. Graph showing the effect of different levels of damping on the oscillation of a measuring system.

Oscillations are undesirable in physiological measuring systems. These systems require accurate measurement of a maximum amplitude (for instance, that caused by the arterial pulsation), with a rapid response time and rapid return to the set point, ready for the next measurement. The ideal level of damping applied to a measuring system is a compromise between achieving a rapid response time and accurate reflection of maximum amplitude i.e. a system with D close to 0, and needing a system that returns to the resting point without excess oscillation (D around 1). In the case of an IBP monitoring system this would represent the difference between using very compliant measuring apparatus (compliant catheters, tubing) i.e. D approaches 0, and very stiff or non-compliant equipment i.e. D is closer to 1. The value of D chosen for physiological measuring systems such as IBP monitoring equipment lies between 0.6 and 0.7 – it is known as optimal damping.

Natural frequency and resonance

A pendulum of set length and with a set weight at the end will always oscillate at exactly the same frequency, no matter what the initial starting point of the oscillation. In other words, whether you give the pendulum a small push or a really hard shove it will make the same number of oscillations per unit time (although the amplitude of the oscillations will alter). This is why pendulums can be used to keep time. Any system such as this will have a frequency at which it ‘naturally’ oscillates. This frequency is known as the natural frequency.

If the input of energy into a system is occurring at the same frequency (or close to) the natural frequency, a phenomenon called resonance occurs and the output amplitude of the oscillations is greatly magnified. In the case of intra-arterial blood pressure monitoring this could lead to over-reading of the systolic blood pressure. Arterial pulsation is a complex sine wave and is composed of many individual sine waves. It is therefore important that the natural frequency of the measuring equipment (the catheter and column of saline etc) does not correspond to any of the component frequencies of the arterial pulsation input. This is achieved by making sure that the natural frequency of the measuring system is raised above any of the component frequencies of the arterial sine waveform.

The characteristics of the measuring equipment that will ensure that the natural frequency of the system is higher than that of the arterial pulsation are:

- Arterial catheter must be short and with the maximum gauge possible,
- Column of saline must be as short as possible,
- The catheter and tubing must be stiff walled,
- The transducer diaphragm must be a rigid as possible.

SETTING UP THE ARTERIAL LINE AND TROUBLE SHOOTING

The usual location for insertion of the arterial catheter is the radial artery. The advantage of the radial artery is that it is superficial, easily accessible, and there is a collateral blood supply to the hand from the ulnar artery. It is advisable to perform Allen’s test to detect adequacy of collateral supply to the hand via the ulnar artery, although the test is not infallible and can only be performed in conscious patients (see Figure 4).

The brachial artery should be avoided if at all possible (no collateral supply); the femoral artery, the ulnar artery, arteries of the foot and ankle, and even the axillary artery should be used in preference if necessary. Whichever location of artery is used, the distal limb should be monitored regularly for signs of emboli or distal ischaemia.

Insertion of a radial arterial line

This should be performed as an aseptic technique. The wrist should be cleaned with alcoholic chlorhexidine solution prior to cannulation and, in conscious patients, the skin should be infiltrated with 1% plain lidocaine. The arm should be abducted in the anatomical position and the wrist should be hyper-extended to aid cannulation (the radial artery is brought closer to the skin surface and the hand moved out of the way). This is most conveniently done by an assistant. If an assistant is not available use tape to secure the patients hand fingers extended over a bag of fluid (see Figure 5).

There are various types of stiff, short arterial catheter available. Some feature a simple ‘cannula over needle’ design, similar to an intravenous cannula and some incorporate a guide-wire as part of a Seldinger technique – the needle is inserted, a wire passed through the centre of the needle, the cannula threaded over the wire (Figure 6). The correct cannula to use is the type with which you are most comfortable. Ideally a cannula with an injection port should not be used, as this

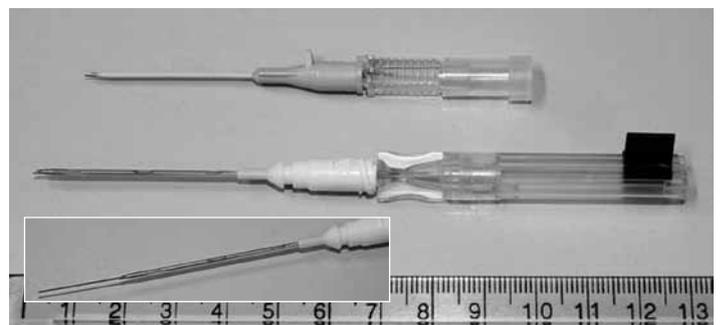


Figures 4a and 4b. Allen's test. Ask the patient to make a fist, use your thumbs to occlude the patient's radial and ulnar arteries. Ask the patient to unclench their fist – the palm will remain pale (a), whilst the blood supply is still occluded. When you remove your thumb that is occluding the ulnar artery, the palm will flush red if the ulnar artery is functional (b).



Figure 5. Technique for securing the patient's wrist extended, using adhesive tape and a fluid bag.

Figure 6. Two 20G arterial cannulae. The lower cannula has a guidewire that can be slid into the artery through the needle to allow smooth placement of the cannula (inset).



may be confused with an intravenous cannula - if such a cannula is used, the injection port should be taped over and the cannula clearly labelled as arterial.

Make sure that you tape the cannula securely in position, and take care not to kink the cannula as you do so. Sometimes it is advisable to suture the arterial line in place.

The arterial catheter should be connected to the tubing, the transducer secured in a position approximately level with the heart and the



Figure 7. Cannula insertion. The usual insertion technique is to palpate the artery with the fingers of one hand and locate the artery with the cannula at an angle of about 30 degrees (a). Once a 'flashback' has been obtained the cannula should be brought level with the skin and then advanced 2-3mm further (b). This should ensure that the entire tip of the cannula, rather than just the needle, is within the arterial lumen. At this stage either the cannula can be advanced over the needle or the guide-wire introduced.

transducer 'zeroed' - that is, closed to the patient and opened to atmosphere to obtain a reading of atmospheric pressure. It is often convenient to tape the transducer to the patient's upper arm to ensure it is level with the heart.

Practical tips and trouble shooting

- Figures 7 and 8 show common techniques for arterial cannula insertion the radial artery is very superficial at the wrist. Often when you think you can't find it, you have in fact transfixed it (a technique some people use preferentially). Remove the needle and then slowly withdraw the cannula, aspirating using a 5ml syringe attached to the hub all the time. As the tip of the cannula re-enters the artery, blood will flow into the syringe briskly. From this point slowly advance the cannula whilst rotating the cannula in a twisting motion about its long axis. This technique will salvage the cannulation more often than not.



Figure 8. If location of the artery is difficult an alternative method involves positioning your thumb so that the radial pulse is running directly under the centre of your thumb. Then advance the cannula at 30 degrees under the centre point of your thumb.

- If you hit the artery but fail to cannulate it a couple of times, it is often wise to move to the other wrist; the artery will go into spasm following repeated trauma making cannulation progressively more difficult.
- Inserting an arterial catheter in shocked patients is very difficult. Do not waste time making repeated attempts to do so; resuscitation of the patient is more important!
- After attaching the catheter to the saline column take great care to ensure there are no air bubbles in the system before flushing it.
- If you suddenly obtain a very high blood pressure reading, check the position of the transducer; it may have fallen on the floor!
- If you lose the waveform on the monitor or it decreases in amplitude, the catheter may be kinked or blocked with a blood clot, or there may be an air bubble damping the trace. After checking that your patient has a pulse, you can try making sure the wrist is extended, aspirate any air bubbles and then flush the catheter, or withdraw the catheter slightly to check it is not kinked.
- Note that over or under-damped traces will give false blood pressure values. An under-damped trace will overestimate systolic pressure and underestimate diastolic pressure as the system 'over oscillates'. A low amplitude, over-damped trace will underestimate the systolic blood pressure and overestimate the diastolic blood pressure. Fortunately, the value for the mean arterial blood pressure is little affected and can usually be taken as accurate.

PULSE CONTOUR ANALYSIS

Useful clinical information can be obtained by looking at the pattern of the arterial waveform on the monitor.

- A large 'swing' or variation in peak amplitude of the systolic pressure that coincides with the ventilatory cycle often indicates that the patient is hypovolaemic.

- Conscious patients who are in respiratory distress may also have a large swing on the arterial pressure trace, due to large changes in intrathoracic pressure.
- A narrow width, high amplitude pulse combined with tachycardia tends to indicate hypovolaemia.
- The angle of the upstroke of the arterial waveform may give an estimate of myocardial contractility; a steeper upstroke indicates greater change in pressure per unit time and higher myocardial contractility. In practice, this only provides a rough assessment of myocardial contractility.

Analysis of the arterial waveform has been developed mathematically to calculate cardiac output. The term 'pulse contour analysis' is usually used to refer to the cardiac output monitoring systems employed in the PiCCO™ (Pulsation Medical Systems, Germany) and LiDCO™ Plus (LiDCO Ltd, UK) monitors.

The PiCCO™ and LiDCO™ systems both measure cardiac output using both the shape and the area under the arterial pulsation curve. For both techniques a haemodilution method is used to calculate the cardiac output and calibrate the pulse contour analyser. Note that this means that both systems require central venous access. By knowing the exact shape and area under the arterial pulsation curve at the time of calibration, future arterial pulsation curves can be compared and the cardiac output at that point in time extrapolated.

The way in which these two systems calculate the initial cardiac output differs in that the PiCCO™ uses haemodilution of cold saline and the LiDCO™ uses haemodilution of lithium. The LiDCO™ cannot be

used in patients on lithium therapy or for up to two hours following the administration of non-depolarizing muscle relaxants. Both systems need regular recalibration by re-measuring the cardiac output using haemodilution. All the factors previously mentioned that alter the accuracy of the arterial waveform (air bubbles, kinking etc) will affect the cardiac output value that the system gives. The two systems also alter in terms of the mathematical modelling they use to perform the pulse contour analysis. Recently these systems have been adapted so that they no longer need to be calibrated, but use population data to generate measurements (e.g. the LiDCOrapide™). Further clinical evaluation of these systems is needed. Further description of these techniques can be found in the article on page 51.

SUMMARY

Invasive arterial monitoring is a highly useful tool, which allows close blood pressure monitoring for patients undergoing major surgery and the critically ill. It is also useful for repeated arterial blood gas analysis and as an access point for obtaining other blood samples. It is important to understand the principles of biological measurement systems in order to optimise their performance and allow troubleshooting when performance is poor.

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Central venous cannulation

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INTRODUCTION

Central venous cannulation is a relatively common procedure in many branches of medicine, particularly in anaesthesia and intensive care medicine. An estimated 200 000 central venous access procedures are carried out each year in the United Kingdom's National Health Service and over 5 million in the United States. Historically central venous access was gained by a surgical cut-down procedure, but central venous catheters (CVCs) are now predominantly inserted percutaneously, using a technique first described by Seldinger in 1953. There are many different types of catheter and a number of different sites suitable for central venous access. Site selection depends on numerous factors including the indication and duration of access, anatomy of the patient, local resources and operator skill and experience.

INDICATIONS

The main indications for CVC insertion are:

- Administration of drugs
 - Irritant drugs
 - Long-term treatment (chemotherapy, antibiotics)
 - Long stay patients (e.g. tetanus)
 - Parenteral nutrition
- Haemodynamic monitoring
 - Central venous pressure
 - Mixed/central venous oxygen saturations
- Difficult peripheral access
- Haemofiltration / haemodialysis
- Insertion of pacing wires or pulmonary artery catheters.

CATHETER SELECTION

There is a large range of catheters available and selection should be based on site, reason for insertion and length of use. In anaesthesia and intensive care medicine the main considerations are catheter length and the number of lumens. Three to five lumens are ideal for critically ill patients, allowing multiple drug infusions, but the

lumens are usually narrow with a high resistance to flow and so less effective for rapid infusion of fluid during resuscitation. Larger, shorter catheters such as an 8.5F introducer sheath are better suited to this purpose.

Types of catheter

- Single/multiple lumens
- Peripherally inserted central catheters (PICC)
- Tunnelled (the catheter travels a few centimetres under the skin before entering the vessel, in order to decrease the incidence of line infections).
- Specialized
 - dialysis catheters
 - continuous central venous saturation monitoring.

Lumen size

Larger catheters allow greater fluid flow (e.g. for resuscitation and haemofiltration) but have a greater risk of significant haemorrhage or air embolism during insertion or inadvertent disconnection. They also have a significant dead space to consider during administration of potent drugs such as vasopressors - the narrow gauge lumens of multiple channel lines are better for this purpose. Larger catheters are more likely to cause thrombosis or late stenosis of the vessel.

Impregnated catheters

A number of manufacturers make catheters impregnated with antimicrobial agents, such as chlorhexidine and silver sulfadiazine, in an attempt to reduce catheter related infections. Many ICUs use these lines routinely despite the higher cost, the potential for development of drug resistance and the inconclusive evidence for reduced morbidity and mortality.

PRINCIPLES OF INSERTION

In well resourced settings, ultrasound guided insertion has become standard practice. As this is unavailable in most low-income countries, landmark techniques are emphasized here.

The basic preparation and equipment required for CVC insertion is the same regardless of site or technique. A

Summary

Central venous catheters are extensively used in ICUs in high-income countries, but they remain beyond the facilities available in many developing world ICUs. In developing countries, their main use is as access for delivery of irritant drugs such as catecholamine infusions and for intravenous access in patients requiring prolonged organ support due to illnesses such as tetanus. The different sites of insertion are described and the common techniques for insertion are outlined.

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suitable clinical area should be chosen where full aseptic technique can be observed. A trained assistant is useful and the patient should be monitored with continuous ECG, oxygen saturations and blood pressure measurement. The suggested essential equipment is listed in Table 1. There is evidence that the use of a dedicated 'lines trolley' increases compliance with best practice. Confirm that the CVC is still needed and select the most appropriate route (see below). Explain the procedure to the patient.

Strict asepsis at the time of insertion is a major factor in reducing line related infections - wear sterile gloves, a gown, mask and theatre hat. Drape the surrounding areas of the patient and bed as thoroughly as possible. Good positioning and identification of anatomical landmarks will minimise the risk of failure and complications. In conscious patients local anaesthetic should be used.

Table 1. Suggested essential equipment for CVC insertion.

It is well worth having all of your equipment laid out in a logical order before you proceed. Make sure that you are familiar with the set provided.

- Patient on a tilting bed, trolley or operating table
- Hat, mask and sterile gown and gloves
- Large sterile drapes and gauze swabs
- Antiseptic solution (chlorhexidine in alcohol)
- Local anaesthetic agent with needle and syringe
- Saline flush
- Appropriate central venous catheter set
- Three-way taps
- Scalpel blade
- Sutures

General technique (Seldinger)

The most common method of insertion is the 'catheter-over-guidewire' (Seldinger) technique (see Figure 1). The vein is punctured with a small gauge needle (18 or 20G) attached to an empty syringe and blood is aspirated easily. If the blood appears bright red, is at high pressure or pulsatile consider the possibility of an arterial puncture.

The guidewire commonly has a J-shaped tip to reduce risk of damage to the vessel wall and help negotiate tortuous vessels. It should advance and withdraw easily at all times.

After removing the needle, a dilator is then passed over the guidewire and a small incision made in the skin to allow the dilator to advance through the skin, subcutaneous tissues and a short distance into the vein (further passage along the vein may cause damage to the vessel or distal structures). Gentle skin traction and a twisting motion aids passage of the dilator and prevents kinking of the guidewire. Remove the dilator and insert the catheter over the guidewire. The guidewire is held whilst the catheter is advanced to the desired length. Care should be taken not to advance the guidewire with the catheter, as this may

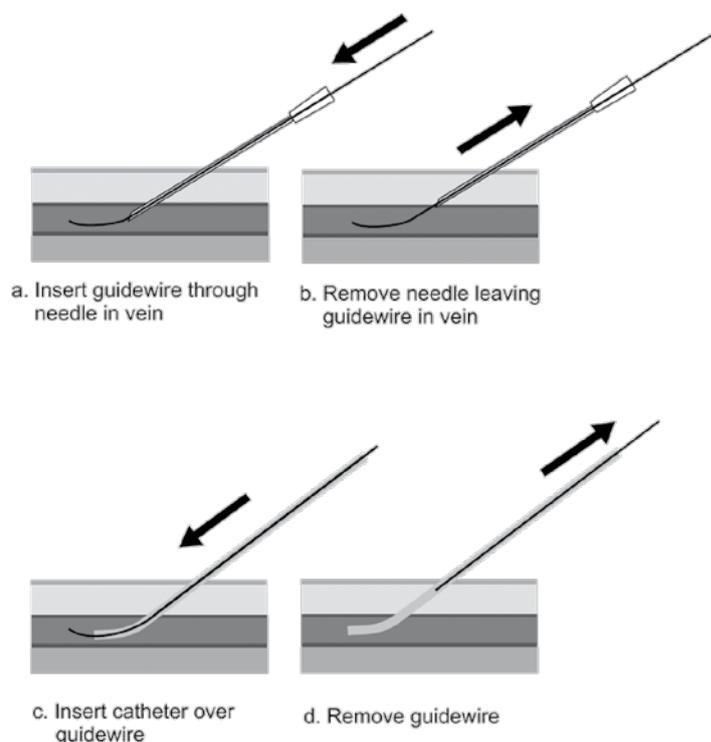


Figure 1. The Seldinger technique.

precipitate arrhythmias and intravascular loss of the guidewire has been reported.

You can usually get some idea of the length required prior to insertion by laying the catheter on the patient's chest prior to insertion. Map out its course and note the distance between the tip at the medial right second intercostal space and the site of skin puncture. Remove the guidewire and aspirate and flush all the lumens with saline to check for free flow. Finally secure the catheter in place with sutures and a sterile non-occlusive dressing.

SITE SELECTION (Figure 2)

There are a number of approaches to the central venous system and these veins may be deep structures, running close to arteries, nerves and other structures (e.g. the pleura in the case of the subclavian vein). You must know the deep and surface anatomy of the area to undertake a landmark technique safely. 2-D ultrasound is increasingly used, where resources allow, and is well suited to the internal jugular, femoral and peripheral approaches. Ultrasound allows visualisation of the vessel, confirmation of placement of the wire within it and identification of anatomical variation.

The main entry sites are:

- Internal jugular vein
- Subclavian vein
- Femoral vein
- External jugular vein
- Veins of the arm or antecubital fossa (basilic or cephalic veins).

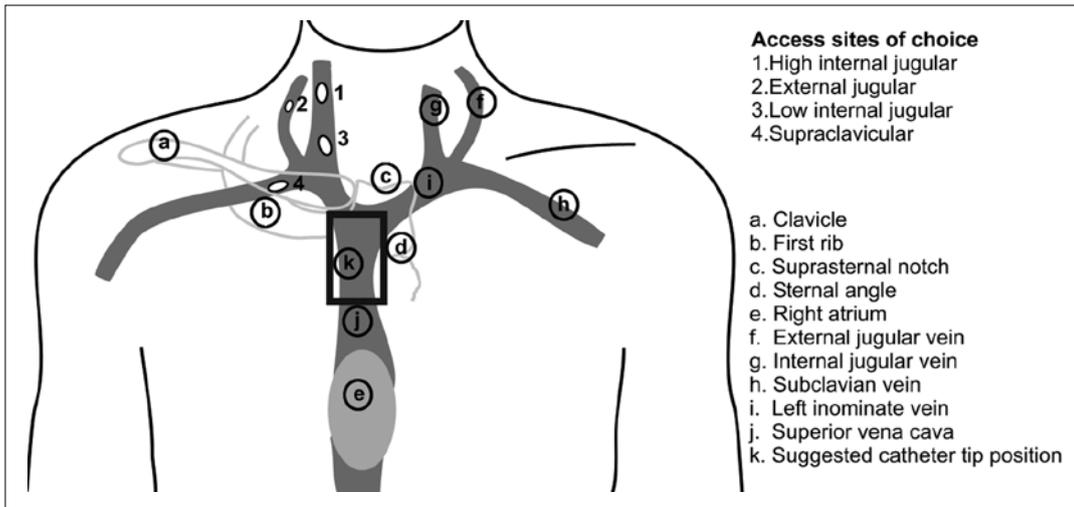


Figure 2. Common sites for intrathoracic CVC placement.

Factors determining choice

Duration of use

- Consider a tunnelled line for prolonged administration of antibiotics or where intravenous access has become difficult.
- Femoral lines are only appropriate for use for up to 48 hours due to the higher infection risk.

Suitability of site for planned CVC use

- e.g. for CVP measurement, catheter tip must be in thorax.

Operator

- Knowledge and practical experience of the technique – it is better to have a few clinicians in each area who perform all the central venous cannulations and gain experience (a ‘central venous access team’).

Technique characteristics

- Success rate for cannulation and central placement
- Complication rate

- Ease of learning
- Puncture of visible/palpable vein versus blind, landmark technique.
- Applicability to patients of different ages.

Equipment available

- Availability of suitable apparatus (including ultrasound)
- Cost.

SPECIFIC CVC SITES

Internal jugular vein

The internal jugular vein (IJV) is most frequently chosen site for CVC insertion. It is a potentially large vein with a lower risk of pneumothorax compared with the subclavian approach. Inadvertent arterial puncture can be controlled easily with manual compression. Many approaches have been described depending on the level of the neck at which the vein is punctured. A high approach reduces the risk of pneumothorax but increases the risk of arterial puncture. For lower approaches the converse is true. With experience this route has a low incidence of complications.

Anatomy (Figure 3)

The IJV arises from the jugular foramen at the base of the skull and is a continuation of the sigmoid sinus (within the skull). It descends in the neck in the carotid sheath, with the carotid artery and the vagus nerve. It lies initially posterior to internal carotid artery before becoming lateral then anterolateral to the artery. Behind the medial end of the clavicle it joins the subclavian vein to form the brachiocephalic vein. The vein has dilatations at both ends, the superior and inferior jugular venous bulbs. Cannulation can be difficult in the morbidly obese, as landmarks are often obscured and those patients with very short necks or limited range of movement can also be a challenge. The IJV is unilaterally absent in 2.5% of patients and is outside the predicted path in 5.5% of patients. The right IJV offers some advantages in that it tends to be larger and straighter than that on the left, it is more convenient for the right-handed practitioner and avoids the possibility of thoracic duct injury.

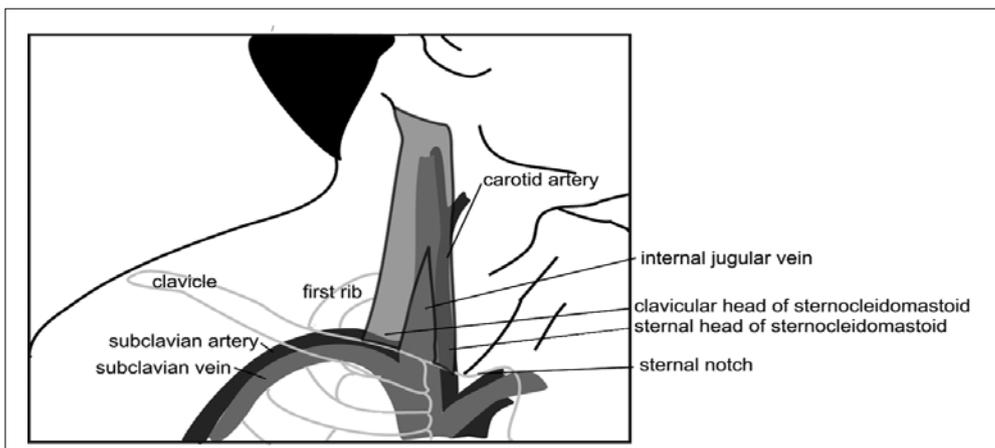


Figure 3. The anatomy of the right internal jugular and subclavian veins

Positioning

The patient is supine, arms by their sides, with a head down tilt to distend the veins and reduce the risk of air embolism. The head should be slightly turned away from the side of cannulation for better access (excessive turning should be avoided as it changes the relationship of the vein and artery and can collapse the vein). The patient’s neck can be extended by removing the pillow and putting a small towel under the shoulders.

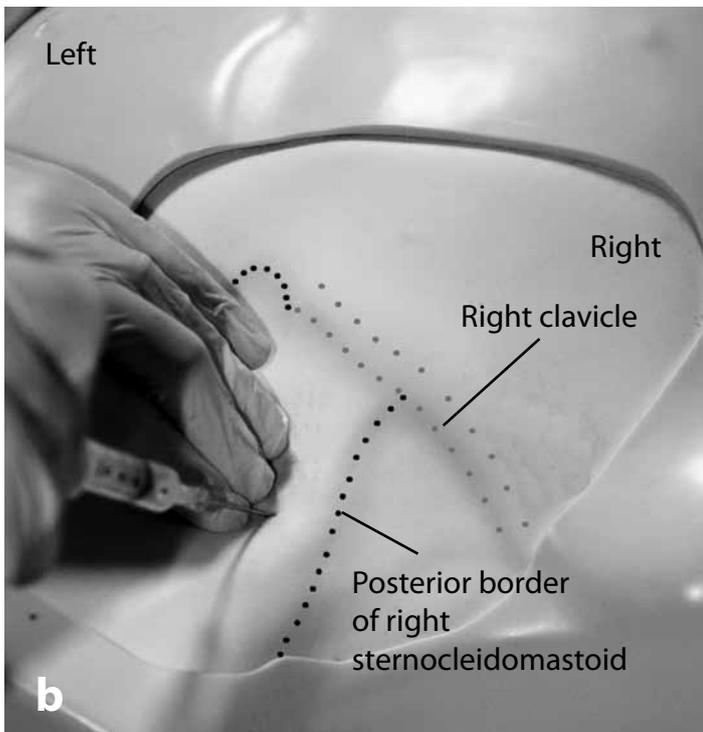
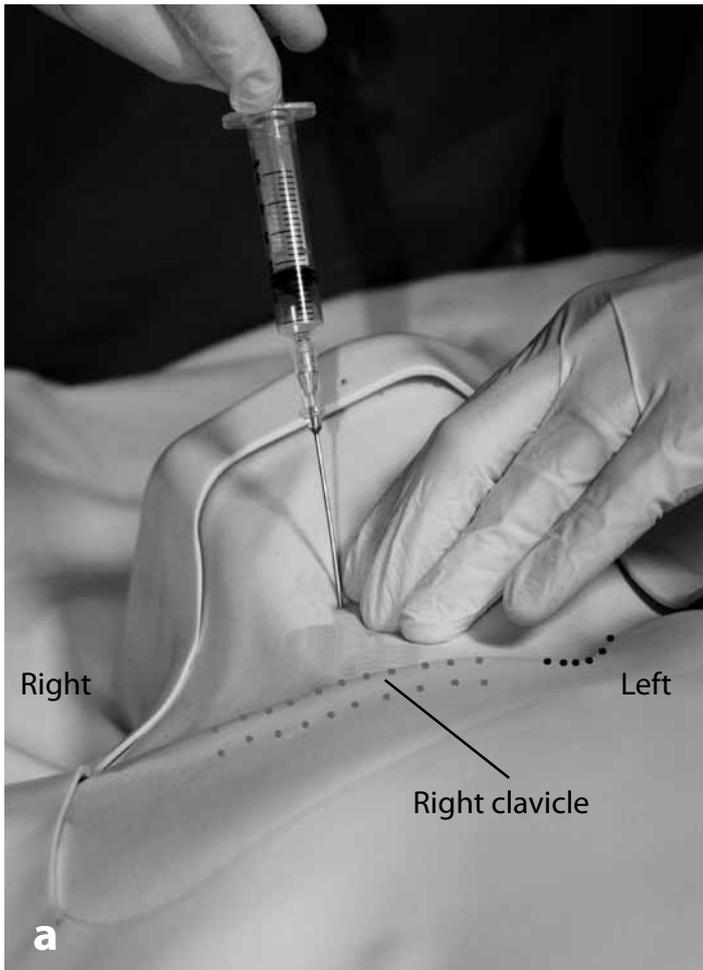


Figure 4. Right IJV cannulation, (a) view from caudal aspect; (b) view from cranial aspect.

Technique

Stand at the head of the patient and palpate the mastoid process and the sternal notch. The entry level is half way along a line joining these two landmarks. Palpate the carotid artery at this level and check your entry point is lateral to this. It is sometimes possible to ballot the vein which can aid accurate needle placement. Keeping your finger gently over this point (even small amounts of pressure can collapse the vein) insert the needle at 30-40° to the skin directed caudally towards the nipple on the same side (in females guess where it would be if it were a male) aspirating as you go. The vein is usually very superficial and only 0.5-2cm under the skin.

Practical problems

If the vein is not found recheck your landmarks, ensure the patient is adequately head down and consider rehydration if the patient is hypovolaemic. After a failed attempt to locate the vein, continue to aspirate as you slowly withdraw the needle; the vein may have collapsed on the way in and be transfixed as the needle has gone through the posterior wall. Resist the urge to advance the needle deeper into the tissues, as you are most likely to be in the wrong place rather than too superficial. If ultrasound is available use it to check that the anatomy is normal.

Subclavian vein

The subclavian vein (SCV) has a calibre of 1-2cm in adults and is thought to be held open by its surrounding tissues, even in severe circulatory collapse. It is often preferred for long-term central access as it is generally more comfortable for patients, can be easily tunnelled and has a lower risk of infection and other long-term complications. This route may also be preferred in trauma patients with suspected cervical spine injury.

This route is best avoided in patients requiring long-term renal replacement, as there is a significant risk of venous stenosis, causing problems for existing or future arteriovenous fistulae. The subclavian route is best avoided in patients with abnormal clotting or bleeding diatheses, as the vessels are inaccessible to direct pressure after inadvertent arterial puncture. Serious immediate complications are uncommon but occur more frequently than other routes. Pneumothorax is one of the most common major complications with an overall incidence of 1-2%. This figure increases to 10% if multiple attempts are made. Although possible in some patients, visualisation of the subclavian vein with ultrasound is difficult in most.

Anatomy

The SCV is a continuation of the axillary vein as it reaches the lateral border of the first rib (Figure 3). It ends at scalenus anterior where it joins the internal jugular vein, to form the brachiocephalic (innominate) vein, behind the medial end of the clavicle. Its only tributary is the external jugular vein and it lies anterior and parallel to the subclavian artery throughout its course. The cervical pleura lies behind the artery.

Initially the vein arches upwards and across the first rib and then inclines medially, downwards and slightly anteriorly across the insertion of scalenus anterior.

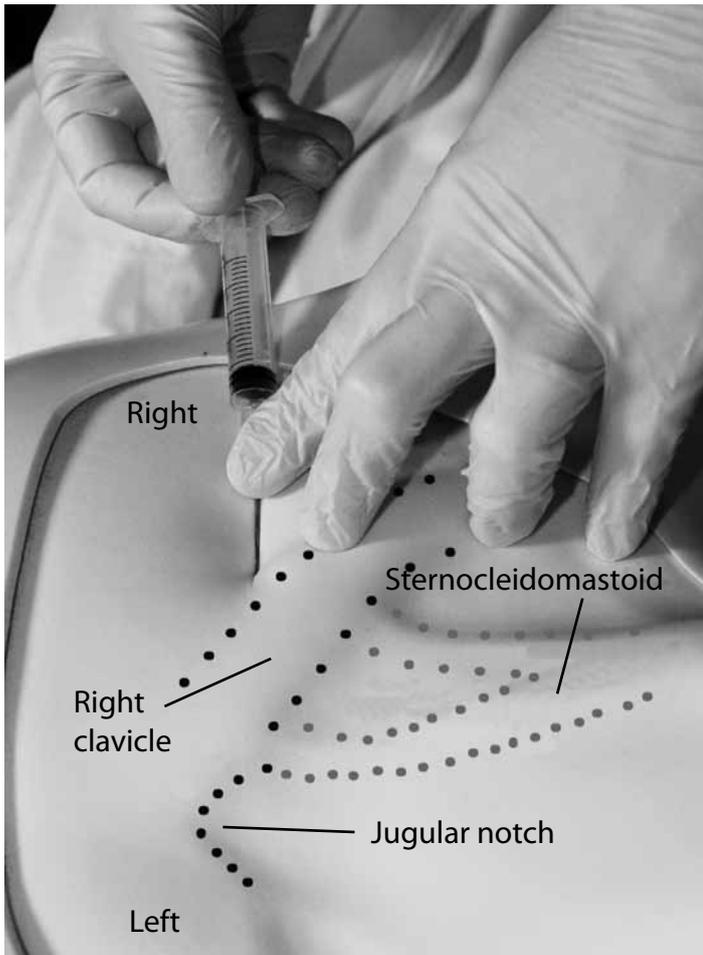


Figure 5. Right SCV cannulation (mannequin).

Positioning

The patient should be positioned as for the internal jugular approach with the head down to fill the veins and reduce the risk of air embolism.

Technique

The right SVC is usually preferred as this approach avoids damage to the thoracic duct. However in the presence of unilateral lung pathology, cannulation should be performed on the same side so that a pneumothorax will not affect the healthy lung. The infraclavicular approach is most commonly used, where the needle is inserted into the skin slightly below the lower border of the clavicle, at the junction of the middle and medial thirds of the clavicle. The needle is kept in the horizontal plane advancing medially, posterior to the clavicle aiming for the sternal notch. The needle should not pass beyond the sternal head of the clavicle.

Practical problems

If you are unable to get beneath the clavicle consider starting more laterally and bending your needle upward slightly. Some axial traction on the arms by your assistant and a pillow or rolled up towel between the shoulder blades may also improve success. If you still cannot find the vein, direct the needle a little more cephalad - place your finger fully into the sternal notch and aim for the middle of it. Do not persist after repeated attempts as the complication rate increases dramatically.

Try an alternative route on the same side unless Xray is available to confirm there is no pneumothorax.

External jugular vein

As the external jugular vein (EJV) lies superficially in the neck it is often visible or palpable, which negates many of the complications of the deep vein approaches. It is a useful when expertise is lacking, for emergency fluid administration and in cardiac arrests where no carotid pulse is palpable. A long catheter will not reliably thread into the SCV (due to the presence of valves and other anatomical abnormalities), so it is usual to use a short peripheral cannula.

Anatomy

The EJV drains blood from the superficial facial structures and scalp and passes down in the neck from the angle of the mandible, crosses the sternocleidomastoid muscle obliquely and terminates behind the middle of the clavicle where it joins the SCV. The vein is variable in size and contains valves which may prevent the passage of the guidewire and catheter. There is a wide range in EJV size and prominence due to natural variation and disease states.

Positioning

As for IJV.

Technique

Standing at the head of the patient identify the EJV as it crosses the sternocleidomastoid. Insert the needle into the vein where it is most easily seen or palpated.



Figure 6. Cannulation of the external jugular vein.

Practical problems

If the vein is not visible or palpable, press on the skin above the middle of the clavicle and reduce drainage into the SCV, thereby distending the vein (Figure 6). Alternatively ask the patient to do a valsalva manoeuvre, tilt the patient more head down or hold in inspiration if ventilated. If there is difficulty threading the guidewire or catheter, try twisting whilst advancing or flushing saline through the catheter as you insert it. Slowly moving the head from one side to the other may also help. Caution should be used when manipulating the wire

with the needle attached as there is a risk of the needle shearing of the end of the wire (a plastic cannula is safer)

Femoral vein

The femoral vein (FV) may be cannulated with low risk of serious short-term complications and, for this reason, is preferred by less experienced operators. This route is also useful in urgent situations when the patient is coagulopathic and is perhaps the safest central vein in children requiring resuscitation, where central access is needed for vasopressor therapy. The large diameter of the FV allows large fluid volumes to be removed and infused and is commonly used in the ICU for placement of short-term haemofiltration catheters.

Femoral catheters are better suited to ventilated, sedated patients as excessive movement can cause kinking of the catheter and mechanical complications. The CVP measurement from a femoral catheter can be affected by intra-abdominal pressure, although in ventilated patients values correlate well with those from intra-thoracic catheters. Arterial puncture or femoral nerve damage are both possible if insertion is too lateral. The risk of infection in the medium and long-term is higher with femoral catheters compared with most other routes because of the greater degree of bacterial colonisation found in the groin compared to other sites. There is also an increased risk of thromboembolic complications compared with internal jugular and subclavian approaches. For these reasons femoral catheters should be removed within 48-72 hours of insertion.

Anatomy

The FV starts at the saphenous opening in the thigh and runs alongside the femoral artery to the inguinal ligament where it becomes the

external iliac vein. In the femoral triangle the FV lies medial to the artery in the femoral sheath.

Positioning

The patient should be supine with a pillow under the buttocks to elevate the groin. The thigh should be abducted and externally rotated.

Technique

Palpate the femoral artery 2cm below the inguinal ligament and insert the needle 1cm medial to the pulsation and aim cephalad and slightly medially at an angle of 20-30° to the skin. In adults the vein is usually 2-4cm below the skin. In children the FV is more superficial so the angle should be 10-15°. Cannulation can be difficult because of the lack of landmarks especially in obese patients.

Practical problems

It can be difficult to feel the arterial pulsation especially in obese patients. Get an assistant to retract the abdomen if this is a problem and recheck the landmarks. As with the internal jugular approach 2-D ultrasound, if available can be very useful to assess anatomy and guide the needle. As with other routes, ensure no digital pressure is collapsing the vein.

The antecubital veins

The superficial, palpable veins of the antecubital fossa provide a very safe route for central access. Risk of infection is lower than other routes and lines can be used for longer periods (e.g. TPN, prolonged antibiotic courses or chemotherapy). A long catheter is required (around 60cm) to thread the tip into the central veins and for this reason flow rates are low, with large dead space making them less useful for resuscitation and inotropes. Tip position is important as migration can occur with movement of the arm (up to 7cm in cadaveric studies but around 2cm in vivo).

Anatomy

Two main veins are available but the more medial basilic vein has a smoother, more direct route to the SCV. The more lateral cephalic vein turns sharply to pass through the clavipectoral fascia and also has valves at its termination. These factors frequently cause difficulty in advancing the catheter.

The basilic vein ascends along the medial side of the forearm before moving anterior to the medial epicondyle, where it is joined by the median cubital

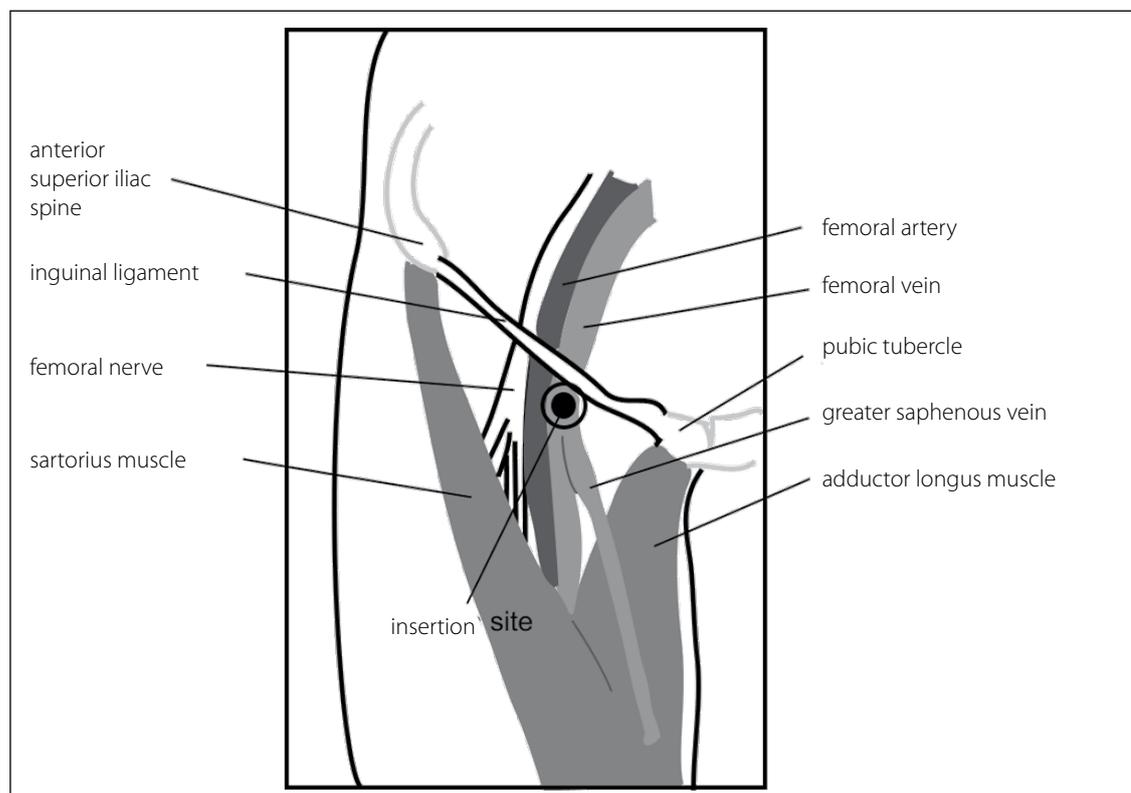


Figure 7. Anatomy of the right femoral vein.

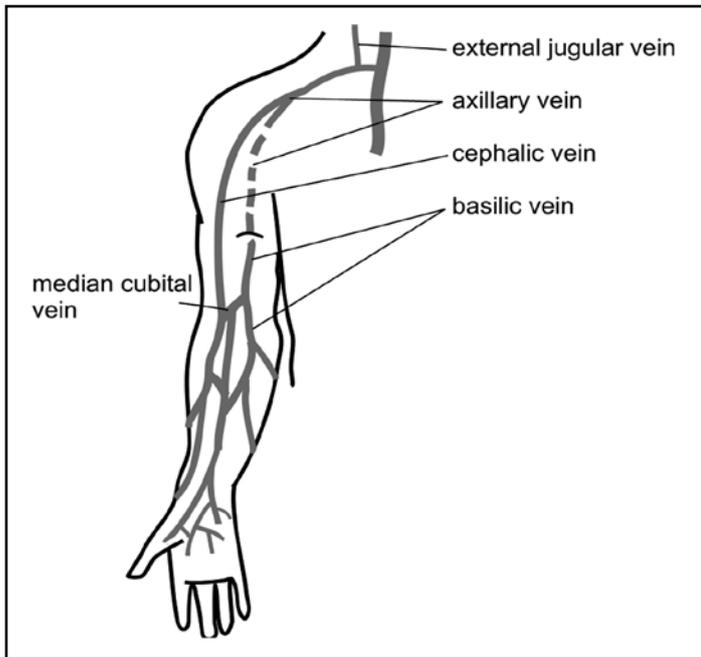


Figure 8. Anatomy of the peripheral veins of the right arm.

vein. It then runs along the medial edge of the biceps muscle to the middle of the upper arm, where it pierces the deep fascia and runs alongside the brachial artery, becoming the axillary vein.

The cephalic vein ascends on the front of the lateral side of the forearm to the front of the antecubital fossa, where it communicates with the basilic vein via the median cubital vein. It ascends along the lateral edge of the biceps muscle until it reaches pectoralis major, where it pierces the clavipectoral fascia to pass beneath the clavicle, where it usually terminates in the axillary vein (occasionally it may join the EJV).

Positioning

Apply a tourniquet to the upper arm and select the best vein. The medial side of the arm is best for the reasons mentioned above. Lie the patient supine with the arm abducted at 45° to the patient and the head turned towards the ipsilateral arm (this may help prevent the catheter passing into the IJV).

Technique

Estimate the length of catheter required to reach the SCV. Insert the cannula supplied in the set and remove the needle. Thread the catheter through the cannula and advance it 2-4 cm before releasing the tourniquet. Continue to advance the catheter until the desired length is inserted. The cannula is often designed to tear apart to remove it from the catheter. Other sets contain a guidewire and dilator for a Seldinger technique which is useful for smaller vessels.

Practical problems

In critically ill patients numerous attempts at venepuncture and cannulation have usually occurred, leaving vessels thrombosed and unusable. Looking more proximally may reveal untouched veins, especially on the inner aspect of the upper arm. 2-D ultrasound can be very useful for locating and checking patency of veins as well as guiding the needle. A more proximal approach can improve patient

comfort as the line does not cross the joint and will be less prone to kinking and other mechanical complications. If difficulty in threading the catheter is encountered first check the tourniquet has been released and check you are definitely in the vein. Flushing with saline as the catheter is advanced may facilitate passage through valves. Further abduction of the arm may also help.

CHECKS BEFORE USING THE CATHETER

It is important to ensure that the catheter is within the vein prior to use. This is best done by transducing the pressure waveform or comparing synchronous arterial and venous blood gases. Dark blood at low pressure is not always a reliable sign especially in a hypoxaemic, poorly perfused patient. The position of catheters that enter the chest (i.e. jugular or subclavian approach) should be confirmed on chest Xray (Figure 9). The tip of the catheter should lie in the SVC, just above its junction with the right atrium. On chest Xray it should be above or overlying the right main bronchus. Check there is no pneumothorax.

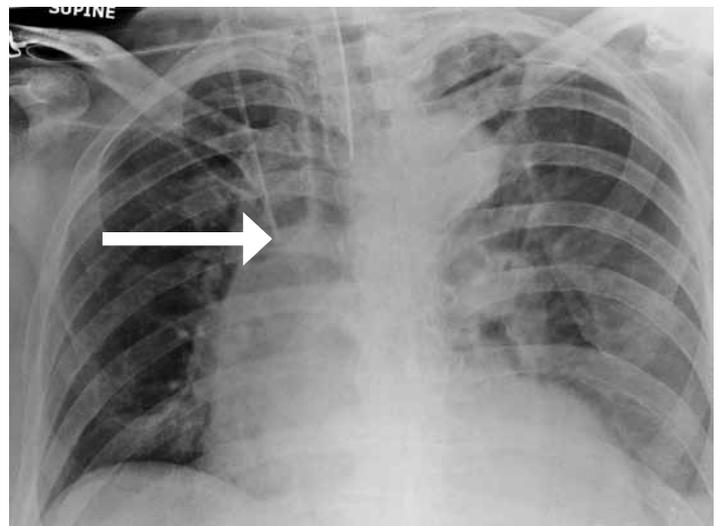


Figure 9. Chest Xray showing optimal CVC tip position (arrow).

COMPLICATIONS

Complications occur in up to 10% of CVCs and can be divided into mechanical, infectious and thromboembolic aetiologies, the most common of which are listed below. The complication rate is dependant on a number of factors including site, patient factors (concurrent illness and variations in anatomy) and operator skill and experience. Interventions recommended to prevent complications are also listed below. There are no absolute contraindications to central venous cannulation, as it can be a lifesaving procedure, but serious complications, including death, may occur during insertion or ongoing use of a CVC. Operator training and experience are important factors in reducing complication rates and experienced help should be sought after repeated attempts. The frequency of mechanical complications is six times greater than after a single attempt. Caution should be used to try and avoid complications in high risk patients and may influence site of access. There is a higher risk of pneumothorax with the subclavian approach and as the vessels are not amenable to direct compression. This site is least appropriate in patients with severe respiratory disease or bleeding diatheses. Penetrating abdominal trauma or known inferior vena caval disruption would make the femoral approach less desirable.

Mechanical complications
Arterial puncture Haematoma Pneumothorax Haemothorax Haemorrhage Arrhythmias during procedure Cardiac tamponade Respiratory obstruction Thoracic duct injury Brachial plexus injury
Infectious complications
Local infection Bacteraemia, sepsis
Thromboembolic complications
Thrombosis of vessel Thrombus formation Venous air embolism Catheter/guidewire embolism
Interventions to prevent complications
Use antimicrobial-impregnated catheters Insert in the subclavian vein Strict asepsis at insertion Avoid antibiotic ointment Remove catheter when promptly when no longer required Recognize risk factors for difficult catheterization and seek experienced assistance Avoid femoral route Use ultrasound during internal jugular insertion

ULTRASOUND GUIDANCE

In 2002 the National Institute for Clinical Excellence (NICE) in the United Kingdom recommended the use of ultrasound for the elective placement of CVCs into the IJV. Since this time the use of ultrasound use has increased dramatically. More clinicians are becoming experienced in its use and there is now increasing evidence showing a reduction in number of passes, failure rates, arterial puncture and time to placement and infectious complications using this technique.

Ultrasound guidance is particularly suited to the IJV, FV as well as peripheral veins. It is not possible to visualise the subclavian vein easily with ultrasound, due to the shadow cast by the clavicle, however the axillary vein can be visualised more laterally on the chest. The ultrasound image provides information about the patency and location of the vessel and can be used to guide the needle in real time (Figure 10).

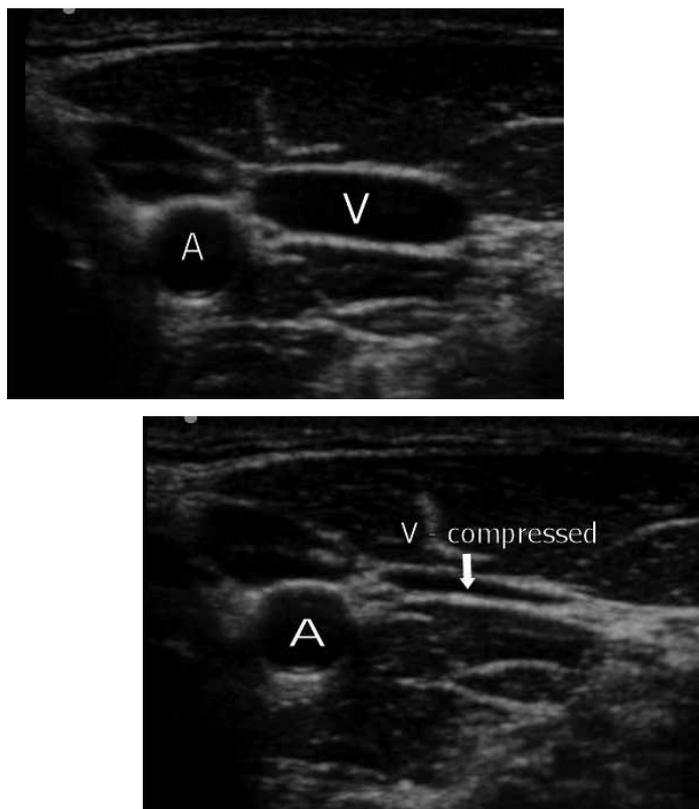


Figure 10. Ultrasound images of internal jugular vein. Application of pressure using the probe identifies the vein as the compressible structure.

SUMMARY

Central venous access is a commonly performed procedure that can be lifesaving, but is associated with significant complication rates. Operator experience, familiarity with the range of sites available, along with sound knowledge of anatomy and use of ultrasound can help to minimise some of the mechanical complications. Strict asepsis at the time of insertion, use of impregnated catheters, proper maintenance and timely removal can minimise infective complications.

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Cardiac output monitoring

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DEFINITIONS

Before describing the different types of cardiac monitoring, it is essential to understand some basic definitions:

The cardiac output is determined by, and therefore can be manipulated by, alterations to the heart rate or rhythm, the preload, the contractility and the afterload.

Cardiac output informs us of global blood flow and therefore oxygen delivery (the product of cardiac output and blood oxygen content), but does not describe delivery of oxygen to each organ, whose function must be assessed individually.

An appreciation of how information is measured and derived using a cardiac output monitor is essential in order to use the information accurately and appropriately. Thorough assessment of a patient's clinical status strongly influences interpretation of the measurements made. For example, cardiogenic shock and obstructive shock due to tamponade will both give a low cardiac output, but can be differentiated by the patient's clinical signs. There is a wide variability between practitioners in the measurement and interpretation of cardiac output data, using the various techniques that are currently available. For this reason, clear evidence that they benefit patient outcome is difficult to obtain.

Cardiac output is the volume of blood ejected from each of the ventricles of the heart per minute, and is therefore the product of stroke volume and heart rate. The unit of cardiac output is $L \cdot \text{min}^{-1}$.

Cardiac index is the cardiac output of a patient referenced to their body surface area and has units of $L \cdot \text{min}^{-1} \cdot \text{m}^{-2}$.

Stroke volume is the volume of blood ejected by each contraction of the ventricle and is determined by the preload, afterload and contractility. The stroke volume is usually 60-80ml for an average sized adult.

Preload describes the tension developed in the ventricular wall at end-diastole (i.e. at maximal filling just prior to contraction). This tension is difficult to measure and end-diastolic pressure is taken as a surrogate (or estimate) measurement. It is mainly determined by venous return and gives an indication of the filling pressure of the ventricle.

Contractility refers to the amount of work the heart can generate, at given levels of preload and afterload, and is estimated by the maximum rate at which the ventricle can generate a change of pressure over time. Inotropy is used to explain an increase in the work done by the heart that is independent of heart rate, preload and afterload.

Afterload is the tension that needs to be generated in the ventricular wall in order to eject blood into the arterial system during systole. This is largely determined by the resistance of the arterial system – the systemic vascular resistance (SVR). It is calculated by:

$$\text{SVR} = \frac{\text{Mean arterial pressure (mmHg)} - \text{Central venous pressure (mmHg)}}{\text{Cardiac output (L} \cdot \text{min}^{-1})} \times 80$$

(Recall that Ohm's Law describing electrical resistance is analogous to this: $V = IR$)

Mean arterial pressure (MAP) is the average arterial blood pressure throughout the cardiac cycle. As 2/3 of the cardiac cycle is spent in diastole, and 1/3 in systole, MAP may be calculated using the formula:

$$\text{MAP} = \text{Diastolic BP} + \frac{1}{3}(\text{Systolic BP} - \text{Diastolic BP})$$

Ejection fraction is the fraction of total blood in a ventricle that is ejected per beat. It applies to both the left and right ventricles. It gives an index of contractility. Normal value is in the region of 55-65%.

Summary

Estimation of cardiac output has an important role in patient management during anaesthesia and critical care. Cardiac output can be measured in a number of ways, from simple clinical assessment to invasive haemodynamic monitoring. Advanced monitoring techniques are often used when clinical signs are difficult to interpret. While there has been much research looking at the accuracy of these monitors there is currently very little information in the literature regarding the effectiveness of these monitors in improving clinical outcomes.

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CLINICAL INDICATORS OF CARDIAC OUTPUT

The interpretation of data from invasive haemodynamic monitoring is made in light of the clinical examination. No single clinical sign can be used to make an accurate assessment of cardiac output. Heart rate, blood pressure, pulse strength at various sites, patient colour, respiratory rate and core to peripheral temperature gradient all give an indication to a patient's haemodynamic status. Note that although blood pressure is often used as an indicator of cardiac output, it is frequently unhelpful. Blood pressure may be maintained by intense peripheral vasoconstriction in the face of a perilously low cardiac output.

A patient's ability to compensate for a haemodynamic insult is highly variable, depending on age, premorbid status and other comorbidities. An example is the rise in the diastolic pressure in early hypovolaemic shock, associated with peripheral vasoconstriction that is usually only seen in young, fit individuals. In addition, clinical parameters such as urine output, capillary refill time and cognitive function give a guide to end organ perfusion. Change in heart rate, blood pressure and central venous pressure in response to a straight leg raise is useful to predict a patient's response to a fluid bolus.

Measurement of lactate and base deficit in arterial blood and, in particular, the trend of these variables over time gives non-specific information about a patient's organ perfusion. Lactate is produced by anaerobic metabolism, and is an indicator of tissue hypoperfusion. It is measured on most modern blood gas machines. It can be used to monitor therapy, as it will fall as oxygen delivery improves, and as liver perfusion (which enables lactate metabolism) increases.

The oxygen saturation in central venous blood ($ScvO_2$) also gives a global indication of haemodynamic status, is useful in directing fluid therapy³ and is a reliable surrogate of mixed venous oxygen saturation (see under pulmonary artery flotation catheters, below).

Learning point – blood pressure is a poor indicator of cardiac output.

OVERVIEW OF THE ROLE OF CARDIAC OUTPUT MONITORING

Mortality in sepsis increases by 15-20% for each 'organ failure' that a patient develops.¹ Organ failure results when delivery of oxygen is inadequate for the organ's requirements. Since the 1980s, research has suggested that optimisation of oxygen delivery (a product of cardiac output and blood oxygen content) in high risk surgical patients prevents organ failure and improves mortality.² This has been investigated early in critical illness, and prior to, during and after surgery.² Although no single study provides categorical evidence, the weight of evidence suggests that therapies directed at enhancement of oxygen delivery (goal-directed therapy) should be our aim. There is also increasing evidence that, while hypovolaemic septic patients need fluid to optimise their cardiovascular delivery of oxygen, excessive liberal fluid therapy may be harmful.

The major factor limiting this field of clinical practice has been development of a monitoring device that will reliably and accurately guide our use of fluid therapy - to recognise where fluid is needed and give enough, but not too much. Measurement of 'filling' is difficult. We aim to apply Starling's Law, where cardiac performance

improves with stretching of the ventricular muscle fibres, to a certain optimal point beyond which further stretching impairs performance (see Figure 1). To apply this strategy we would like to know the left ventricular end-diastolic volume (LVEDV) and monitor changes in the LVEDV as we give fluid boluses. The best surrogate estimate of LVEDV we have is to use a pulmonary artery catheter (PAC) to measure pulmonary artery occlusion ('wedge') pressure, which gives us an estimate of left atrial pressure, which is in turn an estimate of LVEDP, which is a surrogate of LVEDV (and makes assumptions about normal compliance of the left ventricle). This is not a reliable measure of filling, particularly given the effects of ventilation, applied PEEP and the anatomical location of the catheter tip in different lobar pulmonary artery branches. Thermodilution using the PAC does provide an accurate measurement of cardiac output, which can be measured continuously given the correct equipment, however use is diminishing in many parts of the world, due to concerns over safety and lack of robust evidence to support their use.

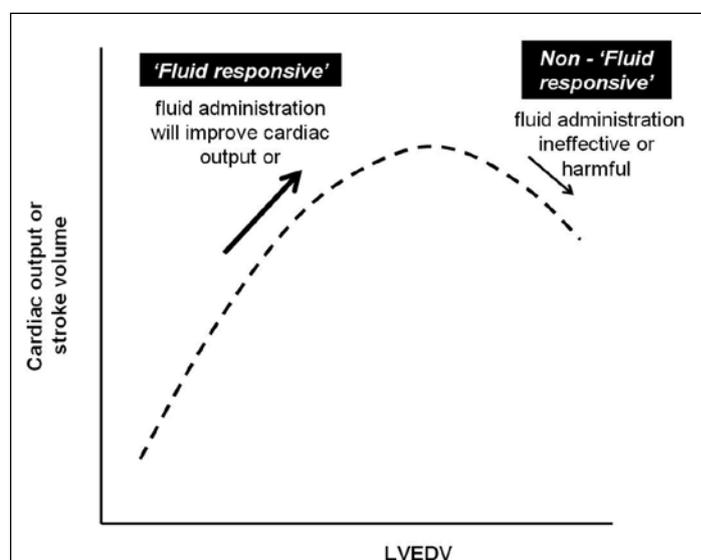


Figure 1. Simplified explanation of Starling's Law.

Currently, the main focus of research and development is towards less invasive monitors with inherently lower risks of use. Broadly these are monitors that use Doppler analysis of the aortic blood velocity (viewed from the oesophagus) or monitors that analyse the shape of the arterial waveform ('pulse contour analysis').

Some of the cardiac output monitors that rely on arterial waveform analysis, use thermo- or indicator dilution to obtain an accurate estimate of cardiac output, which can then be used to calibrate continuous analysis of the waveform, transduced from a modified arterial catheter. In order to make these easier to set up and use, more recent models calibrate their pulse contour analysis using population data, based on age, weight and height. The disadvantage is that the population data is derived from healthy volunteers, and so is not validated for patients with abnormal vascular resistance, which undoubtedly has a major effect on derived indices such as stroke volume. The oesophageal Doppler also uses population data to estimate aortic diameter.

However, even if we are sceptical about the absolute numbers generated, these monitors can be reliably used to observe trends in stroke volume, and the effect of interventions such as fluid administration. The key feature is to determine whether the patient is fluid responsive; meaning

that a bolus of fluid augments their cardiovascular performance (for example their stroke volume), thereby improving oxygen delivery. Fluid responsiveness implies that we have moved the patient up the Starling curve.

A current and future area of development is the use of stroke volume variation (SVV) or pulse pressure variation (PPV) that is measured from the transduced arterial waveform. We have long observed that hypovolaemia causes an exaggerated swing in systolic pressure during the respiratory cycle; SVV and PPV quantify this swing or variation as a single number. Again, it is a change in the number, rather than the absolute value that is useful in assessing the fluid responsiveness of your patient.

From a pragmatic perspective, these monitors are most useful when observing the effect of a single intervention (such as fluid administration) in isolation - this is often difficult during the changing stimuli of surgery, or when the physiological response to sepsis is changing rapidly. Measurements are most plausible when interventions and pre- and post- stroke volume, SVV or PPV measurements are performed during a 'lull' in other stimulating activity.

DOPPLER ULTRASOUND AND ECHOCARDIOGRAPHY

Ultrasound

Ultrasound is any high-frequency sound wave. Ultrasound is used medically to create a 2 dimensional image by using a probe to transmit high-frequency sound waves (1-5MHz) into the body, and to detect the waves as they are reflected off the boundaries between tissues interfaces. By using a mathematical model involving the speed of sound and the intensity and timing of each echo's reflection, the distance from the probe to the tissue boundaries is calculated, and used to create a two- dimensional image.

Doppler ultrasound

When sound waves are reflected from a moving object, their frequency is altered. This is the Doppler effect. By using an ultrasound probe to visualise directional blood flow, the phase shift (i.e. the change in frequency before and after reflection off moving red blood cells) can be determined. This, together with the cross-sectional area of the blood vessel being observed (measured or estimated) can be used to determine flow, where:

$$\text{Flow} = \text{area} \times \text{velocity}$$

Oesophageal Doppler

Theory of technique

A Doppler probe is inserted into the distal oesophagus (Figure 2) and is directed to measure the blood flow in the descending aorta at about 35 to 40cm from the incisors. The monitor calculates cardiac output using descending aorta diameter, which is either obtained from an age-related nomogram or measured directly in newer machines. The ventricular ejection time, corrected for heart rate (the corrected flow time, FTc), gives an indication of preload and the peak flow velocity (PV) estimates the contractility of the ventricle. Newer probes incorporating M-mode Doppler measurement may improve accuracy and reliability.

Practical application

The technique is straight-forward, easily learned and relatively non-invasive. The disposable probes are easy to insert, however some expertise must be gained in recognition of intracardiac and pulmonary artery signals. Continuous measurement is possible, although frequent positional adjustments are needed. Some user variability is inevitable. The cardiac output data is best used as a trend to guide the effectiveness of interventions such as fluid challenges.

Wave form interpretation

A full description of the use of oesophageal Doppler is beyond the scope of this article but guidance can be obtained from the NHS Technology Adoption Centre at <http://www.ntac.nhs.uk/searchresent.aspx?search=cardioQ>

Advantages

- Minimally invasive
- Minimal interference from bone, lung and soft tissue
- Quickly inserted and analysed
- Little training required
- The system is small and relatively portable
- Paediatric probes are available.

Disadvantages

- May require sedation
- User dependent
- Interference from surgical instruments (e.g. diathermy)
- Depends on accurate probe positioning
- Probe may detect other vessels e.g. intracardiac/intrapulmonary
- Assumes a constant percentage of cardiac output (approx 70%) enters the descending aorta. May therefore be inaccurate in a hypovolaemic patient where flow may be redirected to the cerebral circulation.
- Contraindicated in the presence of oesophageal varices.

Transthoracic echocardiography

Echocardiography is cardiac ultrasound and can be used to estimate cardiac output by direct visualisation of the contracting heart in real time. Echocardiography is becoming widely accepted as one of the safest and most reliable cardiac output monitors in the critically ill.

A focused echocardiogram can be performed in a matter of minutes and assist in determining the cause of haemodynamic instability. Using transthoracic echocardiography four views are obtained (parasternal long axis, parasternal short axis, apical, and subcostal), and it is possible to make an assessment of ventricular function and size of cardiac chambers with these.

Figure 2. Image of descending aortic waveform obtained using an oesophageal Doppler probe, CardioQ® (Courtesy of Deltex Medical).

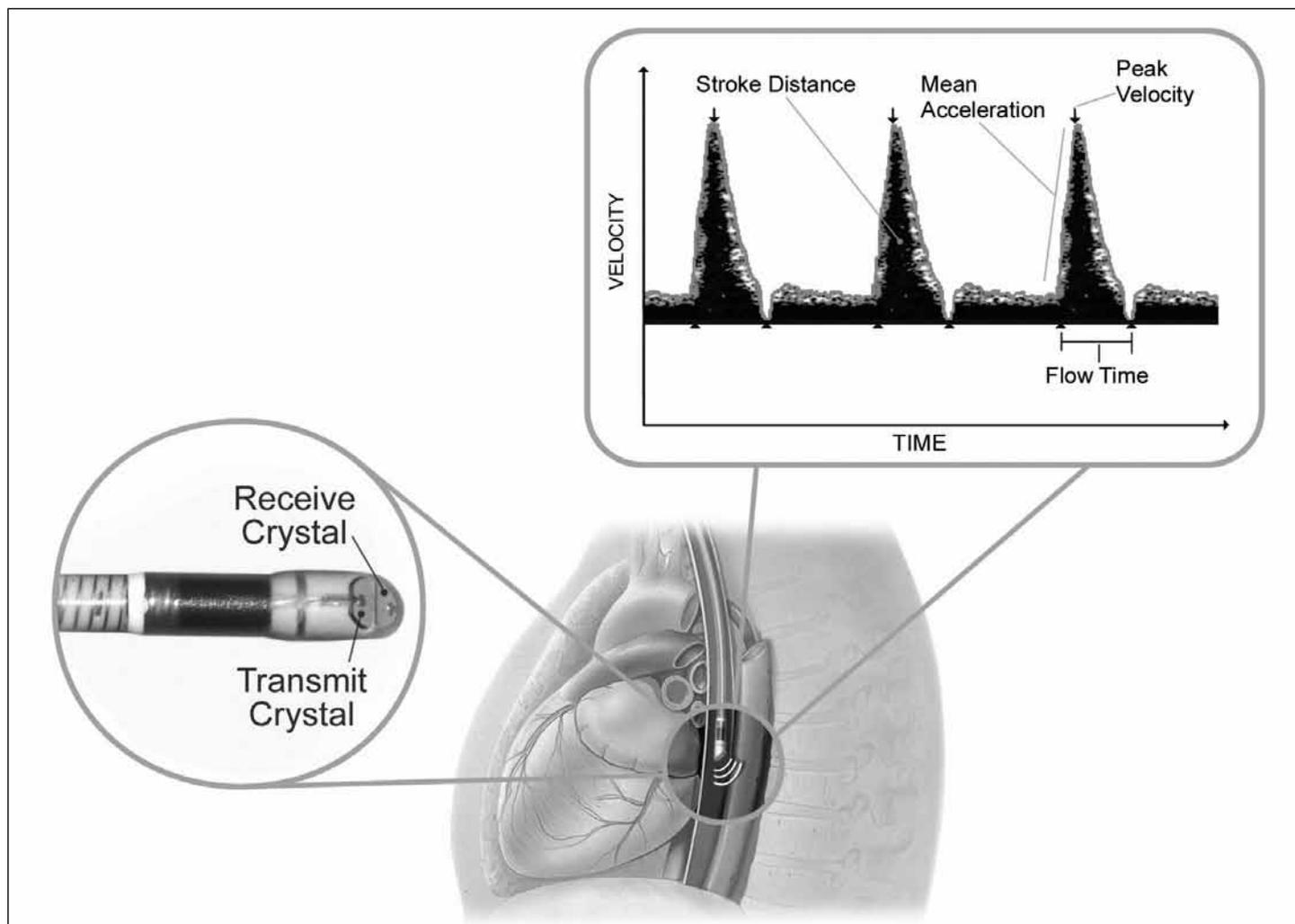


Table 1. Summary of variables obtained from oesophageal Doppler

Variable	Description	Interpretation
Height	Peak velocity	The highest detectable aortic flow – can be used as a measure of afterload, vascular resistance and contractility
Slope of upstroke	Mean acceleration	Measure of contractility
Width of base	Flow time	Left ventricular ejection time, i.e. duration of aortic blood flow. When corrected for heart rate gives an index of preload (e.g. if base is narrow suggests hypovolaemia)
Area under waveform curve	Stroke distance	Distance a column of blood travels along the aorta during each ventricular systole
Stroke distance	Stroke volume	Aortic cross-sectional area
Afterload	SVR	Shown by a reduction in waveform height and base

Transoesophageal echocardiography

Theory of technique

A specialized probe is inserted into the oesophagus, providing real-time, high resolution ultrasound images. Both qualitative and quantitative values for cardiac output are available, using a two dimensional cross-sectional area measurement, a Doppler flow measurement at that point and the heart rate.

Practical application

A multiplane transducer is inserted into the oesophagus and stomach, where various standardized views are gained.

Advantages

A large amount of haemodynamic information is available beyond just cardiac output.

Disadvantages

The probes are still expensive and the machinery is large and bulky. Various levels of examination skill are required and these take time and resources to learn. A full study can take over twenty minutes. Some form of local pharyngeal anaesthesia or sedation is required to tolerate the probe. There is a risk of trauma from the probe, although the risks are low in patients with no oesophageal disease. The probes generate a degree of heat and are therefore not suited to continuous measurement. As the technology advances and costs decrease, TOE may find more applications in theatre and the ICU.

DILUTION METHODS

These techniques require:

- a marker substance that can completely mix with blood, remain within the circulatory system, and is minimally metabolised.
- a central vein (into which the marker substance is injected) and a peripheral artery (from which the arterial content of the substance can be measured) must be cannulated.

As long as blood flow between the injection and measuring sites is constant, flow (i.e. cardiac output) can be calculated from the area under a concentration versus time graph, using a modified Stewart-Hamilton equation.

Advantages of dilution methods

- Less invasive than PAFC (see below).

Disadvantages of dilution methods

- Can only be used to calculate cardiac output in ventilated patients in sinus rhythm.
- Specific heart-lung interaction is required for the calculation of stroke volume variation (SVV) and pulse pressure variation (PPV)
- Invasive and associated morbidity / mortality.
- User dependent.
- Can underestimate cardiac output in low output states.

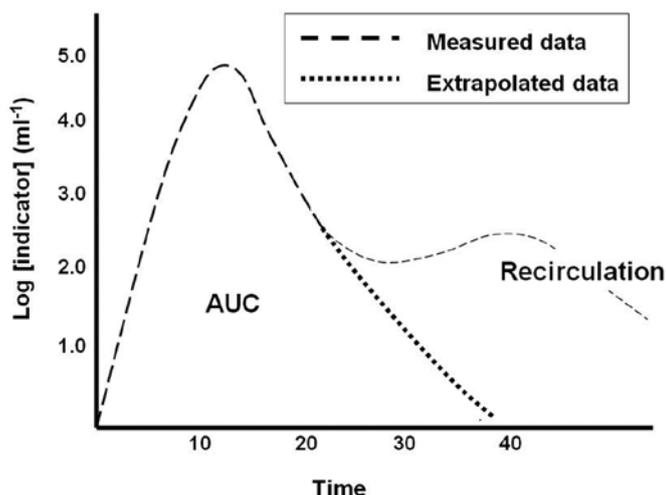


Figure 3. Concentration-time graph for determining cardiac output.

Lithium Dilution Monitoring – Lidco® and PulseCO® and Lidcoplus®

Theory of technique

This technique combines the techniques of lithium dilution (Lidco and Lidcoplus) and pulse contour analysis (PulseCO). A small dose of lithium is injected into a peripheral vein and an ion selective electrode is attached to a peripheral arterial line. The area under the curve of a plot of lithium concentration against time allows calculation of the cardiac output. This information is then used to calibrate the PulseCO which provides 'beat-to-beat' cardiac output measurement, using *pulse contour analysis* of the arterial waveform.

Practical application

The convenience of this system is that it uses catheters which are likely to be in place or are likely to be needed in a critically ill patient. The system requires some familiarity to set up, but is relatively quick. The total dose of lithium is small and is clinically insignificant. Calibration is recommended every 8 hours, or after any significant change in the patient's clinical condition.

Advantages

A figure for stroke volume variation is produced and provides an indicator of volume responsiveness to fluid therapy.

Disadvantages

The system cannot be used for patients taking lithium and those who have recently received vecuronium or atacurium. The monitor performs poorly in the presence of atrial fibrillation and other tachyarrhythmias. The system is prone to technical difficulties related to damping and resonance within the measurement system (see page 38).

Thermodilution pulse contour monitoring – PiCCOplus®

Theory of technique

This technique utilises thermodilution in combination with Pulse Contour Analysis (PulseCO) to measure cardiac output, and correlates well with the PAFC (below). 'Stroke volume variation' (the mean difference between the highest and lowest arterial pressure wave peaks over 30 seconds) gives an indication of the blood volume status of the patient.

The system is calibrated using intermittent cold transpulmonary thermodilution, where cold fluid is injected through a central venous catheter and traverses the pulmonary circulation. A curve of blood thermodilution is measured in a systemic artery and, in addition to cardiac output, other data is derived. The calculated *extra-vascular lung water* (EVLW) gives an indication of the water content of the lungs and is increased in left ventricular failure, pneumonia and sepsis. The normal range is 3-10ml.kg⁻¹ and values greater than 14ml.kg⁻¹ are associated with an increased mortality. The *intra-thoracic blood volume index* gives an indication of blood volume status (normal value 850-1000ml.m²).

PiCCOplus replaced the original PiCCO machines in 2002 and has subsequently been replaced by PiCCO₂ with improved displays, automated features and the use of room temperature injectate for calibration.

Practical application

A specialised arterial catheter, inserted into either the brachial artery or femoral artery is required, along with either a thoracic or femoral central line. Some centres use treatment algorithms based on these variables, to guide use of fluid and inotropes in an attempt to maximise intravascular filling, without increasing the EVLW and causing pulmonary oedema. The use of EVLW as an endpoint for resuscitation has not been validated.

Advantages

The arterial line can be simultaneously used for blood pressure monitoring and for blood sampling. The system is relatively easy to set up and calibrate. It can also be used to estimate preload using global-end-diastolic volume and index (GEDI), intra-thoracic blood volume (ITBV) and pulmonary vascular permeability index (PVPI) which gives a ratio of EVLW to pulmonary blood volume. Note that pleural effusions do not affect measurements.

Disadvantages

The arterial catheter is relatively large gauge and expensive, although few complications have been reported. Recalibration is required every 12 hours, or following a major change in the patient's clinical condition. Variations in speed of injection and thermistor positioning may affect results. Results can be affected by arrhythmias, shunting, positive pressure ventilation and tricuspid regurgitation.

Pulse contour analysis

ProAQT (Pulsion), Vigileo (Edwards Lifesciences) and LIDCOrapid (LIDCO) are all similar, minimally invasive cardiac output monitors. They all work by pulse contour analysis using a specialised transducer on any arterial line. Parameters obtained may include: continuous cardiac output, stroke volume, stroke volume variation (SVV) and pulse pressure variation (PPV). In order to obtain SVRi (the systemic vascular resistance index), the patient needs CVP monitoring. To obtain values for PPV and SVV, the patient should be ventilated with a fixed tidal volume and so is less useful when weaning respiratory support in intensive care. dP max gives an indication of contractility.

Pulmonary artery flotation catheters (PAFC)

The use of PAFCs has been hotly debated in recent years and use in

the United Kingdom is currently low. The PAC-Man trial showed no improvement in survival for patients randomised to have a PAFC inserted, compared to those who were not.³

Theory of technique

A flexible balloon-tipped, flow-directed catheter is inserted via a wide-bore catheter sited in a central vein. The catheter is 'floated' through the right atrium and ventricle to enter the pulmonary trunk. From this position it can intermittently be 'wedged' in one of the pulmonary arteries.

The catheter allows a number of variables to be measured and others to be derived.

The measured variables are pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), cardiac output and mixed venous oxygen saturation. Traditionally, cardiac output is measured by thermodilution of 10ml iced water, injected through the proximal lumen of the catheter. Measurement of the fall in blood temperature against time from injection, as the cooled blood passes the distal end of the catheter, allows calculation of the cardiac output of the right (and therefore the left ventricle). Semi-continuous cardiac output measurements are now available which use warming coils in the right ventricular portion of the catheter. A sequence of heating and recording gives an averaged cardiac output after a short delay.

Practical application

The catheter is inserted with reference to certain waveforms seen in the right atrium, right ventricle, pulmonary outflow tract and when wedged in the pulmonary artery. Insertion may take several attempts and is more difficult in patients with a low cardiac output.

Advantages

Measurement of cardiac output is probably the most reliable of the variables measured using a PAFC and is therefore a valuable guide to interventions introduced to increase cardiac output. The numerous assumptions made in interpretation of the PCWP as a measure of preload or ventricular filling make the PCWP a less reliable measurement. Some units use the mixed venous oxygen saturation, measured using a sample taken slowly from the pulmonary artery aperture of the catheter, as a further indicator of a patient's overall tissue perfusion (see below).

Table 2. Interpretation of SvO₂ readings.

SvO ₂	Interpretation
>75%	Increased O ₂ delivery e.g. high FiO ₂ , or Decreased O ₂ utilization e.g. sepsis causing shunt
50-75%	Maybe normal or reflect compensation by increase O ₂ extraction by tissues
30-50%	O ₂ demand is greater than supply Implies tissue beyond maximal O ₂ extraction
25-30%	Severe lactic acidosis
<25%	Cellular death

Disadvantages

This invasive monitor is associated with a number of potential complications. The PAC-Man study recorded non-fatal complications in 10% of insertions. In addition to the usual complications of central venous access, PAFCs may cause arrhythmias, heart block, rupture of the right heart or pulmonary artery, thromboembolism, pulmonary infarction, valvular damage, endocarditis.³

Mixed venous oxygen saturation (SvO₂)

Mixed venous oxygen saturations can be used as a surrogate marker of the global balance between oxygen delivery and consumption. Oxygen delivery depends on cardiac output and the oxygen content of the blood. In the face of an increased demand for oxygen, there will be a greater degree of oxygen extraction. Occasionally SvO₂ may be increased in severe sepsis due to decreased extraction resulting from shunting (where blood bypasses the tissues). SvO₂ can be used as an early warning system where a sudden decrease in SvO₂ of 10-20% requires immediate assessment. SvO₂ can also be used to assess treatment.

Central venous oxygen saturation (ScvO₂)

Measurement of ScvO₂ requires a central venous catheter rather than a pulmonary artery catheter. ScvO₂ can be used as a surrogate marker of the regional balance between oxygen delivery and consumption in the head, neck and upper body. The value is usually 2-7% less than SvO₂ – partly due to mixing with returning venous blood. Under non-shock conditions, ScvO₂ correlates well with SvO₂. In shock states the

difference from SvO₂ increases – and can be up to 7% higher than SvO₂. ScvO₂ trends with SvO₂ in a parallel manner but should be used in combination with other markers of perfusion.

CeVox (PULSION) is a system which monitors continuous SvO₂ and can calculate oxygen delivery, consumption and oxygen extraction. It uses a fiberoptic probe that can be inserted through any central line.

Thoracic bioimpedance

Theory of technique

The technique depends on the change in bioimpedance of the thoracic cavity during systole. Impedance is a measure of the opposition to alternating current. Baseline impedance reflects total thoracic fluid volume. Cardiac output is estimated by measuring changes in electrical resistance through the thorax, since blood volume within the aorta changes during systole and diastole. Magnitude and rate of change reflects LV contractility.

Practical application

A series of ECG type electrodes are placed on the thorax and neck. A small, non-painful current is passed and measurements made.

Advantages

Derived stroke volume is calculated and cardiac output computed. Thoracic fluid content is also measured. This is the least invasive method of cardiac monitoring and was initially conceived for space flight monitoring.

Table 3. Comparison of different cardiac output monitors.

Method	Technique	Invasiveness	Cannulae	Continuous	Limitations
PAFC	Thermodilution	High	PA catheter	Yes	Shunts, arrhythmias. Requires regular injection speed and thermistor positioning
LiDCO	Lithium-dilution + pulse contour analysis (PCA)	Moderate	Any venous + arterial	Yes	Shunts, arrhythmias, haemodynamic instability, cannot be used if on lithium therapy or if pregnant, lithium can accumulate. PCA requires good quality waveform
PiCCO	Thermodilution + pulse contour analysis (PCA)	Moderate	Central venous + arterial	Yes	Shunts, arrhythmias, haemodynamic instability. PCA requires good quality waveform.
ProAQT Vigileo LiDCOrapid	Pulse contour analysis	Low	Arterial line	Yes	Waveform dependant, useful for trend only.
TOE	Doppler / two-dimensional imaging	Moderate	None	No	User dependent, needs sedation
TOD	Doppler	Low	None	Yes	User dependent, needs sedation, may pick up interference from other vessels
NICO	Partial CO ₂ rebreathing Fick principle	Nil (although requires intubation)	None	Yes	Needs intubation, poor accuracy in lung disease
Thoracic Bioimpedance	Measurement of change of impedance	Nil	None	Yes	Inaccurate in the critically ill in general

Disadvantages

It is not useful with significant aortic regurgitation and open chest procedures. The correlation with PAFC in critically ill patients is inconsistent.

Bioreactance

The NICOM (non-invasive cardiac output monitor) measures the 'phase shift' of pulses of alternating current, passed through the body using three electrodes. Early studies show promising correlation with passive leg raise, as an indicator of fluid responsiveness.⁴

SUMMARY

At present no perfect system exists, but each of the monitors above, can aid the clinician when uncertain about the patient's condition. The information gained must be understood in the context of how

it was gathered and interpreted alongside clinical evaluation of the patient. Only then can it be safely used to guide subsequent therapeutic strategies.

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Acid-base disorders in critical care

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INTRODUCTION

Metabolic acidosis is a common component of critical illness. Evaluation of this component can aid diagnosis,

assess severity (and likely outcome) and allow the clinician to determine whether current treatments are working.

CASE EXAMPLES

Case 1

A known diabetic patient presented with severe diabetic ketoacidosis. He was drowsy, exhibited classical Kussmaul respiration and proceeded to have a respiratory arrest whilst being admitted to the ICU. After immediate intubation the trainee ventilated the patient with the ventilator's default settings (rate 12, tidal volume 500ml, PEEP 5, FiO₂ 0.5) and attempted to secure arterial and central venous access. Shortly after intubation the patient became asystolic and could not be resuscitated.

- Why did this patient have a respiratory arrest?
- Why did he deteriorate after intubation?

Case 2

A young woman was admitted to the surgical ward with a history of severe vomiting and increasing right iliac fossa abdominal pain. On examination she was found to have a rigid abdomen, with visible sub-diaphragmatic gas on chest Xray. She was cardiovascularly unstable and her admission bloods showed Hb 17.4, WCC 24.6, Plt 79, Na⁺ 125, K⁺ 4.3, Cl⁻ 93, urea 20.4, creatinine 310 (mcmol.L⁻¹) and blood gas analysis showed:

pH	7.10
PaCO ₂	5.2kPa
PaO ₂	29.3kPa
HCO ₃ ⁻	14.3mmol.L ⁻¹

- Interpret these results. What is the likely cause of her acidosis?
- How do you interpret her chloride level?
- Is her compensation adequate/maximal?

Case 3

An elderly lady was admitted from a care home with a one week history of severe diarrhoea. She

was dehydrated and hypotensive. Admission bloods revealed Na⁺ 134, K⁺ 2.5, Cl⁻ 122, urea 15.4, creatinine 280, and blood gas analysis revealed:

pH	7.21
PaCO ₂	2.9 kPa
PaO ₂	19.5 kPa
HCO ₃ ⁻	6.4mmol.L ⁻¹

- Describe the acid-base disorder present. What is the likely cause?
- Is her compensation adequate?

Case 4

A man was brought in to the emergency room heavily intoxicated. He was known to be alcohol dependent and attended regularly. Blood analysis confirmed normal biochemistry apart from a borderline low glucose (3.8mmol.L⁻¹) and arterial gas analysis showed pH 7.43, PaCO₂ 4.8, PaO₂ 15.7, HCO₃⁻ 20. He was placed into an observation bed overnight with a diagnosis of alcohol intoxication but later became tachypnoeic and hypotensive. Repeat gas analysis showed pH 7.0, PaCO₂ 4.2, PaO₂ 24, and HCO₃⁻ 9.

- What is the cause of his deterioration?
- What other information would be useful?

Case 5

The same man re-presented a month later, again heavily intoxicated. Blood analysis confirmed normal biochemistry and arterial gas analysis showed pH 7.43, PaCO₂ 4.8, PaO₂ 15.7, and HCO₃⁻ 20. Toxicology was requested and minimal ethanol was measured and no methanol found. Urinalysis revealed ketones but no blood or protein. He became more deeply unconscious and on intubation his arterial gases showed pH 7.1, PaCO₂ 9.5, PaO₂ 21, HCO₃⁻ 27. Serum osmolarity was measured at 336 (calculated 284).

- What is the cause of his deterioration?

Summary

Disorders in acid-base balance are commonly found in critically ill patients. Clinicians responsible for these patients need a clear understanding of acid-base pathophysiology in order to provide effective treatment for these disorders. This article concentrates on aspects of metabolic acidosis often seen in intensive care, including poisoning with the alcohols (ethanol, methanol and ethylene glycol).

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DEFINITIONS

An **acid** is a substance that has the ability to give up a proton (H^+ - a positively charged hydrogen ion), and so when in an aqueous solution they have a low pH.

pH is a format used to describe the proton concentration in a solution. It is the negative logarithm₁₀ of the H^+ concentration, so when the blood pH is normal (7.40) the H^+ concentration in the blood is 40nmol.L^{-1} . For every ten-fold increase in H^+ concentration the pH goes down by 1 unit.

A **base** is a substance that has the ability to accept a proton and has a high pH in solution.

Metabolic acidosis (a low pH in the tissue) exists when there is an excess level of fixed or exogenous acids in the body. Fixed acids include hydrochloric acid, sulphuric acid, phosphoric acid, ketoacids and lactic acid. Examples of exogenous acids are salicylate and methanol. Metabolic acidosis is accompanied by a drop in plasma bicarbonate concentration (relative to the bicarbonate concentration present prior to the onset of the acidosis). This drop in bicarbonate can either be caused by bicarbonate loss or by the presence of extra acid.

The body can accommodate significant alterations in acid levels through buffering. The primary buffer in the blood is bicarbonate, which combines with excess acid (hydrogen ions) to make carbon dioxide, which decreases the effect of the acid on the blood pH. Buffering means that metabolic acidosis (a low tissue pH) does not always lead to the presence of metabolic acidaemia (a low blood pH). Blood pH only falls appreciably when the buffering capacity of the blood becomes overwhelmed.

A drop in bicarbonate concentration is the hallmark of metabolic acidosis

EVALUATION

When evaluating a critically ill patient with a metabolic acidosis it is necessary to determine the type of acidosis in order to identify the cause of the acidosis. To classify metabolic acidosis it is useful to calculate the anion gap and, if present, the size of the osmolar gap. These concepts are explained below.

The role of the anion gap

The anion gap is defined as the concentration difference between the major measured cations (ions which are positively charged) and anions (ions which are negatively charged) within the plasma and is normally 12 to 18 mmol.L^{-1} .² Anionic proteins, phosphate, sulphate and low levels of organic acids, which are not measured, account for the difference (i.e. the 'gap'). When examining the cause of a metabolic acidosis it is useful to calculate the anion gap.

$$\text{Anion gap} = [\text{Na}^+ + \text{K}^+] - [\text{HCO}_3^- + \text{Cl}^-] = 15(\pm 3)\text{mmol.L}^{-1}$$

A normal anion gap implies that an acidosis is due to primary bicarbonate loss:

- Plasma bicarbonate is low (the hallmark of acidosis) and chloride concentration is raised.
- This bicarbonate loss may be:
 - gastrointestinal (diarrhoea, fistula)
 - renal (renal tubular acidosis, drug effect).
- Also occurs with rapid intravenous infusion of normal saline (excess chloride) or intravenous nutrition rich in cationic amino acids (e.g. arginine).

An increased anion gap implies that fixed acids are being retained or an abnormal organic acid is present.

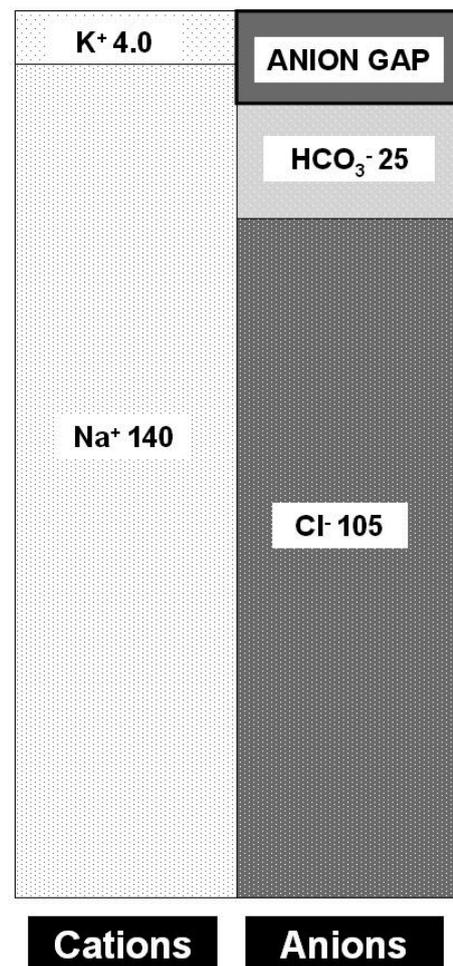


Figure 1. Illustration of the anion gap (all figures are mmol.L^{-1})

- Plasma bicarbonate is low and chloride concentration is normal.
- Fixed acids may be retained in:
 - uraemia
 - ketoacidosis (diabetic, alcoholic)
 - lactic acidosis.
- If fixed acids are normal, exogenous acids should be considered:
 - salicylate (aspirin) poisoning
 - methanol poisoning
 - ethylene glycol poisoning.

Limitations of the anion gap

While the anion gap is useful in evaluating metabolic acidosis, it is not sensitive. The normal range is quoted as 12 to 18 mmol.L⁻¹ which means it is possible for a patient with a normal anion gap of 12 to acquire a severe lactic acidosis (plasma lactate greater than 5mmol.L⁻¹) without generating an anion gap outside the normal range. The anion gap is also affected by plasma albumin (an important unmeasured anion) and low albumin levels can significantly offset an anticipated rise in anion gap.

Role of the osmolar gap

The osmolar gap represents the difference between a sample's measured osmolality (number of osmoles of solute per kilogram of solvent) and its calculated osmolality (number of osmoles of solute per litre of solution). It is a useful calculation to perform if alcohol poisoning is suspected (see later in this article).

Osmolality is measured in the laboratory with an osmometer that either assesses the depression of a sample's freezing point or the depression of its vapour pressure. It is preferable to use the former as any volatile alcohols in the sample will evaporate as the sample is heated and the results from this method will be inaccurate.

Osmolality can be calculated using various formulae. One such formula is:

$$\text{Calculated osmolality} = 2 [\text{Na}^+] + \text{urea} + \text{glucose}$$

Osmolality and osmolarity differ according to whether the number of osmotically active particles is dissolved in a kilogram or a litre of solvent respectively. The calculated osmolarity utilises the plasma concentration of sodium, glucose and urea. Even though sodium and chloride represent the most important determinants of osmolarity in plasma, chloride concentration is not commonly available. The formula is simplified by taking into account the incomplete dissociation of sodium chloride in plasma.

The measured and calculated values should lie within 10mmol.L⁻¹ of each other (the difference being created by the inaccuracy of the calculation and the inaccuracy of the osmometer) and if the gap is larger it suggests the presence of unmeasured osmotically active species.

It is important to realise that the osmolar gap also has significant limitations. When considering alcohol poisoning the osmolar gap is only present as an early feature and returns towards normal as the alcohol is metabolised and the associated metabolic acidosis

develops. Similarly the osmolar gap is not sensitive in ethylene glycol poisoning as the large molecular weight of this substance determines the mortality, only causing a small rise in osmolar gap.

COMPENSATION FOR METABOLIC ACIDOSIS

When treating critically ill patients with metabolic acidosis, it is important to consider the adequacy of their ventilatory response to acidosis when deciding on treatment priorities. Buffering provides the main means of accommodating a metabolic acidosis. As buffering capacity is exceeded, acidaemia develops. Once this rise in hydrogen ion concentration has reached the CSF, it is detected by chemoreceptors and compensation occurs by reducing carbon dioxide levels through hyperventilation (first described by Kussmaul). Detection of low pH in CSF rather than blood explains the delay in this compensation; rapid onset acidosis (for example during convulsions) tends not to stimulate respiration in spite of a low blood pH.

Even though respiratory compensation occurs relatively quickly, it can take up to twelve hours to reach maximal capacity. This maximal capacity can be calculated:

$$\text{PaCO}_2 \text{ (maximal change, in kPa)} = 0.2 [\text{HCO}_3^-] + 1$$

If the patient's PaCO₂ lies within 0.5kPa of this calculated value, then the respiratory response is appropriate to the level of metabolic acidosis. If the PaCO₂ is higher, then the compensation is in a very early stage or the patient has a superimposed respiratory acidosis. If this is the case then earlier intervention with respiratory support is indicated.

When providing respiratory support in patients with a metabolic acidosis it is important to remember that respiratory compensation causes an increased minute volume. If you instigate controlled ventilation with a normal minute volume, then the PaCO₂ level will rise rapidly towards normal, the acidaemia will worsen, and the patient will become acutely unstable. Young fit patients with severe diabetic ketoacidosis can generate huge minute volumes (20-30 l.min⁻¹) and drop their PaCO₂ to below 2kPa.

PITFALLS IN ASSESSING METABOLIC ACIDOSIS

It is impossible to interpret arterial gases accurately without considering the history and presentation first. Consider the following arterial gas:

pH	7.1
PaCO ₂	10.5kPa
PaO ₂	29.3kPa
HCO ₃ ⁻	24.3mmol.L ⁻¹

The interpretation of this result will vary according to the clinical presentation:

- If the gas sample was taken from a young unconscious patient, admitted through the emergency room, with pinpoint pupils then you would interpret the gas as showing primary respiratory acidosis from opiate overdose.
- If the gas was taken from an elderly man with severe COPD presenting with sepsis, then the gas interpretation will be different.

Full compensation for a chronic respiratory acidosis should raise the bicarbonate by $3 \times (\text{PaCO}_2 - 5.3)$. If the PaCO_2 level is chronically raised then you would expect the bicarbonate to be 36mmol.L^{-1} .

This bicarbonate is significantly lower and this suggests a metabolic acidosis superimposed on the background of a compensated respiratory acidosis.

This highlights the importance of basing gas interpretation on clinical assessment. Other pitfalls arise from failing to recognise the limitations of the anion gap and osmolar gap.

METABOLIC ACIDOSIS DUE TO ENDOGENOUS ACIDS

Lactic acidosis

Lactic acid is a weak acid that is present in the blood in low levels ($1\text{-}2 \text{mmol.L}^{-1}$). It is produced from pyruvate, the end substrate in glycolysis, the process by which carbohydrates are broken down to produce energy. Since some tissues (such as skin) produce more pyruvate than their mitochondria can handle, excess pyruvate is converted to lactate, released into the blood and metabolised by the liver (60%, Cori cycle) or kidney (40%).

A rise in the lactate level in the blood suggests increased lactate production or decreased lactate metabolism. As the liver's capacity to metabolise lactate is large, a rise in blood lactate levels suggests that a degree of impaired liver lactate handling is present; however, increased lactate production is still the primary feature of lactic acidosis that is amenable to treatment. Lactic acidosis is categorised according to the state of oxygen delivery.

If oxygen delivery is inadequate (type A lactic acidosis), then aerobic metabolism is impaired, pyruvate accumulates and lactate is produced. We know oxygen delivery is a product of cardiac output and blood oxygen content, but in lactic acidosis low cardiac output is invariably the most important consideration. Oxygen content is rarely low enough to create a lactic acidosis in isolation – the haemoglobin would need to be less than 5g.dl^{-1} or the PaO_2 less than 4kPa .

Treatment aims concentrate on restoring correct distribution of cardiac output and, to a lesser extent, ensuring adequate blood oxygen content (this is one situation where the low transfusion threshold of 7g.dl^{-1} for the critically ill should not apply).

Type B lactic acidosis occurs when oxygen delivery is normal and a problem in carbohydrate metabolism is present. Causes of type B acidosis are subdivided as follows:

- B1 Underlying disease, also called 'stress lactate' (ketoacidosis, haematological malignancy)
- B2 Drug or toxin effect (e.g. salbutamol)
- B3 Inborn error of metabolism

Treatment in this situation depends on determining the cause from the history and clinical signs and addressing the root cause, rather than attempting to correct the acidosis directly.

Ketoacidosis

Ketone bodies include β -hydroxybutyrate, acetoacetate and acetone. When lipids are metabolised by β -oxidation, acetyl co-enzyme A is

produced (as the central conversion molecule of cellular metabolism). Acetyl coA normally binds to oxaloacetate (OAA) to enter the citric acid cycle and generate high energy substrates. However if inadequate levels of OAA are present, then acetyl coA is converted into acetoacetate. If adequate levels of NAD^+ are present, then acetoacetate is subsequently converted into β -hydroxybutyrate. Ketones can be used as energy sources by the brain and the heart.

The main causes of ketoacidosis include:

- Starvation ketoacidosis
- Alcoholic ketoacidosis
- Diabetic ketoacidosis.

Starvation ketoacidosis

This occurs when glycogen levels in the liver have become exhausted and the liver attempts to make more glucose via the gluconeogenesis pathway. Gluconeogenesis requires OAA and the subsequent drop in OAA levels limits the ability of the citric acid cycle to utilise acetyl coA provided by lipid metabolism. The excess acetyl coA is converted into ketone bodies and ketoacidosis develops. The acidosis tends to be within buffering capacity and the anion gap rise is small. The situation is resolved by supplying glucose in a controlled fashion and allowing the liver to revert back to the usual metabolic pathways.

Alcoholic ketoacidosis

This condition develops when ethanol is taken without enough calories. The starvation response is now complicated by the liver's effort to metabolise ethanol. The conversion of ethanol into acetaldehyde requires NAD^+ (a proton carrier with a vital role in the generation of the fuel molecule, ATP) and the excess NADH generated inhibits gluconeogenesis. This exacerbates the glucose deficiency and the corresponding drop in insulin levels stimulates lipid metabolism and ketoacidosis.

The anion gap in this instance will be raised and the acidosis more severe (pH approaches 7.0). Analysis of the acid-base balance can be complicated by an appropriate compensatory respiratory alkalosis and a metabolic alkalosis if the patient has been vomiting. If significant dehydration is present these patients can also get a lactic acidosis, amplified by the relative excess of NADH.

Treatment involves restoration of adequate circulating volume and the administration of both insulin and glucose. With prompt treatment the acidosis should resolve rapidly.

Diabetic ketoacidosis

Diabetic ketoacidosis develops when inadequate amounts of insulin are available. The insulin deficit reduces available intracellular glucose and increases fat breakdown and free fatty acid levels. The liver responds, as if in a starving state, by increasing lipid metabolism (further encouraged by increased levels of 'stress' hormones) and, as gluconeogenesis depletes available oxaloacetate, the acetyl CoA generated is converted into ketone bodies. Acetoacetic acid and β -hydroxybutyric acid dissociate and the H^+ ion released is buffered by bicarbonate. An increased anion gap acidosis develops.

This acid-base picture may be complicated by various factors. Patients are often severely dehydrated and this can cause lactic acidosis due to inadequate tissue perfusion. Ketoacidosis causes vomiting and the resulting loss of acid can cause the calculated anion gap to under-represent the severity of the acidosis. In addition, initial resuscitation with chloride rich solutions (0.9% saline) will increase chloride levels and further decrease the anion gap.

Renal acidosis

The kidney's ability to regulate acid-base balance can be adversely influenced in numerous ways. It is useful to categorise these conditions according to their effect on glomerular filtration.

Acidosis associated with decreased glomerular filtration

The most common forms of renal acidosis seen in intensive care are associated with a profound drop in glomerular filtration. Acute kidney injury (commonly due to acute tubular necrosis), and acute exacerbation of chronic kidney disease, both cause a metabolic acidosis because the kidney is unable to excrete fixed acids.

The acidosis is exacerbated by the associated tubule damage. This damage prevents bicarbonate production from CO₂, and ammonia excretion and buffering capacity is reduced as a result. Bicarbonate levels drop and chloride tends to remain stable and as a result the anion gap rises. Treatment involves correction of the precipitating factors and supporting renal function (with renal replacement therapy if required).

Acidosis associated with preserved glomerular filtration

This is renal tubular acidosis (RTA), which is less common in the critically ill and usually associated with either inherited disorders or pre-existing renal disease. While the glomerular filtration rate may be depressed, the acidosis is disproportionate to this minor reduction and tends to exhibit a normal anion gap.

Renal tubular acidosis (RTA) is subdivided according to the site of the tubular defect:

Type 1	Distal tubular defect
Type 2	Proximal tubular defect
Type 4	Distal tubular resistance to aldosterone (or aldosterone deficiency)

Type 1 RTA is the most common form and is caused by the distal convoluted tubule failing to excrete hydrogen ions when attempting to reabsorb sodium. A metabolic acidosis develops as a consequence and the urine fails to acidify. Potassium excretion is unaffected and potassium loss in the urine may be increased as a result. This type of RTA has numerous causes including drug induced damage (amphotericin), autoimmune disorders (lupus) and nephrocalcinosis. It is diagnosed by confirming a high urine pH (greater than 5.5) in the presence of a severe metabolic acidosis. The underlying disorder should be addressed and the episodes of acidosis prevented by giving adequate dietary bicarbonate.

Type 2 RTA is much less common and is caused by a defect in the proximal convoluted tubule that prevents bicarbonate reabsorption. It can be inherited or associate with Fanconi syndrome (generalised defect of tubular amino acid reabsorption.) Urinary bicarbonate loss

is increased and the urine pH is raised. However, as the proportion of bicarbonate filtered by the kidney is proportional to the plasma bicarbonate concentration, the acidosis is less severe than with type 1 RTA. The condition tends to be self-limiting and the bicarbonate tends not to drop below 15mmol.L⁻¹. Potassium loss is less marked than with distal RTA but can be a problem if bicarbonate supplements are given to correct the acidosis. Any supplements need to include both bicarbonate and potassium.

Type 4 RTA is also rare and tends to occur while aldosterone is deficient or the distal tubule becomes resistant (papillary necrosis). Both acid and potassium secretion are reduced and the urine remains relatively alkali whilst a metabolic acidosis develops in the presence of raised potassium. If severe this condition can be treated with oral fludrocortisone (0.1mg.day⁻¹).

Other causes of normal anion gap acidosis

Normal anion gap acidosis occurs due to primary bicarbonate loss and this can occur through the kidney or the gut.

Renal loss occurs with renal tubular acidosis as discussed above but can also occur as a drug effect (acetazolamide) or when the ureters are diverted to the bowel (ureterosigmoidostomy). The latter causes a problematic acidosis that responds poorly to dietary supplements and can be difficult to treat.

Gut losses occur with severe diarrhoea or via nasogastric aspirates in patients with small bowel obstruction. Pancreatic fistulae, biliary drains and some bowel tumours also lose bicarbonate and cause a hyperchloraemic normal anion gap acidosis.

METABOLIC ACIDOSIS DUE TO EXOGENOUS ACIDS

Alcohol poisoning

Ethanol, methanol, ethylene glycol and isopropanol represent the main alcohols encountered in poisoning. Ethanol is by far the most common cause of alcohol poisoning. Specialist laboratories are able to measure plasma alcohols but this is often not immediately available, therefore the diagnosis of alcohol poisoning can be helped by estimation of the osmolar gap. In order to understand the patterns seen in alcohol poisoning it is necessary to discuss how the various alcohols are metabolised.

Metabolism of alcohol (methanol, ethanol and ethylene glycol)

Ethanol, methanol and ethylene glycol are metabolised by the same enzyme systems, but produce different metabolites. Collectively they are termed alcohols.

With methanol and ethylene glycol poisoning, only the parent compounds and the first metabolites (formaldehyde and glycoaldehyde respectively) are osmotically active. The subsequent metabolites are weak acids that dissociate into electrically charged ions that become balanced by sodium, and so cease to exert an osmotic influence. In the initial stages, metabolism generates an osmolar gap with minimal acidosis, however, further metabolism produces formic and glycolic acid respectively. This is not the case with ethanol and accounts for the clinical progression seen in methanol and ethylene glycol poisoning. These metabolites generate a metabolic acidosis and as they are

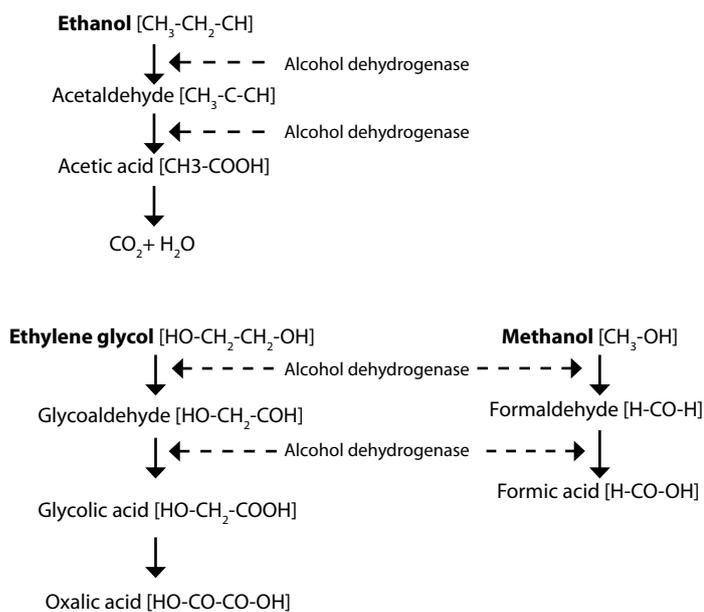


Figure 2. Metabolism of ethanol, ethylene glycol and methanol.

produced the osmolar gap decreases. The enzyme responsible, alcohol dehydrogenase, metabolises both poisons at a lower rate than ethanol and this may result in toxicity being delayed for up to 30 hours for methanol, and twelve hours for ethylene glycol. Use of the osmolar gap may therefore be misleading.

When blood is taken for these tests it is impossible to determine which substance has been taken and how far the metabolism of the alcohol has progressed. If the osmolar gap is normal then either the alcohol metabolism is advanced or the patient has not ingested a large quantity. However, patients usually present to hospital with the onset of symptoms and this normally coincides with intermediate alcohol metabolism and a raised osmolar gap.

Methanol poisoning

Methanol is a potent poison and serious toxicity is seen after an intake of 10ml. Methylated spirits contains 5% methanol and ingestion of over 200ml is required before serious toxicity is encountered. This toxicity presents after a latent period of twelve hours or more. Patients report headache, breathlessness and visual symptoms ranging from blurring to complete blindness. Severe abdominal pain and nausea are common and patients may present with a rigid abdomen. The cardiovascular system is initially stable until a severe acidosis develops, then marked myocardial depression and bradycardia is encountered.

Treatment is directed at reducing the rate of organic acid production with intravenous ethanol and haemodialysis. Ethanol treatment consists of a 50g oral loading dose (125ml of spirits will suffice) followed by an intravenous infusion of $10\text{-}12\text{g}\cdot\text{h}^{-1}$. Treatment should aim to achieve a plasma concentration of $1\text{-}2\text{g}\cdot\text{L}^{-1}$. The indications for dialysis are not well defined but should be considered in the presence of a severe metabolic acidosis, marked visual or mental symptoms or in the presence of a high methanol plasma concentration (over $500\text{mg}\cdot\text{L}^{-1}$). Folinic acid can also be given intravenously to help prevent ocular toxicity (30mg IV 6 hourly).

Ethylene glycol poisoning

Ethylene glycol is less potent than methanol with 100ml ingestion representing a severe overdose. Toxicity initially presents with intoxication - slurring of speech, drowsiness and nausea. This can progress to marked cerebral depression and convulsions. Twelve hours after ingestion significant metabolism to glycoaldehyde has occurred causing cardiorespiratory depression and acidosis. Aldehydes inhibit oxidative phosphorylation, mechanisms for cellular respiration, glucose metabolism, protein synthesis, nucleic acid replication and synthesis. Myocardial depression can be significant and pulmonary oedema is commonly encountered.

Renal tenderness and oliguria may become evident as acute tubular necrosis becomes established. Metabolism of ethylene glycol to oxalic acid causes a demonstrable degree of oxalate crystalluria and accounts for the low plasma calcium seen (chelation to form calcium oxalate). Ethylene glycol poisoning is lethal with levels of $21\text{mg}\cdot\text{dl}^{-1}$ but it must be remembered that this will only generate a late osmolality increase of $4\text{mosm}\cdot\text{L}^{-1}$ (delayed presentation). The treatment approach is similar to methanol toxicity with emphasis on the early use of ethanol infusions and haemodiafiltration. These treatments should continue until ethylene glycol can no longer be detected in blood.

Isopropanol poisoning

Isopropanol should also be considered when patients present with alcohol toxicity. This alcohol forms a major component of rubbing alcohol and is used in windscreen cleaning preparations and de-icer. Unlike methanol or ethylene glycol, isopropanol is metabolised to acetone and excreted in the urine. Acetone is not metabolised further and organic acid production is minimal. Both the parent compounds and metabolites are osmotically active and significant osmolar gaps may be seen with ingestion. Isopropanol toxicity tends to present with intoxication, meiosis (small pupils), and brain stem depression with significant overdose. Isopropanol is irritant and causes marked gastritis, pancreatitis and, if aspirated, causes tracheitis and pulmonary oedema. It is rapidly absorbed from the stomach and gastric lavage is of little benefit. Ketosis is more marked with isopropanol ingestion and this can provide a useful clue to diagnosis. Treatment is supportive and no effort should be made to limit metabolism of isopropanol with ethanol infusions. Isopropanol is readily cleared by haemodiafiltration but this treatment is rarely required.

Salicylate poisoning

Aspirin (acetylsalicylic acid) poisoning causes over 200 deaths a year in the UK. Therapeutic doses of aspirin are absorbed rapidly and completely from the stomach and larger doses may be absorbed for up to 18 hours after ingestion as the tablets coalesce in the stomach.

Metabolism

Acetylsalicylic acid is hydrolysed to salicylic acid and further metabolised in one of three ways.

1. Conjugation with glycine to salicyluric acid
2. Hydroxylated to gentisic acid
3. Conjugation with glucuronic acid to either salicylacyl glucuronide or salicyl phenolic glucuronide.

Conjugation with glucuronic acid is saturable so that levels of non-protein bound salicylate rise disproportionately with increasing dose. The excretion of unchanged salicylate by the kidneys then becomes increasingly important and alkalinisation of the urine will therefore maximise its excretion by ion trapping.

Drug effects

Central to the metabolic disturbances initiated by acetylsalicylic acid is the uncoupling of oxidative phosphorylation. The resulting increase in oxygen consumption and carbon dioxide production leads to a respiratory alkalosis that is worsened by direct stimulation of the respiratory centre. Bicarbonate excretion is enhanced and sodium, potassium and water loss also occurs. When this is combined with hyperpyrexia and sweating, then marked dehydration and electrolyte imbalance follow. Stimulation of the chemoreceptor trigger zone may induce vomiting and this will further exacerbate this imbalance.

Uncoupled oxidative phosphorylation enhances glycolysis and increases the peripheral demand for glucose. This occurs mainly in muscle and may provoke hypoglycaemia. The brain is particularly sensitive to this and neuroglycopenia may then lead to depression of the respiratory centre.

The metabolic acidosis seen in acetylsalicylic acid poisoning is caused by the stimulation of lipid metabolism (increasing the formation of ketoacids) and the inhibition of enzymes within the Krebs cycle (increasing levels of pyruvic and lactic acid). The acidosis is poorly tolerated due to the reduced buffering capacity following the initial respiratory alkalosis and bicarbonate excretion.

Clinical presentation

The clinical picture depends on the age of the patient and on the total dose ingested. Acute overdose in the setting of chronic use augments toxicity. Plasma salicylate levels 6 hours after ingestion can be classified as mild ($300\text{--}500\text{mg.L}^{-1}$), moderate ($500\text{--}750\text{mg.L}^{-1}$) and severe ($>750\text{mg.L}^{-1}$) poisoning. Below ten years of age respiratory alkalosis tends to be a transient feature with metabolic acidosis predominating. However, respiratory alkalosis is more marked in adults, where it helps to keep salicylate in the ionised form, preventing it from crossing cell membranes. The following features are usually present regardless of the severity: sweating, vomiting, pyrexia, tinnitus and epigastric pain. As the metabolic acidosis worsens more salicylate enters the central nervous system and tremor, delirium, convulsions and eventually coma ensues. Non-cardiogenic pulmonary oedema and acute renal failure are also features of acetylsalicylic acid toxicity.

Treatment involves vigorous gastric lavage to limit continued absorption. Dehydration and electrolyte disturbances (particularly hypokalaemia) should be corrected. Severe toxicity requires more than these basic manoeuvres and alkalinisation of the urine should be performed. Urinary salicylate excretion is encouraged with intravenous infusions of bicarbonate, aiming to raise urinary pH >7.5 while avoiding a plasma pH >7.55 . Haemodialysis has also been used to augment salicylate excretion.

CASE EXAMPLES - DISCUSSION

Case 1

The patient presented with a metabolic acidosis caused by loss of diabetic control, relative insulin deficiency and consequently ketoacidosis. Kussmaul respiration is seen in respiratory compensation through hyperventilation - the rise in minute volume can be substantial and maintaining this compensation is very strenuous. As time passes patients tire, the minute volume decreases and the acidosis worsens rapidly. Young patients in particular can maintain full respiratory compensation, almost to the point of respiratory arrest, as in this example. Elderly patients tend to tire earlier.

When taking over a patient's ventilation, in the setting of a metabolic acidosis, it is vital that the minute volume used is raised appropriately. If standard ventilation settings are applied, as in this case example, the drop in alveolar ventilation post-induction will remove the respiratory compensation and the acidosis will deteriorate dramatically. This is the likely cause of this patient's cardiovascular collapse.

Case 2

This patient, presenting with peritonitis, has a raised haemoglobin, urea and creatinine suggesting dehydration and a likely lactic acidosis due to inadequate tissue perfusion. The arterial gases confirm that acidaemia is present (low pH) and the low bicarbonate level implies that the acidosis is metabolic.

The anion gap is raised at 35 and this strongly suggests the presence of an increased anion gap acidosis. The vomiting that occurred in the days leading up to admission may have caused a metabolic alkalosis (loss of hydrogen ions and chloride) that has been masked by the superimposed lactic acidosis. Therefore a severely increased anion gap acidosis has only dropped the pH to 7.1, when you would expect the pH to be lower.

Using the bicarbonate level (14.3mmol.L^{-1}), the calculated PaCO_2 during maximal compensation would be 3.8kPa ($[14.3 \times 0.2] + 1$). The fact that her PaCO_2 is higher should serve as a warning of imminent fatigue and ventilation should be supported as quickly as possible in order to prevent cardiorespiratory collapse.

Case 3

This woman presented with a low pH and low bicarbonate, implying that a metabolic acidosis is present. The extent of the dehydration raises the possibility of a lactic acidosis, however this would create an increased anion gap. The anion gap in is low (8.5), and this strongly supports the presence of a normal anion gap acidosis secondary to bicarbonate loss from the gut.

With a bicarbonate level of 6.4 you would expect the patient to drop her PaCO₂ to 2.28 ($[6.4 \times 0.2] + 1$) and in this instance her respiratory compensation is appropriate.

Case 4

This patient was initially felt to be intoxicated with alcohol and the low blood glucose raised the possibility of alcoholic ketoacidosis. The initial arterial gas does not support this as a low bicarbonate and an increased anion gap would be expected. The subsequent deterioration however is typical of methanol poisoning.

Methanol metabolism is often delayed for 12 to 18 hours especially if taken with ethanol. The first stage in metabolism generates formaldehyde which is not an acidic species – metabolic acidosis will not feature at this stage. When the formaldehyde is metabolised into formic acid then the increased anion gap acidosis develops.

It would have been useful to determine whether there was an osmolar gap on initial presentation. If this was raised then it would have alerted the clinicians to the possibility of poisoning with an alcohol, and ethanol treatment would have prevented the deterioration.

Interestingly the subsequent arterial gas shows a severe metabolic acidosis but the PaCO₂ has only dropped minimally. The calculated PaCO₂ for maximal compensation suggests the PaCO₂ should have dropped to 3.0kPa. The relative respiratory acidosis arises from methanol induced respiratory depression and should prompt early ventilatory support.

Case 5

In this example the same patient re-presents with an intoxicated picture but ethanol and methanol are not detected on this admission. In spite of this, and the normal arterial gases on admission he became comatose with arterial gases suggesting a primary respiratory acidosis (low pH, raised PaCO₂). The rise in bicarbonate is appropriate for the rise in PaCO₂ (expected bicarbonate rise = $0.75 [\text{PaCO}_2 - 5.3]$ for an acute respiratory acidosis), so no metabolic effects are demonstrated.

This presentation is typical for isopropanol poisoning. Metabolic acidosis is not a feature of isopropanol poisoning; however the alcohol is heavily intoxicating and can easily cause respiratory depression as seen in this example. The key to aid diagnosis is the presence of the increased osmolar gap combined with the urine ketosis (from the metabolite, acetone). Treatment is supportive (the airway will need to be secured in this example and respiratory support provided) until the alcohol has been metabolised.

SUMMARY

Metabolic acidosis is commonly encountered in intensive care and correct management requires confirmation that an acidosis is present, determination of its nature and then determination of the probable cause. Identification of the root cause will then allow specific treatment with improved efficacy.

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Delirium in critical care

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INTRODUCTION

Delirium is a common complication of critical illness. It has conventionally been regarded as an unavoidable and benign side effect of long-term sedation on an intensive care unit (ICU). However in recent years this pre-conception has been challenged by the publication of studies demonstrating poorer outcomes in ICU patients with delirium. This article will define delirium, summarise the risk factors, provide an overview of the current evidence for its detection and discuss its management.

DEFINITION AND CLASSIFICATION

The American Psychiatric Association defines delirium as 'a disturbance of consciousness, attention, cognition and perception which develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day'.¹ Delirium can be sub-classified according to aetiology using the DSM IV criteria. This is difficult to apply to the critical care population in whom a multifactorial origin is likely. A more useful clinical classification system was first described in elderly patients by Lipowski in 1983.² Three sub-types of delirium were described:

- **Hypoactive delirium** – Patients appear subdued, withdrawn and have a poor response to stimulus.
- **Hyperactive delirium** – Patients may display agitation or aggression and may experience delusions or hallucinations.
- **Mixed delirium** – Patients fluctuate between hypo- and hyperactive subtypes.

Quimet et al first defined sub-syndromal delirium in a patient sub-group who displayed some features of delirium, but didn't meet the full diagnostic criteria. This introduced the concept of delirium as a spectrum of disease rather than a single entity.³

RISK FACTORS

Numerous risk factors have been identified for the development of delirium on the ICU.⁴⁻⁷ They are summarised in Table 1.

DIAGNOSIS

Delirium was traditionally diagnosed by a psychiatrist using DSM IV criteria. Whilst psychiatric referral can still be helpful, the development of specific delirium assessment tools, for use by the multi-disciplinary team, has greatly improved its recognition on intensive care. However delirium is probably still under-diagnosed, particularly in the hypoactive sub-type, where the more subtle features may be overlooked.

The assessment tool most commonly employed in UK clinical practice is the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).⁸ Both CAM-ICU and the Intensive Care Delirium Screening Checklist (ICDSC) have been specifically validated for use on the intensive care unit.⁴ Both tools are reproduced in the original version of this article (totw.anaesthesiologists.org). Both are easy and quick to perform and have good inter-observer reliability.⁴ CAM-ICU, performed once every 24 hours, directly assesses the patient performing tasks to command and can be used during mechanical ventilation. ICDSC, documented every 8 hours, is more subjective as it relies on data collected during routine nursing care, without direct assessment of the patient. Patients who are experiencing isolated hallucinations may be assessed as delirium negative by CAM-ICU, but delirium positive by ICDSC.

Both CAM-ICU and ICDSC have been shown to have a high sensitivity (97%⁹ and 99%¹⁰ respectively) but CAM-ICU has a much better specificity (99%⁹) than ICDSC (64%¹⁰). Another study, which directly compared the performance of the two scoring systems, suggested a good level of agreement between them.¹¹

INCIDENCE

For many years, the lack of a consistent definition for delirium, that could be applied to intensive care patients, hampered efforts to determine its incidence in this setting. The development of the two delirium

Summary

Delirium is a common problem in ICU patients and results in longer hospital stays, and increased morbidity and mortality. Standardised assessment tools are available and have highlighted a higher incidence than previously believed. Haloperidol is the mainstay of treatment despite lack of a firm evidence base for its use. Benzodiazepines should be avoided unless alcohol withdrawal is the cause of delirium.

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Table 1. Risk factors for delirium on ICU.

Medical history	Acute presentation
Age over 70	Disease severity (APACHE II score)
Hypertension	Metabolic derangement
Congestive cardiac failure	• Thyroid function
Stroke	• Glycaemic control
Epilepsy	• Hyper/hyponatraemia
Depression	• Renal function
Dementia	Thermoregulation
HIV	Sepsis
Renal impairment	Hypoxaemia
Hepatic impairment	Anxiety
Visual or hearing impairment	Uncontrolled pain

Social history	Medications
Smoker	Use of an epidural
Alcohol abuse	Opiates
Malnutrition	Benzodiazepines
	Propofol
	Anti-cholinergics

Environmental
Physical restraints
Rectal or urethral catheter
Central venous catheter
Sleep deprivation

screening tools discussed has gone some way to address this issue. However, reported incidence still varies widely (16.1%-83.3%) depending on the patient demographics, illness severity and screening tool used.^{9,10}

DSM IV

One study in 2001 suggested that the incidence of delirium, when assessed by two independent psycho-geriatricians using DSM-IV criteria, was as high as 81.3% in the 48 study patients.¹² During validation of the ICDSC, a psychiatrist identified delirium in 16.1% of 93 study patients using DSM IV criteria.¹⁰

CAM-ICU

The pilot for the CAM-ICU assessment tool found a high incidence of 83.3% in 111 study patients.⁹ Subsequent studies using CAM-ICU suggest that the incidence varies between 41-74%.^{6,13} This is in comparison to the data from our local mixed surgical and medical ICU in which CAM-ICU screening detected delirium in 31.7% of patients at some point in their admission.¹⁴

Peterson et al noted that the most common delirium subtypes were mixed (54.9%) and hypoactive (43.5%) whilst hyperactive was found to be relatively uncommon (1.6%).¹⁵

ICDSC

Ouimet et al⁷ identified delirium in 31.8% of 764 patients in a mixed specialty intensive care unit using the ICDSC tool.

Whatever the true incidence of delirium is, it appears to be much more common than previously thought and the introduction of validated assessment tools has improved the recognition of this important condition.

PATHOPHYSIOLOGY

Currently there is no comprehensive explanation for the mechanism by which delirium occurs in the critically ill. There are however numerous hypotheses and it seems likely that its pathophysiology is multifactorial. An excellent review by Girard et al¹⁶ covers several of the leading suggestions and these are summarised in Figure 1 (adapted from Figueroa-Ramos et al¹⁷):

1. Increased levels of dopamine and reduced levels of acetylcholine are thought to increase neuronal excitability and precipitate delirium. These changes may be caused by changes in the synthesis, release and inactivation of these neurotransmitters. Whether other neurotransmitters (such as GABA, endorphins, glutamate or histamine) are also involved is unknown.
2. Tryptophan is an amino acid which is actively transported across the blood brain barrier via LAT1 proteins. It is a precursor for serotonin and subsequently melatonin production. Low levels of tryptophan, and thus serotonin and melatonin, are hypothesised to cause hyperactive delirium. High levels of tryptophan, serotonin and melatonin may be responsible for hypoactive delirium.¹⁸ It is unclear whether these effects are due to serotonin, melatonin, the neurotoxic metabolites of tryptophan or all of the above.
3. Phenylalanine is another amino acid which is actively transported across the blood brain barrier via the same transport channel as tryptophan. Consequently, high uptake of phenylalanine will compete with tryptophan and reduce levels of serotonin and melatonin. Once across the blood brain barrier, phenylalanine is converted into DOPA and subsequently dopamine, noradrenaline and adrenaline. High levels of phenylalanine have been associated with delirium,¹⁹ but it is unclear whether this effect is due to increased levels of noradrenaline and dopamine, reduced serotonin and melatonin, or all of the above.
4. The inflammatory response to critical illness causes the release of cytokines into the circulation which results in a pro-thrombotic state. Animal studies suggest that this leads to reduced cerebral blood flow and it is possible that this could trigger delirium.
5. Engel and Romano performed EEG recordings on delirious patients in the 1940s and concluded that the slow EEG appearance they observed was characteristic of a 'derangement in the general functional metabolism of the brain'.²⁰ Other investigators have suggested that this might result in delirium by reducing acetylcholine levels.²¹

PREVENTION

A recent paper by Morandi et al introduces the concept of an 'ABCDE bundle' which uses an evidence-based approach in the prevention of delirium.²² This is summarised in Figure 2.

Awake and breathing

The Awakening and Breathing Controlled Trial found that daily sedation breaks, paired with trials of spontaneous breathing, significantly improved outcome at 1 year.²³ These findings have led to the adoption of this practice in many intensive care units, although in a survey of clinical practice, the majority of practitioners admit that sedation breaks are not performed as frequently as intended.²⁴

Choice of sedation

The mainstay of sedation on ICU has traditionally been propofol, benzodiazepines and opiates, all of which have been implicated in altering sleep patterns.²⁵ Trials involving α_2 receptor agonists (clonidine and shorter-acting dexmedetomidine) have reported a lower incidence of delirium and shorter time to extubation.^{26,27} Remifentanyl is a short-acting pure μ receptor agonist. Its use as a sedative agent in intensive care has been shown to reduce the time to extubation,²⁸ but further work is needed to assess its impact on the incidence of delirium. Interestingly, a Danish study randomised 140 mechanically ventilated patients to receive either 'no sedation' or propofol sedation with daily sedation breaks.²⁹ It reported shorter times to extubation and a lower

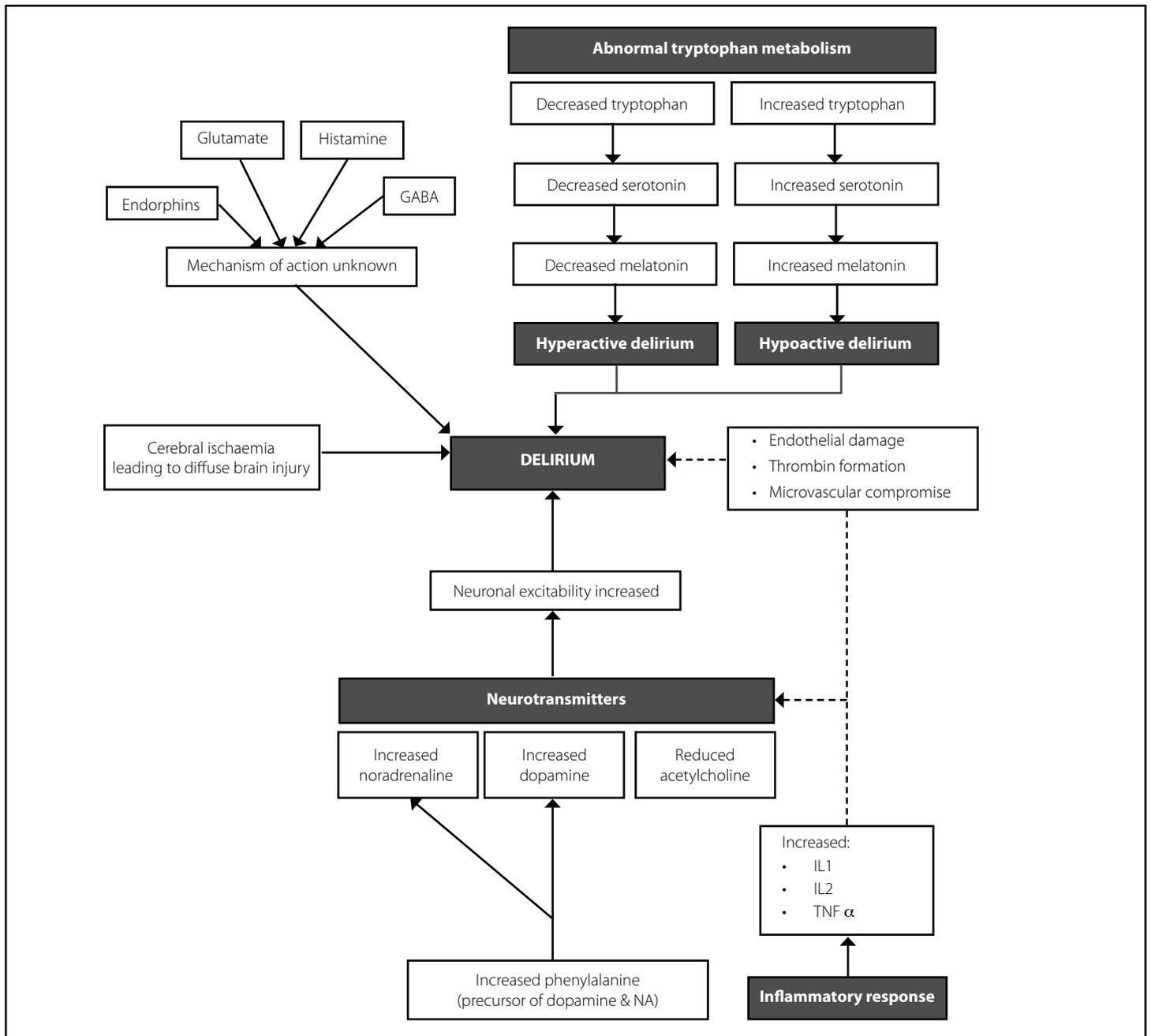


Figure 1. Pathophysiology of delirium¹⁷

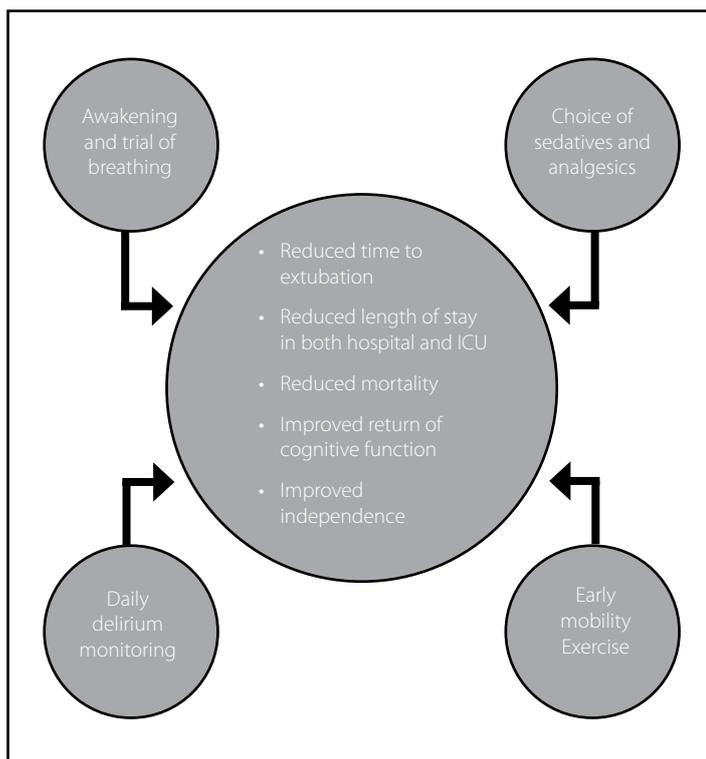


Figure 2. ABCDE bundle²²

incidence of delirium, without an increase in self-extubation in the group randomised to no sedation, but it is unlikely that this practice will become widely adopted.

Daily delirium monitoring

Daily screening for delirium is important as delirium is under-diagnosed without the use of assessment tools.³⁰

Early mobility and exercise

Schweickert et al demonstrated that if physical and occupational therapy was provided at the same time as a sedation break and trial of spontaneous breathing, then patients had shorter episodes of delirium and improved function at hospital discharge.³¹

Sleep

It is unclear whether sleep disruption on intensive care is a cause or a consequence of delirium. Studies have shown that the total sleep time is unaffected by sedation, but that altered REM (rapid eye movement) patterns are observed, suggesting an impact on the quality of sleep.³² High levels of noise or ambient light, drugs, mechanical ventilation and routine patient care at inappropriate times of the day have all been associated with sleep disruption.³³

TREATMENT: NON-PHARMACOLOGICAL

The first stage in the management of delirium is to recognise its presence by use of an appropriate assessment tool. The next stage is to review the delirium risk factors in Table 1, looking for precipitant causes that may be correctable. Some of the risk factors listed are clearly more amenable to modification than others. The more important modifiable factors are seen in Table 2.

Table 2. Modifiable factors in delirium.

General factors

- Correct visual impairment with glasses
- Correct hearing impairment with hearing aids

Medical factors

- Correct metabolic derangement
- Diagnose and treat sources of infection
- Achieve adequate tissue oxygen delivery
- Administer adequate analgesia
- Remove lines and catheters promptly
- Do not use physical restraints routinely but only use acutely to prevent harm

Medications

- Avoid deliriogenic drugs where possible

Environmental factors

- Orientate the patient regularly
- Reduce noise
- Reduce sleep disturbance
- Mobilise where possible

TREATMENT: PHARMACOLOGICAL

There is a lack of randomised control trial evidence for pharmacological treatments for delirium on the intensive care unit. The mainstay of current therapy and that recommended by both the Intensive Care Society (UK) and the American College of Critical Care Medicine (level C recommendation) is haloperidol.^{25,34} Surveys of clinical practice in the US³⁵ and the UK⁸ revealed that the majority of clinicians use haloperidol as their first line treatment for delirium. In the UK this remains an off-licence indication for haloperidol administration.

Haloperidol

Haloperidol is a dopamine receptor (D2) antagonist and acts centrally to reduce hallucinations and delusions. It is hepatically metabolised with an elimination half-life of 10-36 hours, secondary to active metabolites. Recognised adverse effects include extra-pyramidal side effects, prolonged QT interval (which can precipitate torsades de point tachycardia) and neuroleptic malignant syndrome. The optimum dosing schedule has not yet been established by trial evidence, but a commonly used schedule is 2.5-5mg intravenously every 6 hours. Doses may need to be reduced in the elderly. It has also been used as a continuous infusion in severe cases, but this does not represent routine practice.³⁶

A retrospective study of 989 mechanically ventilated patients identified a significant reduction in hospital mortality in those patients who had received haloperidol during their intensive care stay. However, the study design meant that it was not possible to identify if the indication for commencing the haloperidol was delirium.³⁷

Atypical anti-psychotics

Atypical anti-psychotics (such as olanzapine, quetiapine) are also dopamine receptor (D2) antagonists, but have additional antagonistic effects on serotonin receptors (5-HT_{2A}). Enteral administration is required as there are no intravenous preparations available. They are generally metabolised in the liver and have active metabolites. Their half-lives vary according to the preparation, with quetiapine having the shortest half-life of 6 hours. The adverse effects that are most likely to be encountered include sedation and anti-cholinergic symptoms.

A randomised, but unblinded, trial of enteral olanzapine versus haloperidol in 103 patients demonstrated improvement in daily Delirium Index scores and reduced benzodiazepine administration in both trial groups, without a significant difference between them.³⁸

A randomised, double blinded trial of quetiapine against placebo, with rescue haloperidol if required, found that the quetiapine group had a faster resolution of delirium.³⁹

The recently published MIND study randomly assigned 101 patients to haloperidol, ziprasidone (atypical anti-psychotic) or placebo. Doses were adjusted according to the level of delirium as assessed by CAM-ICU. There was no significant difference in the number of days patients survived without delirium or coma, in any of the 3 groups in this small pilot study. A further multi-centre placebo trial is planned.⁴⁰

Benzodiazepines

Benzodiazepines have a role in the management of delirium caused by alcohol withdrawal. However, their administration in other patient sub-groups has been identified as an independent risk factor for delirium development. Their use should therefore be avoided where possible in critically ill patients.

An adapted summary of the delirium treatment guidance produced by the UK Clinical Pharmacy Association and the Intensive Care Society is in reference 25.

PROGNOSIS

Mortality

A 6-month follow up study by Ely et al determined a statistically significantly higher 6-month mortality in ICU patients with delirium (34% v 15%, adjusted hazard ratio of 3.2).⁴¹ Another study of 102 mechanically ventilated patients determined that ICU mortality was higher for patients with delirium compared to those without (63.6% v 32.5%, hazard ratio of 2.5).⁴² Overall ICU mortality rates were lower in Ouimet et al's study of 537 patients, but it was still significantly higher in patients with delirium compared to those without (15.9% v 2.4%).³

Morbidity

Patients with delirium are more likely to self extubate and remove invasive medical devices.⁵

Length of stay

A study of 48 patients demonstrated that delirium significantly increased both the hospital and ICU length of stay.¹² A further study of 224 patients found that patients with delirium spent a median of

10 days longer in hospital than those without.⁴¹ These findings are supported by Ouimet et al's study which demonstrated that even sub-syndromal delirium significantly increased length of stay.³

Cost

Millbrandt et al examined the cost of the hospital and ICU stays of 224 medical ICU patients in 2004.⁴³ They reported that patients with delirium had a significantly higher cost of care than those without and that those costs were dependent on the severity of the delirium.

Long-term cognitive impairment

A long term cohort study of 77 ICU patients determined that 79% of survivors had cognitive impairment at 3 months and 71% at 12 months.⁴⁴ A third remained severely impaired a year following ICU discharge. Delirium was identified as an independent predictor of cognitive impairment in this study. Duration of delirium also seems to be important. Patients who experienced delirium for 5 days scored almost 7 points fewer on cognitive testing, 1 year following discharge than those who experienced 1 day of delirium.

SUMMARY

Despite the surge of research activity into delirium over the past decade, the condition remains an important problem on intensive care. Standardised assessment tools validated for use in the ICU setting have been developed and have demonstrated a higher incidence of delirium than previously thought. Current treatments have a limited evidence base, particularly with respect to improving patient outcome. Whilst haloperidol currently remains the mainstay of pharmacological management, there is increasing interest in prevention of delirium by modification of its risk factors. Recent evidence suggests that delirium results in longer hospital stays, higher associated treatment costs and increased morbidity and mortality.

WEB LINKS

- www.icudelirium.org
- www.icudelirium.co.uk

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Sedation in intensive care patients

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Summary

Many critically ill patients require sedation in order to tolerate more invasive therapies, such as intubation and ventilation. The level of sedation should be assessed regularly and 'sedation holds' may reduce the duration of ventilation. The available drugs are discussed with emphasis on their advantages and disadvantages.

INTRODUCTION

Sedation is an essential component of the management of intensive care patients. It is required to relieve the discomfort and anxiety caused by procedures such as tracheal intubation, ventilation, suction and physiotherapy. It can also minimise agitation yet maximise rest and appropriate sleep. Analgesia is an almost universal requirement for the intensive care patient. Adequate sedation and analgesia ameliorates the metabolic response to surgery and trauma. Too much or too little sedation and analgesia can cause increased morbidity, for example over sedation can cause hypotension, prolonged recovery time, delayed weaning, gut ileus, DVT, nausea and immunosuppression; under sedation can cause hypertension, tachycardia, increased oxygen consumption, myocardial ischaemia, atelectasis, tracheal tube intolerance and infection.

Sedation in the ICU varies widely from producing complete unconsciousness and paralysis to being nursed awake yet comfortable. There are many components to the ideal regimen but key elements include recognition of pain, anxiolysis, amnesia, sleep and muscle relaxation.

Although the mainstay of therapy is pharmacological, other approaches are just as important:

1. Good communication with regular reassurance,
2. Environmental control such as temperature, humidity, lighting and noise,
3. Explanation prior to procedures,
4. Management of thirst, hunger, constipation, full bladder,
5. Variety for the patient - e.g. radio, visits from relatives, washing/shaving,
6. Appropriate diurnal variation - gives pattern to days.

ASSESSING THE LEVEL OF SEDATION

The dosage of commonly used sedative and analgesic drugs varies widely between patients because of variations in pharmacokinetics and pharmacodynamics.

A valid method for monitoring sedation would allow sedation to be tailored to the individual.

Any scoring system needs to be simple, rapidly performed, non-invasive and, most importantly, reproducible. Physiological variables, serum concentrations of drugs and neurophysiological tools such as EEG, bispectral index and lower oesophageal contractility have all been used, but are expensive, unreliable and unavailable.

The best systems are clinically based. Commonly used ones include the Richmond Agitation Sedation Scale and the Ramsay Scale.

Table 1. *The Ramsay Scale - six levels of sedation are used.*

1. Anxious and agitated
2. Cooperative, orientated and tranquil
3. Responds to verbal commands only
4. Asleep but brisk response to loud auditory stimulus/light glabellar tap (to the forehead)
5. Asleep but sluggish response to loud auditory stimulus/light glabellar tap
6. Asleep, no response.

This should be completed hourly by the attending nurse, but can be reduced in frequency as the patient stabilizes. Levels 2 to 5 can be considered suitable for patient in the ICU.

An increase in the sedation score must prompt the physician to make a differential diagnosis between over sedation or neurological/biochemical disease.

As a rule, the aim for the majority of patients is for them to be sleepy, although easily rousable and hence cooperative. There is a definite trend and increasing body of evidence towards less sedation and more analgesia, with daily sedation holds and spontaneous breathing trials.¹ It is preferable to allow the patient to breathe as soon as possible with triggered ventilation, such as pressure support. Ventilators are becoming increasingly sophisticated to allow a patient to

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Table 2. The Richmond Agitation Sedation Scale - the score ranges from +4 to -5.

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tubes, catheters, aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening >10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice but no eye contact
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unroutable	No response to voice or physical stimulation

This should be repeated regularly and a suggested aim should be for a score of 0 to -1.

synchronise with the ventilator. Deep sedation with or without paralysis is reserved for severe head injury, critical oxygenation (reduces work of breathing and improves chest compliance) and diseases such as tetanus.

DRUGS USED IN SEDATION

The ideal sedative agent should possess the following qualities:

- Both sedative AND analgesic
- Minimal cardiovascular side effects
- Controllable respiratory side effects
- Rapid onset/offset of action
- No accumulation in renal/hepatic dysfunction
- Inactive metabolites
- Cheap
- No interactions with other ICU drugs.

Such a drug does not exist and therefore typically drug combinations are required. Sedative drugs may be given as boluses or infusions. As a rule, infusions for maintenance are preferable, with boluses for procedures, although continuous infusion results in higher cumulative doses.

Benzodiazepines

These are particularly useful because they are anxiolytic, anticonvulsant, amnesic and provide some muscle relaxation in addition to their hypnotic effect. Their effects are mediated by depressing the excitability of the limbic system, via reversible binding at the gamma aminobutyric acid (GABA)-benzodiazepine receptor complex. They have minimal cardiorespiratory depressant effects and are also synergistic with opioids. However rapid bolus doses can cause both hypotension and respiratory arrest. They are all metabolised in the liver. The common drugs used in this class are diazepam, midazolam and lorazepam. Diazepam use has decreased because of concern about its active metabolites (especially nor-desmethyldiazepam), which has a long half

life and can accumulate, particularly in the elderly and patients with hepatic impairment. It is safe to give in single boluses, if given sensibly.

Midazolam is water soluble at pH 4, yet fat soluble at pH 7, thus avoiding the unnecessary solvents required with the other two drugs and hence causing less irritation at the injection site. It has three metabolites, one of which (1-hydroxymidazolam) can accumulate in the critically ill. The normal elimination half life is 2 hours but can be as long as a few days in the long term sedated, critically ill patient.

Lorazepam undergoes glucuronidation and has metabolites that are thought to be inactive. Overdose or accumulation can be reversed by flumazenil, the benzodiazepine receptor antagonist. It should be given in small aliquots as large doses can precipitate seizures. It has a half life of only 1 hour so may need to be given as an infusion. There is wide inter-patient variability in the potency, efficacy and pharmacokinetics of benzodiazepines, so the dose must be titrated to the level of sedation.

After long term administration the dose should be reduced gradually or a lower dose reinstated if there is withdrawal (symptoms include insomnia, anxiety, dysphoria and sweating.)

Propofol (2,6-diisopropylphenol)

The mode of action is via the GABA receptor, but at a different site to the benzodiazepines. It was first developed as an intravenous anaesthetic agent and has a rapid onset of action yet, because it is metabolised rapidly both hepatically and extra-hepatically, it is ideal for continuous infusion. Recovery usually occurs within 10 minutes but it can accumulate with prolonged use, particularly in the obese patient. It is solubilised as an emulsion and the formulation can cause thrombophlebitis and pain, so ideally it should be infused via a large or central vein. Prolonged infusions can lead to increased triglyceride and cholesterol levels and its use is not licensed in children because of associated deaths attributable to this fat load. A theoretical maximum recommended dose is thus $4\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ to avoid 'propofol infusion syndrome', a rare syndrome leading to cardiac failure, rhabdomyolysis, metabolic acidaemia and renal failure. It is often fatal, treatment is supportive but early recognition reduces mortality.

Disadvantages also include cardiorespiratory depression, particularly in the elderly, septic or hypovolaemic patient. Infusions may cause the urine to turn green.

Ketamine

Ketamine acts at the N-methyl-D-aspartate (NMDA) receptor. In sub-anaesthetic doses ketamine is sedative and also analgesic. However it is generally not used because of the rise in blood pressure, ICP and pulse rate that may result. It also causes hallucinations but these can be avoided if administered concomitantly with a benzodiazepine. It appears not to accumulate and sometimes has a role in severe asthma given its bronchodilatory properties.

Etomidate

Historically was used in ICU as an infusion but is now no longer used as it has been shown to cause adrenal suppression, even after a single dose.

Barbituates

These, for example thiopentone, have been used, especially in the management of patients with head injuries and seizure disorders. They cause significant cardiovascular depression and accumulate during infusions leading to prolonged recovery times. Thiopentone is still used occasionally in severely raised ICP to induce a 'barbituate coma', and in intractable seizure activity. Its effect can be titrated using EEG burst suppression.

Butyrophenones and phenothiazines

Strictly these are classed as major tranquillizers but they remain useful in ICU, particularly in agitated/delirious patients.

A 'sliding scale' of haloperidol may be particularly useful in a patient with delirium to promote calmness i.e. increasing doses if no effect after 15 minutes until the desired response is achieved. Haloperidol in particular causes minimal respiratory depression and has less alpha blocking tendency than chlorpromazine and hence less hypotension. Other side effects include prolongation of the QT interval (caution when given with erythromycin), extrapyramidal effects or neuroleptic malignant syndrome.

Clonidine

This is the most well known of the alpha-2 agonists but also has alpha-1 agonistic properties. A more specific agonist is dexmedetomidine but this is expensive and rarely available at present. It is particularly useful in patients with sympathetic overactivity, such as alcohol withdrawal and tetanus, as it inhibits catecholamine release. It is also synergistic with opioids and acts at the spinal cord to inhibit nociceptive inputs, thus imparting analgesia. It is contraindicated in hypovolaemia and can cause hypotension, bradycardia and dry mouth.

Chlormethiazole

This is a vitamin B derivative widely used for treatment of delirium tremens. It is not a respiratory depressant and is an anticonvulsant.

Chloral hydrate

This is used in paediatric intensive care as an adjunct, usually to a

benzodiazepine such as midazolam. It is metabolised in the liver to the active compound trichloroethanol. Metabolites can accumulate in renal dysfunction.

Volatile agents

Isoflurane has been used in concentrations of up to 0.6% and produces good long term sedation with minimal cardiorespiratory side effects and yet rapid awakening. Scavenging and pollution are a problem as is incorporating the vaporiser into the ventilator. Free fluoride ions from metabolised methoxyfluorane can cause renal failure. More recently desflurane has been shown to be effective in sedation with rapid offset of effects.

DRUGS USED FOR ANALGESIA (in combination with sedation)

Opioids are the mainstay of treatment and possess sedative, antitussive (cough suppressant) and hypnotic effects, besides the obvious analgesic effects. They work at the opioid receptors, reclassified in the late 80's to OP1 (old delta), OP2 (old kappa), OP3 (old mu). Most of the recognised effects are mediated via the OP3 receptor. Undesirable effects include gastrointestinal stasis and respiratory depression. Newer opioids have fewer side effects and accumulate less. It is equally important however to remember other analgesic techniques such as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and regional techniques (e.g. epidural infusions).

Morphine

This is a commonly used drug. All other opioids are measured against morphine, although some newer agents have specific advantages. The dose required for analgesia is very variable and it can be delivered as intermittent boluses (problems with peak and trough effects, but less accumulation) or as a continuous infusion.

Morphine is metabolised mostly in the liver to two main products, morphine-3-glucuronide and morphine-6-glucuronide (M-6-G). Both are excreted renally and accumulate in renal dysfunction. The M-6-G metabolite also has independent long lasting, sedative activity. Morphine has minimal cardiovascular side effects, unless given as a large bolus to hypovolaemic patients or secondary to histamine release. It can be used in renal failure as long as the dosing interval is increased or the infusion rate reduced. Normal duration of action after a single dose is about 2 hours. Care should be taken, as with all opioids, in hepatic failure.

Fentanyl

Fentanyl is a potent synthetic opioid. It is presented as a short acting opioid, with a rapid onset. After prolonged infusion the duration of action approaches that of morphine, although it does not accumulate in renal failure. It does not cause histamine release and is suitable for analgesia in the haemodynamically unstable patient.

Alfentanil

Alfentanil is one of the newer synthetic opioids and has an onset of action about five times faster than fentanyl, due to the small volume of distribution, but is less lipid soluble so is not prone to accumulation. The duration of action is about a third that of fentanyl and it too

is safe in renal failure. It has minimal cardiovascular effects and is a potent antitussive agent.

Remifentanil

Remifentanil possesses many of the qualities desired of the ideal ICU analgesic and sedative agent. Remifentanil is an ultra short acting opioid metabolised by non-specific tissue and blood esterases. It has a rapid onset of action and does not accumulate after infusion even in organ dysfunction. It enables predictable recovery, facilitating patient interaction and assessment and therefore enables a shorter weaning time and potentially a reduction in the time spent on mechanical ventilation.^{2,3} Many claim that remifentanil could help control ICU costs, by reducing the time spent in ICU.^{2,3} It is however very expensive and each intensive care unit would need to determine its own cost saving analysis.

DRUGS USED FOR MUSCULAR RELAXATION

In some patients muscle relaxation may be needed in addition to sedation and analgesia. Such indications include:

- Early resuscitation (including intubation)
- Refractory hypoxaemia e.g. ARDS - will decrease oxygen consumption and optimise chest wall compliance
- Raised intracranial pressure - stops coughing and patients resisting ventilation
- Tetanus
- During patient transfer
- To allow inverse ratio/prone ventilation

It is vital to remember that relaxants have no effect on conscious level or comfort and should be avoided if possible. There are no standard clinical techniques to monitor conscious level in the paralysed patient so it is necessary to give generous doses of sedative drugs. In the UK, use of relaxants has fallen from about 90% of patients in the 80s to 10% of patients in the 90s.

Some relaxants used in anaesthesia are less suitable for use in the ICU. Suxamethonium is predominantly used during emergency tracheal intubation, but the resultant rise in serum potassium must be expected which makes it inappropriate for use in cases of renal failure. Excessive potassium release also occurs after 48hrs in extensive burns and spinal cord injury.

Pancuronium is long acting, but it may cause tachycardia and accumulates in renal failure. Vecuronium is an analogue of the aminosteroid pancuronium, but causes minimal cardiovascular side effects. It is suitable for intubation and infusion. Atracurium is a benzyloquinolinium and is metabolised by ester hydrolysis and Hoffman (spontaneous) elimination. Its metabolites are inactive and it doesn't accumulate in renal or hepatic dysfunction. Histamine release occasionally occurs with boluses, but recovery occurs predictably within one hour, regardless of duration of infusion. The intubating dose is $0.5\text{mg}\cdot\text{kg}^{-1}$, infusion $4\text{-}12\text{mcg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$.

Monitoring should ideally be performed using a nerve stimulator (e.g. train-of-four count). Clinical monitoring such as cardiovascular reflexes to noxious stimuli should also be observed. Full 'surgical' relaxation may not be necessary.

Problems with relaxants

1. The patient may receive inadequate sedation and be aware. This can be checked by withdrawing muscle relaxants for a time to allow recovery of muscular function and assessment of sedation levels.
2. Accumulation (especially with aminosteroids) in acute renal failure.
3. Critical illness polyneuropathy and myopathy (esp. if steroids also used).
4. Tendency to over-sedate.
5. Enhanced paralysis from other common ICU problems such as hypokalaemia, aminoglycoside antibiotics, hypophosphataemia.

RECOMMENDATIONS

Non-ventilated patients

Pain should be titrated with opioids to the desired level. Cooperative patients may benefit from patient-controlled analgesia. Regional techniques in selected patients are ideal. Always use simple analgesics in combination, and consider other causes for pain e.g. full bladder.

Postoperative/short-term mechanical ventilation

If available, then a combination of remifentanil or alfentanil and propofol allows a rapid wake up, but is only beneficial if used for less than 72 hours. Sometimes the high costs of short acting agents can be offset against the higher hidden costs of delayed weaning/ prolonged ICU stay. Alternatively a benzodiazepine/morphine combination can be used.

Long term mechanical ventilation

There is little logic in using very short acting substances in these cases. Kress et al performed a randomised controlled trial that showed that daily interruption of sedative infusions reduced the duration of mechanical ventilation and intensive care stay in the critically ill. Infusions were interrupted until the patient was awake and could follow instructions or became agitated or uncomfortable.⁴

Morphine plus midazolam or propofol were the agents used and the daily wake up procedure helped prevent excessive administration of these agents. A policy of interruption of sedation should be considered in all patients every day.

In some centres a newer technique of sedation is employed - patient controlled sedation - using increments of propofol, as opposed to morphine/fentanyl that is usually used in patient controlled analgesia. This is a very effective technique in the awake, orientated patient. It minimises nursing time, is inherently safe and gives control to the patient. However, it does require specialised, expensive equipment and is unsuitable for the majority of ICU patients.

SUMMARY

Good sedation can be achieved with a simple combinations of drugs. Over sedation is widespread but use of sedation scoring and adequate nursing staff provision should reduce its frequency. Use of sedative drugs should be reviewed daily, just as we assess use of vasopressors and inotropes. Sedation should be prescribed on an individual basis as requirements vary widely and sometimes analgesia alone may suffice.

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APPENDIX - DRUG DOSE COMMENTS

Drug	Dose	Comments
Propofol	0.5-4mg.kg ⁻¹ .h ⁻¹ Bolus 5-50mg	Not licensed for children for ICU sedation Care in hypovolaemia. Rapid recovery
Midazolam	0.5-10mg.h ⁻¹ Bolus 2-4mg Paeds: 5mg.kg ⁻¹ dissolved in 50ml (1ml.h ⁻¹ = 100mcg.kg ⁻¹ .h ⁻¹) Infuse 1-2ml.h ⁻¹	Cheap. CVS stable. Good for prolonged sedation. May result in very prolonged sedation, particularly in the elderly
Morphine	1-5mg.h ⁻¹ . Bolus 2-5mg Paeds: 1mg.kg ⁻¹ added to 50ml 0.9% saline. Infuse at 1-4ml.h ⁻¹ (1ml.h ⁻¹ = 20mcg.kg ⁻¹ .h ⁻¹)	Accumulates esp. in renal failure. Histamine release
Fentanyl	1-3mcg.kg ⁻¹ .hr ⁻¹ Bolus 50-100mcg Paeds: 50mcg.ml ⁻¹ Infuse 0.3 - 0.5ml.h ⁻¹ (= 5-10mcg.kg ⁻¹ .h ⁻¹)	Less accumulation in renal failure Less histamine release
Alfentanil	1-5mg.h ⁻¹ Bolus 0.5-1mg to supplement	Short acting and little accumulation Expensive
Haloperidol	5-10mg bolus	Minimal effect on respiration
Ketamine	Bolus 1-2mg.kg ⁻¹ then infuse 10-45mcg.kg ⁻¹ .min ⁻¹	Beneficial in severe asthma (bronchodilator) CVS stable Emergence delirium
Thiopentone	50-250mg.h ⁻¹	Use in epilepsy/raised ICP Very prolonged wake up
Remifentanyl	Start at 0.1-0.15mcg.kg ⁻¹ .min ⁻¹ titrate to range of 0.05-0.6mcg.kg ⁻¹ .min ⁻¹	Rapid onset and offset, does not accumulate in organ failure. Expensive. Can cause bradycardia

Nutrition in the critically ill

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INTRODUCTION

Nutrition is an intrinsic part of critical care and evidence about effectiveness, timing, composition and route of administration has evolved considerably within the last 10-20 years. The understanding of the molecular and biological effects of nutrients in maintaining homeostasis in sick patients has contributed significantly.

Diets are composed of nutrients: *macronutrients* (protein, fats, carbohydrates and alcohol) and *micronutrients* (vitamins, minerals and trace elements). Malnutrition is caused by an imbalance (deficiency or excess) of energy, protein and other nutrients and leads typically to adverse effects on tissue/body form, function and clinical outcome. Undernutrition may be due to failure of food supply or intake, deliberate starvation or an illness and is characterised by weight loss and changes in body composition, with a relative increase in extracellular fluid volume.

Malnutrition/undernutrition is common in hospital patients worldwide and is present in over 40% of patients on admission in the UK.¹ Malnutrition is often unrecognized and is an independent risk factor for increased morbidity, increased length of hospital stay, delayed recovery, higher readmission rates, lower quality of life as well as increased hospital costs and higher mortality.²

Sepsis, trauma and major surgery cause complex metabolic and inflammatory reactions in the body. The metabolic picture of the stress response is characterized by catabolism, hypermetabolism, hyperglycaemia and increased lipolysis. This is caused by increased output of hormones that are counter-regulatory to insulin (catecholamines, cortisol, glucagon, growth hormone) and specific cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor (TNF). Skeletal muscle is used as an energy source.

DIAGNOSIS OF MALNUTRITION

Accurate estimation of the nutritional requirements in critically ill patients is challenging and traditional nutritional assessment tools have not been validated in critical care. Examples are:

Anthropometric measurements (e.g. skin fold thickness, mid-arm circumference). These are unreliable due to weight gain/loss, fluid shifts and oedema.

Biochemical tests

These have limitations:

- Albumin falls as part of the acute phase response,
- Haemoglobin may be affected by disease process, haemorrhage, transfusion, haemolysis, bone marrow suppression,

Body Mass Index

$$\text{BMI} = \text{mass (kg)} / \text{height (m)}^2$$

Although low BMI is a predictor of higher mortality in ICU, acute changes do not accurately reflect nutritional status.

General observation, a targeted history and examination of a patient for malnutrition is better than any specific test. Assessment should include evaluation of weight loss and previous nutrient intake before admission, disease severity, co-morbid conditions and gastrointestinal function.³ One structured method that is widely accepted is the **Subjective Global Assessment (SGA)** (Table 1). As the name implies this is a subjective tool, however it is reproducible and correlates with mortality in a variety of conditions.⁴ Assessment of nutritional status should also be used to identify patients at risk of re-feeding syndrome, which is described later in this article.

DOES NUTRITIONAL SUPPORT AFFECT PROGNOSIS?

The main goal in initiating nutritional therapy is to prevent or treat malnutrition/undernutrition among patients unable to sustain sufficient oral intake. The patients who are likely to benefit most are those who are already malnourished, who would otherwise undergo a long period of starvation, and who are therefore less able to tolerate further catabolism. However, for many clinical conditions, it remains unclear whether nutritional support is able to counteract the negative effects of malnutrition, or if the underlying disease itself renders substrate supplementation insufficient.

Summary

The aim of this article is to give an overview of the nutritional aspects in critically ill patients and summarise the latest guidelines and recommendations in establishing adequate nutritional support.

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Table 1.**Subjective Global Assessment***History*

1	Weight change	Both chronic (over 6 months) and acute (over 2 weeks)
2	Changes in food intake	
3	Gastrointestinal symptoms	e.g. nausea, vomiting, diarrhoea and anorexia
4	Functional impairment	

Physical examination looking for:

1	Loss of subcutaneous fat	Looking especially at the chest and triceps
2	Muscle wasting	Temporal region, deltoids and gluteal muscles
3	Oedema	
4	Ascites	

For some conditions, there are disease specific formulae to optimise the patient's nutritional status by managing nutrients, fluid and electrolytes, adjusted to the specific pathophysiological processes.

DOES A SHORT PERIOD OF STARVATION OUTCOME?

Critically ill patients are not a homogenous population and no single study that has evaluated the best timing for initiating nutritional support. There is now improved awareness about complications related to the use of enteral and parenteral nutrition, and the importance of improved control of blood glucose levels and delivery of reduced caloric loads.⁵⁻⁸

The gut is vulnerable to injury, especially ischemia and reperfusion, and also acts as an important immune organ due to its barrier function and reservoir of immune cells. However it contains potentially harmful microorganisms and it has often been postulated as 'the motor of multiple organ failure', by a process of bacterial translocation from the lumen to the blood stream.

The use of parenteral nutrition (PN) in ICU has declined markedly, in light of evidence that enteral nutrition (EN) may be generally superior in terms of clinical outcomes.⁶⁻⁸ After reviewing all relevant studies, the European⁹ and Canadian¹⁰ clinical guidelines recommend starting enteral nutrition when the patient is adequately fluid resuscitated, within 24 hours or 24-48 hours respectively after admission to ICU. Early feeding provides a safety margin against failed attempts to establish feeding, it may reduce disease severity, diminish complications, decrease length of stay in the ICU and improve patient outcome.

WHAT ARE THE NUTRITIONAL REQUIREMENTS IN CRITICAL ILLNESS?

A careful balance of macronutrients (protein, lipid and carbohydrate) provides energy requirements, whilst micronutrients (vitamins and

minerals) are required in very small amounts to maintain health but not to provide energy.

Macronutrients

The variability in resting energy expenditure makes it very difficult to predict caloric requirements. Both underfeeding and overfeeding can be harmful. Resting energy expenditure (REE) can be measured using indirect calorimetry and calculated using the Oxford equation,¹¹ which has now largely replaced the abbreviated Weir equation and the Harris Benedict equation. The Oxford equation gives lower estimated basal metabolic rate (BMR) values than its alternatives (including the Schofield equation, used in the WHO recommendations). There is little population data from China and Africa, so calculations cannot be validated for these populations.

These equations estimate BMR in afebrile healthy individuals and therefore needs to be modified in the following circumstances:

<i>Fever</i>	Increase by 10% for each 1°C above 37°C (up to max of 40°C).
<i>Sepsis</i>	Increase by 9% regardless of temperature
<i>Surgery</i>	Increase by 6% if patient has had surgery or trauma
<i>Burns</i>	Increase by 100% if any size over 30% (or use Toronto formula).

These factors are additive, so the energy requirements for a 33-year-old man (height 1.80m, weight 75kg), admitted after a laparotomy for a ruptured appendix and sepsis (temperature 39°C), work out to approximately 2460kcal.kg⁻¹.day⁻¹ as follows:

25kcal.kg⁻¹.day⁻¹ is generally recommended for most acutely ill patients. Protein requirements are determined and the remaining calories divided between glucose and lipid. During recovery the aim should be to provide values of 25-30kcal.kg⁻¹.day⁻¹ to support the process of anabolic reconstitution.^{12,13}

BMR	=	(13.75 x 75kg) + (5 x 180cm) – (6.78 x 33 years) + 66
	=	1773.5kcal.day ⁻¹
REE	=	1773.5 x 1.2 (add 20% for temperature) x 1.09 (for sepsis) x 1.06 (surgery)
	=	2458.9kcal.day ⁻¹ (i.e. roughly 2460 kcal.day ⁻¹)

Failure to deliver at least 25% of calculated requirements is associated with worse outcome, however it is better to underfeed rather than attempt to match a calculated energy requirement, particular in sepsis and trauma.¹⁴ The National Institute for Clinical Excellence (UK) has recommended that parenteral nutrition should be limited to a maximum of 50% or the calculated requirements for the first 48 hours after initiation.¹⁵

Predictive equations should be used with caution, as they provide a less accurate measure of energy requirement than indirect calorimetry. They are even more problematic in the obese patients. For all classes of obesity (BMI above 30), the goal of an enteral nutrition regime should not exceed 60-70% of target energy requirement or 11-14kcal.kg⁻¹ actual body weight per day (or 22-25% kcal.kg⁻¹ ideal body weight per day).¹⁶

The proportion of a feed made up by protein is sometimes expressed as a calorie: nitrogen ratio. 6.25g of protein contains 1g of nitrogen. The ratio is then calories (kcal) divided by nitrogen (g). Recommended calorie: nitrogen ratios are around 100:1 which will be achieved using the above figures. The optimal ratio for lipid:carbohydrate is not known.

<i>Protein</i>	<ul style="list-style-type: none"> Provides 4kcal.g⁻¹ Around 1.5g.kg⁻¹.day⁻¹ (range 1.2 to 2g.kg⁻¹.day⁻¹ for ICU patients) Use 2g.kg⁻¹.day⁻¹ if severely catabolic e.g. severe sepsis, burns or trauma Should be a mixture of essential and non essential amino acids
<i>Lipid</i>	<ul style="list-style-type: none"> Provides 9.3kcal.g⁻¹ Calories from lipid should be limited to 40% of total calories
<i>Carbohydrate</i>	<ul style="list-style-type: none"> Provides 3.75kcal.g⁻¹ in vivo 3 to 4g.kg⁻¹.day⁻¹ Give the remaining energy requirements as carbohydrate

Micronutrients

Vitamins are organic compounds that usually act as cofactors for enzymes involved in metabolic pathways. Trace elements are ions that act as cofactors for enzymes or as structurally integral parts of enzymes and are often involved in electron transfer.

Effects of micronutrient deficiency

<i>Zinc</i>	Impaired T-cell function, reduced antioxidant defence, increased susceptibility to infection.
<i>Copper</i>	Reduced antioxidant defence, reduced tissue repair, increased susceptibility to infection.
<i>Selenium</i>	Reduced antioxidant defence, reduced tissue repair, increased susceptibility to infection
<i>Thiamine</i>	Impaired carbohydrate metabolism, neurological deficits
<i>Riboflavin and Folic acid</i>	Impaired immune function

Water and electrolytes

Water and electrolyte requirements vary between patients and regular assessment of hydration and correction of electrolytes is fundamental in critical care. Average daily requirements are:

Water	30ml.kg ⁻¹
Na ⁺	1.0 – 2.0mmol.kg ⁻¹
K ⁺	0.7 – 1.0mmol.kg ⁻¹
Ca ²⁺	0.1mmol.kg ⁻¹
Mg ²⁺	0.1mmol.kg ⁻¹
Cl ⁻	1.0 – 2.0mmol.kg ⁻¹
PO ₄ ²⁻	0.4mmol.kg ⁻¹

WHAT IS THE PREFERRED FEEDING METHOD IN A GIVEN SITUATION?

Any nutrition support, alone or in combination, needs to be commenced if the patient is already malnourished or at risk of malnutrition. Patients at risk include those who:

- have eaten little or nothing for more than 5 days and/or are likely to eat little or nothing for the next 5 days or longer, or
- have a poor absorptive capacity, and/or
- have high nutrient losses and/or
- have increased nutritional needs from causes such as catabolism.¹⁴

Potential swallowing problems should be taken into account.

Oral feeding is the optimal route of nutritional support. However most ICU patients are incapable or intolerant of oral diet and are therefore fed enterally or parenterally. Enteral nutrition is recommended over parenteral nutrition by practice guidelines in Europe and North America. This is based on numerous trials involving a variety of critically ill patients, including trauma, burns, head injury, major surgery and acute pancreatitis.^{7,16}

Parenteral nutrition is indicated where enteral nutrition is contraindicated, for example in intestinal obstruction/perforation, non-functioning gut, gastrointestinal fistula, prolonged ileus, oesophageal/gastric surgery, perforation or malignancy.

TYPES OF NUTRITIONAL SUPPORT

Food fortification

This is the process of adding micronutrients to food.

Enteral nutrition

This can be either oral supplement or tube feeding:

<i>Tube feeding</i>	
Nasogastric	Most commonly used, depends on gastric emptying Allows use of hypertonic feed, high feeding rates and bolus feeding
Orogastric	Not suitable for awake patients In intubated patients to reduce sinusitis
Enterostomy (gastrostomy or jejunostomy)	Better for patients who require support for > 4 weeks
Post-pyloric feeding (nasojejunal or jejunostomy)	Avoids problem of gastroparesis Recommended if high risk of aspiration In major intra-abdominal surgery Intolerance of gastric feeding Acute pancreatitis

Parenteral nutrition (via either peripheral or central vein)

- *Peripheral access*: low osmolarity fluids only (<850mOsm.L⁻¹). Limited by large volumes needed to provide calories.
- *Central access*: solutions usually hypertonic.

ENTERAL NUTRITION

Enteral nutrition should be started within the first 24-48 hours of admission. It is also important to try to achieve the estimated caloric target within 48-72 hours. The use of enteral feeding protocols increases the overall percentage of goal calories provided since they avoid slow initiation and premature cessation of feed. An example is shown in Figure 1. If caloric and protein needs cannot be met by enteral feeding alone, parenteral feeding or a combination of both needs to be considered.

Important steps to ensure adequate enteral nutrition:

1. Confirm tube position (clinically and radiographically).
2. Secure tube well and check site regularly for potential tube dislodgment.
3. Start feeding early.
4. Aspirate regularly (4 hourly) and accept gastric residual volumes of 200-250ml. Adjust feeding rates accordingly. Once feeding is established this can be stopped.
5. Minimise aspiration risk via the following:
 - Patient should be head-up tilt at least 30°.
 - Avoid bolus feeds.
 - Use prokinetics early: metoclopramide 10mg IV 8 hourly +/- erythromycin 75mg IV 6 hourly.
 - Consider switch to post-pyloric tube feed.
6. Development of diarrhoea associated with tube feeding needs further evaluation.

Which enteral feed to use?

There are many commercially prepared feeds on the market, although these may not be available or affordable in many settings. The choice of feed will be influenced by the patient's requirements and underlying pathology. Most come as ready to use liquid microbial free preparations that contain all the necessary macro- and micronutrients as well as fluid and fibre. They are usually nutritionally complete within a specific volume, but expert dietetic advice should be sought. A ready to use standard feed will usually contain 1kcal and 0.04g protein per ml, but many other types of enteral feed preparations are available with differing energy:protein ratios and types of fat or protein.

The following feeds are generally used:

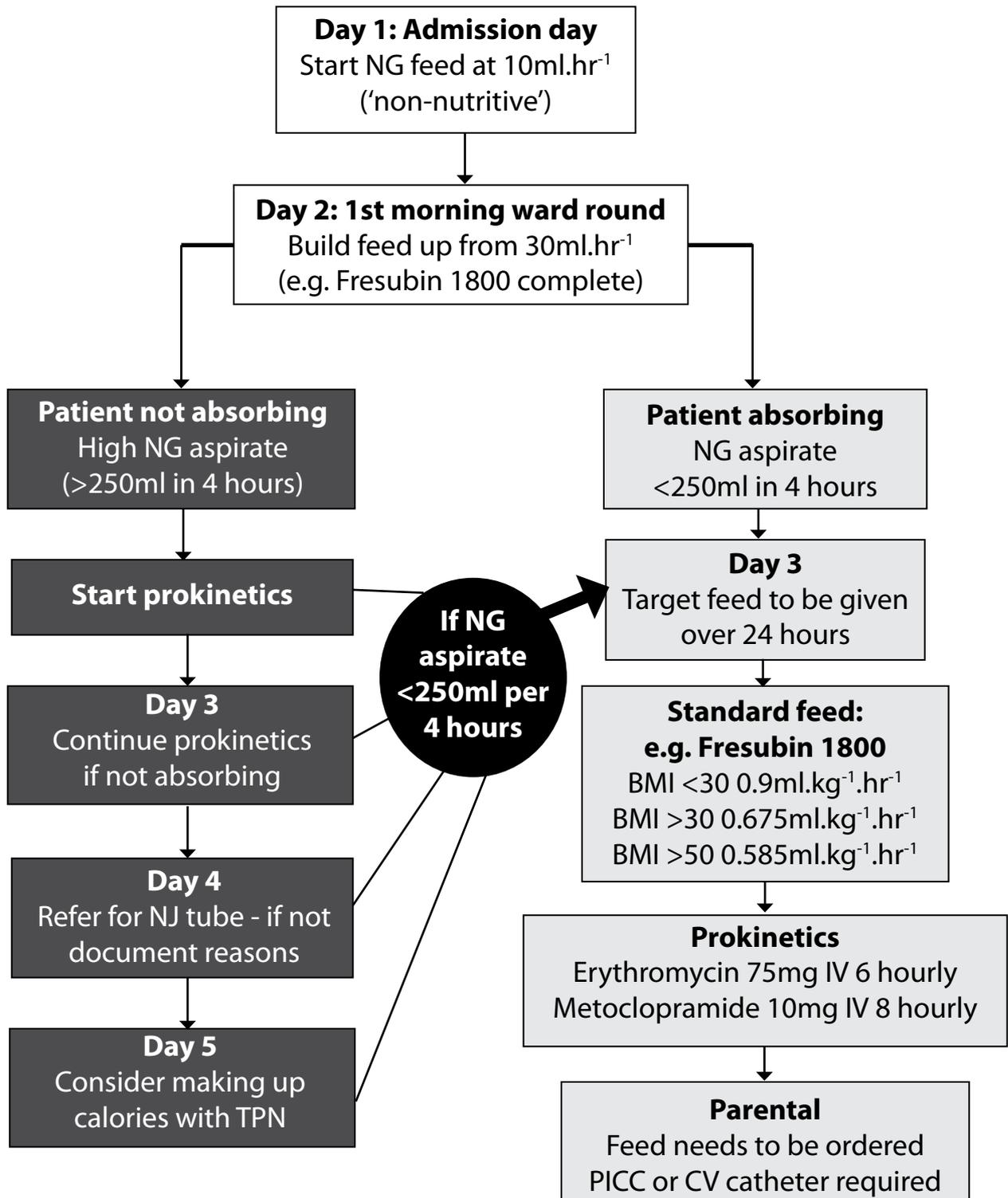
Hospital prepared feeds

Recipes vary according to country and available ingredients, but can include hard-boiled eggs, milk powder, soya, maize oil, rice, squashes, flour, sugar and fruit. These hospital-prepared feeds are much cheaper than commercially prepared feeds, but can block tubes and some recipes have been shown to give unpredictable levels of both macro- and micronutrients. In addition, they may contain contaminated ingredients and are not sterile. As a result, they must not be used for post-pyloric feeding or in patients with achlorhydria (insufficient gastric acid production). These feeds should only be used where commercial feeds are either not available or not affordable.

Polymeric preparations

These contain intact proteins, fats and carbohydrates (which require digestion prior to absorption), in addition to electrolytes, trace elements, vitamins and fibre. Fibre is broken down by colonic bacteria to produce a variety of compounds including butyric acid, an energy substrate for colonic enterocytes. These feeds tend to be lactose-free as lactose intolerance is common in ill patients. The different preparations vary in their osmolality, calorie to nitrogen ratio and carbohydrate to lipid ratio and can provide between 0.5 and 2kcal.ml⁻¹ although

ICU Enteral Feeding Protocol



Stop feed and aspirate stomach immediately before airway procedures or going to theatre.
Stop enteral nutrition on 2 hours prior to and post administration of enteral phenytoin.

Figure 1. An example of an enteral feeding algorithm. Reproduced courtesy of Charlotte Battle, Chris Day, Sheena Hubble, Beth Thompson (Royal Devon and Exeter NHS Foundation Trust, UK).

most are around 1kcal.ml⁻¹. Commonly used ingredients include the protein casein (from milk), soy protein, maize and soya oils and the carbohydrate maltodextrin. The vast majority of patients can be given standard polymeric feeds.

Elemental (pre-digested) preparations

These preparations contain the macronutrients in a readily absorbable form (i.e. proteins as peptides or amino acids, lipids as medium chain triglycerides and carbohydrates as mono- and disaccharides). They are expensive and only indicated for patients with severe malabsorption or pancreatic insufficiency. In patients with a short gut and no colon their high osmolality can cause excessive water movement and higher stoma losses.

Disease-specific formulae

These are usually polymeric and include feeds designed for:

<i>Liver disease</i>	Low sodium and altered amino acid content (to reduce encephalopathy).
<i>Renal disease</i>	Low phosphate and potassium. 2kcal.ml ⁻¹ rather than standard 1kcal.ml ⁻¹ to reduce volume.
<i>Respiratory disease</i>	High fat content (reduces CO ₂ production).
<i>Diarrhoea</i>	Reduce fibre content.
<i>Hypernatremia</i>	Low sodium.
<i>Catabolic state</i>	High energy and high protein if lower volume feed needed.

Specific additives

Critical illness and injury are characterized by oxidative stress and excessive inflammation. There is a lot of interest in feeding formulas with specific pharmaconutrients that can help to moderate tissue damage and hold inflammation.

Antioxidants (vitamins A, C, E and selenium) stabilize free radicals in cells and hence reducing their potential for tissue damage. Where they can be sourced, a combination of antioxidant vitamins and trace minerals (specifically including selenium) should be provided to all critically ill patients. Dietary fish oils (mainly omega-3-fatty acids) are thought to blunt excessive inflammatory processes. Other immune modulating enteral nutrients such as arginine, glutamine and possible nucleotides have shown to lower the risks of infectious complications in certain patient groups, since they are thought to be depleted by stress of critical illness and injury.¹⁷ Both the Canadian and European guidelines support the use of glutamine in burn and trauma patients.

In general these feeds tend to be more expensive and there is currently not enough data or a consensus to support their role in critically ill patients.

PARENTERAL NUTRITION

Parenteral feeding is the intravenous administration of nutrients. This may be supplemental to oral or tube feeding, or it may provide the only source of nutrition as total parenteral nutrition (TPN).

The only absolute indication for parenteral nutrition (PN) is gastrointestinal failure. All efforts to improve tolerance of enteral feeding such as the use of pro-kinetic agents and/or a post-pyloric feeding tube should be tried before starting PN. Patients receiving less than 25% of their predicted needs are at increased risk of sepsis and those who are intolerant of enteral nutrition, despite all attempts to improve this, should be considered for parenteral supplementation.

How much parenteral nutrition should critically ill patients receive?

During acute illness, the aim should be to provide energy as close as possible to estimated or measured energy expenditure in order to decrease the negative energy balance. In the absence of indirect calorimetry, ICU patients should receive 25kcal.kg⁻¹.day⁻¹ increasing to target levels over the next 2–3 days.

PN can be given as separate components but is more commonly given as a sterile emulsion of water, protein, lipid, carbohydrate, electrolytes, vitamins and trace elements according to the recommendations discussed earlier regarding nutritional requirements. Standard formulations require thorough mixing before infusion. The electrolyte concentration can be altered for each patient and additional trace elements and vitamins may be added.

Protein

Protein is given as amino acids and needs to include essential amino acids. It should also ideally include most of the non-essential amino acids. Critical illness results in a relative deficiency of glutamine. In a number of small studies IV glutamine has been shown to improve survival and infection rates in patients on PN, particularly in trauma and burns patients. Glutamine supplementation is likely to be beneficial in patients receiving TPN for more than 10 days.

Lipid

This is commonly given as Intralipid®, an emulsion made from soya with chylomicron-sized particles. It provides a source of essential fatty acids, (linolenic acid, an omega-3 fatty acid and linoleic acid, an omega-6 fatty acid) and is a vehicle for delivery of fat-soluble vitamins. Lipid preparations are expensive and it is possible to give parenteral nutrition with low levels of lipid; giving 6% of total energy requirement as lipid is enough to avoid essential fatty acid deficiency.

If no parenteral lipid is given, vegetable oil should be massaged into the patient's limbs once a day; lipid is absorbed through the skin and may prevent or delay essential fatty acid deficiency, although requirements in critical illness may be too high for this to be sufficient. Watch for signs of deficiency: dry, scaly skin, with or without hair loss, and abnormal liver function tests. Most vegetable oils can be used (safflower, corn, soya, groundnut or sunflower) but not palm oil, as it contains virtually no linolenic acid. Fat-soluble vitamins will need to be given separately.

Carbohydrate

Carbohydrate is given as glucose. The minimal amount of carbohydrate required is about 2g.kg⁻¹ glucose per day. It should provide approx 60% of non-protein calories.

Electrolytes and micronutrients

Critically ill patients are prone to fluid and sodium overload, and renal dysfunction is frequent. The exact electrolyte requirement needs to be determined by close plasma electrolyte monitoring and should not be a fixed element of parenteral nutrition prescription.

Patients with sepsis have been shown to have large vitamin A losses in their urine, burns patients lose selenium, zinc and copper via their exudates and trauma patients lose selenium and zinc through their drains. Selenium impairs the role of glutathione peroxidase as a free radical scavenger and selenium supplementation may be helpful in general ICU patients.

Monitoring

The following schedule is recommended for all patients receiving parenteral nutrition:

- Baseline level for FBC, B₁₂ and folate, electrolytes and creatinine, magnesium, phosphate, calcium and glucose; LFTs, albumin, prealbumin, C-reactive peptide (CRP), zinc and copper.
- Blood glucose every 4-6 hours.
- Daily FBC, electrolytes and creatinine. Magnesium and phosphate should be measured if there is a high risk of refeeding syndrome.
- Liver function tests, lipid profile, calcium, albumin, prealbumin, transferrin and CRP once/twice weekly.
- Zinc, iron, selenium and copper levels every 2-4 weeks.
- Manganese and 25-OH-vitamin D levels 3-6 monthly.

The frequency of these tests is dictated by local availability and can be reduced once the patient's condition is stable.

When should parenteral nutrition be initiated?

Current guidelines regarding the timing differ.¹⁸ For patients who cannot be enterally fed, the European guidelines recommend starting PN within 24 to 48 hours, if the patient is not expected to be on oral nutrition within 3 days.¹⁸ US guidelines recommend standard care (IV fluids) first and PN initiated only after 7 days in well-nourished patients.¹⁶ Both guidelines recommend starting PN within 24 hours of admission in patients who are malnourished.

Should we combine enteral and parenteral feeding?

When enteral feeding alone is inadequate, experts have advocated using PN and EN together to meet the energy and protein targets.¹⁸ Clinical evidence for combined feeding and when to start additional PN remains unclear. Two recent randomised trials tried to clarify this subject, but the evidence remains controversial. The key conclusions are that supplemental parenteral nutrition should not be started on admission, but subsequently may improve outcome in patients with a high mortality risk.^{20,21}

COMPLICATIONS OF NUTRITIONAL SUPPORT

Re-feeding syndrome

Patients who are severely malnourished, or have undergone a

significant period of starvation, are at risk of refeeding syndrome during the first few days of nutritional support, regardless of the route of administration. Starvation causes a loss of intracellular electrolytes secondary to leakage and reduced transmembrane pumping. Intracellular stores can become severely depleted even though serum levels may be normal. When carbohydrate is available again there is an insulin-dependent influx of electrolytes into the cells, which can result in rapid and severe drops in serum levels of phosphate, magnesium, potassium and calcium. There is also a risk of lactate acidosis secondary to conversion of pyruvate. The clinical features include oedema, weakness, diarrhoea, respiratory failure, cardiac failure, arrhythmias, seizures, coma and death.

Risk factors for re-feeding syndrome

Two or more of the following:

- BMI less than 18.5 kg.m⁻²
- Unintentional weight loss >10% within last 3-6 months (>15%)
- Little or no nutritional intake for more than 5 days
- History of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics
- Critically low levels of phosphate, potassium and magnesium.

At risk patients should be identified and feeding must be introduced slowly, starting with 5-10kcal.kg⁻¹.day⁻¹ and gradually increasing after 4 to 7 days. Circulatory volume must be restored and the above electrolytes should be generously supplemented at the same time as starting feeding and should be closely monitored. Thiamine and other B vitamins should also be given intravenously before starting feeding and then daily for at least three days.

Overfeeding

Deliberate overfeeding, in an attempt to reverse catabolism, is ineffective and is associated with a poor outcome. Overfeeding causes uraemia, hyperglycaemia, hyperlipidaemia, fatty liver (hepatic steatosis) and hypercapnia (especially with excess carbohydrates), with difficulties in weaning from ventilatory support and fluid overload. It is probable that at least some of the risks of parenteral nutrition are actually related to overfeeding and NICE (UK) recommend that PN should be limited to a maximum of 50% of the requirements for the first 48 hours after initiation.¹⁵

Commencing high levels of feeding shortly after major surgery, in severe sepsis or multiorgan failure can cause insulin resistance and other metabolic problems similar to those of refeeding.

Propofol (either 1% or 2%) is formulated in 10% Intralipid and this must be included in the calculations for nutritional support.

Hyperglycaemia

Hyperglycaemia worsens outcome in the critically ill, and is more commonly caused by insulin resistance secondary to the stress response, than overfeeding.

Strict glucose control, keeping serum glucose levels between 80 and 110mg.dl⁻¹, was associated with reduced sepsis, reduced ICU length of stay and lower hospital mortality when compared to conventional insulin therapy, keeping blood glucose levels <200mg.dl⁻¹.²² The effect was more pronounced in surgical than medical patients. However the recent NICE Sugar trial suggested that moderate control (blood glucose levels between 140 and 180mg.dl⁻¹ [7.8-10mmol.L⁻¹]) might avoid problems of hypoglycaemia and subsequently reduce mortality compared to tighter control.²³

The optimal target range for blood glucose in the critical ill patients remains unclear, but the general consensus is to maintain glucose within the range of 6-10mmol.L⁻¹.

Specific complications of enteral nutrition

The commonest risk with enteral feeding is aspiration of feed causing pneumonitis. The implementation of a combination of measures including feeding protocols, nurse education programmes and good oral hygiene has been shown to decrease the risk of ventilator-associated pneumonia. Diarrhoea can also be a problem but is not an indication to stop feeds. Other causes of diarrhoea need to be excluded but if enteral feeds are the cause then a feed with more fibre can be tried.

<i>Insertion</i>	Mucosal damage, pharyngeal/oesophageal pouch perforation, intracranial insertion, bronchial placement, variceal bleeding
<i>PEG/PEJ insertions</i>	Bleeding, bowel perforation
<i>Post insertion</i>	Discomfort, erosions, fistulae, strictures
<i>Displacement</i>	Tube falls out, bronchial administration of feed
<i>Reflux</i>	Oesophagitis, aspiration, ventilator associated pneumonia
<i>Feed intolerance</i>	Nausea, bloating, pain, diarrhoea
<i>Metabolic</i>	Refeeding syndrome, hyperglycaemia, hypercapnia, fluid overload, electrolyte disturbance

Specific complications of parenteral nutrition

Access related

The insertion and presence of a central venous catheter has inherent risks including pneumothorax, haemothorax, arterial or nerve damage, infection, central vein thrombosis and erosion through the wall of the vein or right atrium.

Infusion related

It is thought that some of the increased risk of sepsis seen in patients receiving parenteral nutrition has actually been the result of overfeeding and uncontrolled hyperglycaemia, rather than due to parenteral nutrition itself. Rebound hypoglycaemia with sudden cessation of PN infusions may occur and regular blood glucose checks are essential. Refeeding syndrome, especially in malnourished patients, has a high morbidity and mortality and the feeding protocol needs to be adjusted as discussed earlier.

Infection is a serious risk and the bags must be sterile and discarded within 24 hours of initiation of use. Sterile precautions must be used for bag changes and the lumen of the central venous line must not be used to take blood or give drugs or fluids (this may also result in precipitation of the emulsion).

Parenteral nutrition also predisposes to hepatobiliary disease including fatty liver, cholestasis and acalculous cholecystitis. Great care must be taken to avoid electrolyte imbalances and micronutrient deficiencies particularly in those requiring nutritional support for prolonged periods. If lipaemia becomes a significant problem the rate of PN can be reduced or the lipid component reduced or removed.

Related to deficiencies

All vitamins and trace element deficiencies can develop. Thiamine deficiencies can cause lactate acidosis, wet or dry beriberi, whilst the lack of vitamin K may predispose to an increase bleeding risk. Patients on renal replacement therapy will need water-soluble vitamins replaced.

SUMMARY

Malnutrition/undernutrition is common and associated with a poor outcome in critical illness. Enteral nutrition is the preferred method of feeding and important in counteracting the catabolic state seen in severe disease states. It should be started during the first 24-48 hours in all patients in whom it is safe to do so, using a standard high protein formula. Total energy intake should be measured or estimated, however 25kcal.kg⁻¹ of usual body weight per day is adequate for most patients. Enteral feeding is not without risks, but these can be significantly reduced with simple measures, and adherence to feeding protocols.

Supplementary parenteral nutrition should be given only to those patients who do not reach their target nutrient intake on enteral nutrition alone. There is no general indication for immune-modulating formulae in patients with severe illness or sepsis. Glutamine should be supplemented in patients suffering from burns or trauma. In all patients receiving nutritional support it is vital to maintain moderate glucose control with insulin therapy. Overfeeding should be avoided.

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Evidence-based medicine in critical care

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Summary

Evidence based medicine (EBM) has an established role in management of critically ill patients. However ICU patients form a highly heterogeneous group and present challenges to the conduct of high quality randomised controlled trials. There are relatively few ICU studies that have stood the test of time, with the findings of the majority refuted and then disproved by subsequent larger studies or meta-analyses. This article describes the steps you should take when reading a study report, in order to decide whether it has been rigorously conducted, whether the results are valid and whether they can be applied to the patients that you see on a daily basis.

INTRODUCTION

Evidence-based medicine is an approach to medical practice in which the clinician integrates the best available clinical evidence from systematic research, with his or her own clinical expertise, to treat the individual patient in front of him. EBM and clinical expertise are not mutually exclusive - without reference to current best evidence, clinical practice will become out of date, while the adoption of an entirely evidence-based approach (if this is possible) risks exposing patients to inappropriate or inapplicable interventions. Conversely, treating patients solely on the basis of sensible and intuitive thinking risks exposing them to interventions which later prove to be harmful in subsequent clinical trials (e.g. intravenous beta agonists for Acute Respiratory Distress Syndrome, ARDS²), or denying patients beneficial therapies which were not previously widely practiced (low tidal volume ventilation for ARDS³). Clearly there is a middle ground to be found.

HIERARCHY OF EVIDENCE AND SOME PITFALLS

When assessing the evidence for a particular intervention there is now a widely accepted hierarchy of quality, with systematic reviews of published literature and meta-analyses seen as the most reliable form of evidence, and expert opinion as the least reliable. However not all randomised controlled trials (RCTs) are equal in quality and applicability.

Several recent high-profile cases of alleged research fraud⁴⁻⁶ should alert readers to the fact that even a peer review process may not be sufficient to detect factitious or fraudulent research. Neither are the results of single

RCTs necessarily reliable - the critical care literature is littered with examples of RCTs of interventions which showed early promise (activated protein C, tight glycaemic control, corticosteroids for septic shock), but where subsequent investigation has dampened early enthusiasm or in some cases entirely refuted initial claims. The dangers of changing practice based on evidence provided by a single trial or author are clear to see, and some experts recommend that two positive RCTs are needed to advise change of practice.

Not all interventions have a good evidence base behind them or necessarily require an evidence base to validate them - there has been no clinical trial of the use of parachutes for preventing death or injury from high altitude falls.⁷ Die-hard advocates of EBM could point to the fact that there are examples of people falling from aeroplanes without parachutes and surviving, and falling with parachutes and dying, and that this illustrates the need for a properly conducted trial.

PROBLEMS WITH EBM IN CRITICAL CARE

As critical care grows as a specialty in its own right, there is an ever growing body of evidence available for the intensivist. However performing meaningful studies and then interpreting and applying the results presents particular difficulties in a critical care environment.

Critically ill patients are a heterogeneous group of patients, usually with multiple pathologies and comorbidities and at least one organ failure, who are subjected to variable and non-uniform treatments. Conducting a trial of therapy for ARDS, for example, a disease with a large number of precipitants that occurs in a wide spectrum of patients, means that the characteristics of the individuals within any sample

Box 1. Hierarchy of evidence

Systematic reviews and meta-analyses

RCTs

Cohort and case control studies

Case reports

Expert opinion

Increasing quality of evidence

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group will vary greatly from each other. Although exposed to the same trial management protocols, the benefits or harms accrued may not be evenly distributed across the study population. This heterogeneity can only be accounted for in a study by using large sample sizes that give the trial adequate *power*. The size and complexity of large scale clinical trials makes them costly to run. Financial sponsorship is often provided from pharmaceutical companies, with an interest in subsequent marketing of the intervention, and conclusions of trials funded by for-profit organisations may be more likely to favour the study intervention⁸. This emphasises the importance of scrupulous attention to the conduct of the trial and interpretation of results.

Box 2. Study power

When designing a study the basic premise is taken that there is no difference between an intervention and the control (this is the *Null Hypothesis*).

In statistical testing two types of error may occur:

1. **Type 1 or alpha error** occurs when we reject the null hypothesis (that there is no difference between study groups) incorrectly i.e. our study finds a difference between groups where no difference really exists. Prior to data collection we decide on the value of alpha that we would find acceptable in this study - 0.05 (or 5%) is usually chosen. We will reject the null hypothesis if our P value is less than alpha. The chance that we will correctly accept a null hypothesis is (1 - alpha) is 0.95 (95%), and the chance we will incorrectly reject it is alpha, or 0.05 (5%).

2. **Type 2 or beta error** occurs when our study fails to find a difference between groups when, in reality, there is one. The power of a test is (1 - beta), and reflects the ability of a test to find a difference where there really is one.

The **power** of a test depends on a number of factors:

1. The *statistical significance* criteria used in the test (the more stringent the significance criteria, the more likely we are to accept the null hypothesis that there is no difference between study groups).

2. The *size of the treatment effect* in the population under study (larger effects will be detected, more reliably).

3. The size of the *sample population* (the larger the sample size, the more reliably a difference is detected, where one exists).

Power calculations should be performed prospectively (i.e. before the trial begins) to estimate the size of the sample population needed to find the difference in question. Power may be calculated retrospectively to calculate the beta error rate given the sample size.

While not limited to critical care, the problems associated with duplicate publishing of positive trial results or failure to publish negative trial results (forms of publication bias - see below), and delayed publishing of results (e.g. the Tracman study) mean that even the most

thorough review of the literature may not provide the clinician with all the information which should be available to him to make the correct decision for a patient.

CRITICAL APPRAISAL OF A STUDY

In assessing the usefulness of a particular RCT we need to assess its internal and external validity. The study should be internally valid – that is to say that the results and conclusions drawn from it, by the authors, should be consistent with the design and conduct of the study itself. If we wish then to apply the study result to the particular clinical setting in which we work, we must also assess the study's external validity (also termed generalisability or applicability).

In the following section of this article we will appraise a recent RCT, examining mortality after a fluid bolus in African children with severe infection¹ (summarised in the box below). To do this we will try to answer three questions (using guidelines produced by the Centre for Evidence Based Medicine at the University of Oxford, UK):

1. Are the results internally valid?
2. What are the results?
3. Are the results externally valid?

Maitland K, Kiguli S, Opoka RO et al.

Mortality After Fluid Bolus In African Children With Severe Infection.

N Eng J Med 2011; **364**: 2843-95.

Available at [http://www.nejm.org/doi/pdf/10.1056/](http://www.nejm.org/doi/pdf/10.1056/NEJMoa1101549)

NEJMoa1101549

The FEAST (Fluid expansion and supportive therapy) trial was conducted at six hospitals in sub-Saharan Africa (4 in Uganda, 1 in Kenya and 1 in Tanzania).

The study enrolled children aged between 60 days to 12 years of age, suffering a febrile illness with either impaired consciousness, respiratory distress or both, and with impaired perfusion, indicated by one or more of the following:

- a capillary refill time of 3 or more seconds,
- a lower limb temperature gradient,
- a weak radial-pulse volume, or
- severe tachycardia.

Patients were randomly assigned to receive 20ml.kg⁻¹ 0.9% saline or 20ml.kg⁻¹ 5% albumin or no bolus of fluid. At 1 hour they were administered an additional 20ml.kg⁻¹ 0.9% saline or 5% albumin, if they still had signs of poor perfusion. Children with infective gastroenteritis and severe malnutrition were among those excluded from the study. The primary endpoint was mortality at 48 hours and it was assumed that this would be about 15% in the control (no bolus) group.

All other therapies - maintenance fluids, antimalarials, antipyretics, anticonvulsants and transfusion parameters

(20ml.kg⁻¹ if Hb less than 5.0g.dl⁻¹) - were the same for both treatment groups and the control group.

3141 children entered the main arm of the study; however the study was stopped at this stage (short of the planned 3600 patients), due to safety concerns in the intervention groups. The baseline characteristics of the three groups were similar. Both bolus groups received 20ml.kg⁻¹ in the first hour of treatment, compared to 1.2ml.kg⁻¹ in the non-bolus group, demonstrating that fluid protocols were followed accurately in all groups.

The mortality rates at 48 hours were 10.6% in the albumin bolus group, 10.5% in the saline bolus group and 7.3% in the no bolus group. Children were 1.45 times more likely to die if given a fluid bolus, compared to the children who received no fluid bolus (95% confidence intervals, 1.13-1.86; p=0.003). This difference in outcome was still clear at 4 week follow-up. There was no difference between the albumin and saline bolus groups. Further analysis shows that children who were not given fluid boluses had better survival in almost all subgroups, including those with malaria, profound anaemia, worse acidosis and higher lactate levels.

Are the results of the study internally valid?

We want to know whether the treatment effect reported in the article represent the true direction and magnitude of the treatment effect under investigation. In other words, do these results represent an unbiased estimate of the treatment effect, or have they been influenced in some systematic fashion leading to a false conclusion?

A bias is a systematic error in the results of an investigation, which may underestimate or overestimate the true effect of the intervention. Sources of bias are described in the table below.

There are a number of questions to help us answer this question about internal validity.

Was the assignment of patients to treatments randomised?

Randomisation was performed by a recognised and robust method, permuted blocks of random sizes (see below). It was performed at a remote location, stratified by centre, and used sequentially numbered, opaque, sealed envelopes. Clinicians would have had negligible influence on the allocation of patients to the study or control group, should they have had a preference. Permuted block randomisation ensures that, at any stage of the study, roughly equal numbers of participants have been allocated to each group. The use of random block sizes ensures that knowing the group allocations of the previous subjects doesn't confer an ability to guess the allocation of (and perhaps, therefore, influence the decision to enrol) the next subject.

Randomisation is used to minimise selection bias to ensure that treatment and control groups are as similar as possible, apart from the treatment under investigation. This is achieved by distributing covariates (i.e. variables which may be either independently predictive of outcome, or confounders) equally between study groups, which allows valid comparisons to be made between groups. The beauty of randomisation is that it should allow equal distribution of both known and unknown factors between groups.

Allocation concealment refers to the steps taken to prevent patients or clinicians knowing prior to randomisation, to which group the next patient will be allocated.

Were the groups similar at the start of the trial?

If the randomisation process has been successful there should be little difference in baseline characteristics between treatment and control groups. The characteristics reported should include recognised covariates or variables, which could affect study outcome. When the

Table 1. Sources of bias

Type of bias	Explanation	Avoidance of bias
Selection bias	Systematic differences between baseline characteristics of groups being compared.	Randomisation and allocation concealment should be carried out satisfactorily.
Performance bias	Systematic differences between groups in the treatment that is provided, or in exposure to factors other than the interventions of interest.	Groups should be treated identically except for the intervention in question.
Attrition bias	Systematic differences between groups in rates of withdrawal from a study.	Analysing results on an intention-to-treat basis reduces this.
Detection bias	Systematic differences between groups in how outcomes are determined.	Blinding participants and outcome assessors reduces this.
Reporting bias	Systematic differences between reported and unreported findings.	

study groups are small, chance may place those with apparently better prognosis or confounding variables, in one group, but as sample size increases this becomes less likely. Although frequently seen, statistical analysis (and therefore reporting 'p-values') to describe the random baseline differences between groups is meaningless – any differences observed have, by definition, occurred by chance.

In our example study, mid-upper arm circumference was measured as a surrogate marker of nutritional status (which could potentially have an effect on mortality in severe sepsis) and malnourished patients were distributed equally across groups. In fact there were no clinically significant differences between the study groups in any of the baseline characteristics, which increases our confidence that the randomisation process was effective.

Aside from the allocated treatment, were the groups treated equally?

The two study groups should be treated equally in all respects other than the treatment under investigation, to ensure that differences in outcomes between groups are due to the treatment under investigation, and not some other (known or unknown) factor.

In our example study this appears to be true. All patients received intravenous maintenance fluids, antibiotics, anti-malarials, antipyretics, anticonvulsants, treatment for hypoglycaemia and blood transfusions as appropriate. They were treated in the same hospitals and received the same follow up.

Were all patients who entered the trial accounted for and were they analysed in the groups to which they were randomised?

The greater the number of subjects who are lost to follow-up, the more the trial may be subject to attrition bias. Lost patients may not have outcomes similar to the group they were lost from (e.g. all lost patients may have died, or all may have recovered to the extent that they did not return for reassessment). If few patients have the outcome of interest, then even small losses to follow up can bias the trial result. Loss of subjects should be minimal, preferably less than 20%.

The principle of attributing all patients to the group to which they were randomised, results in an **intention-to-treat analysis** (even if they received no treatment or crossed-over and received treatment in the other arm of the study). It preserves the value of randomisation and minimises some sources of bias.

Also of interest is the total number of patients assessed for eligibility for entry into a trial and the reasons for exclusion of those deemed ineligible. Low rates of recruitment into RCTs are known to be due, in part, to additional (non-specified) selection by participating clinicians. Furthermore it is known that patients recruited into RCTs can differ from those eligible, but not recruited in terms of age, sex, race, disease severity.

The example study provides a comprehensive analysis of the flow of patients from assessment of eligibility to statistical analysis. All patients were analysed on an intention-to-treat basis. Losses to follow-up were approximately 2.5% and equally distributed among the study groups.

Were measures objective, or were clinicians kept 'blind' to the treatment received?

Blinding occurs when either the patient, clinician, or both ('double-blind') are unaware of the group to which the subject has been allocated. Preconceived opinions about a treatment, whether pessimistic or optimistic, can systematically bias other aspects of treatment and the reporting of treatment outcomes.

Blinding reduces the risk that it was the knowledge of which intervention the subject received, rather than the intervention itself, that affected outcome. This is more important for subjective outcome measures (e.g. scores of symptom relief or functional improvement) than objective measures (e.g. death or stroke). Blinding may not always be possible (e.g. in the case of surgery) but is desirable where practicable. In the SAFE study of 0.9% saline versus albumin for resuscitation of the critically ill, both treatment fluids were delivered in glass bottles, concealed within a cardboard box, in order to blind clinicians.

In this study neither the clinician administering, nor the patient receiving, a fluid bolus could be blinded. However, an assessment of neurological sequelae four weeks after recruitment was performed by an assessor who was unaware of (or blinded to) the treatment assignments. Therefore blinding has been performed where possible and applied to the most subjective outcome measure.

What were the results?

Dichotomous results ('yes' or 'no' outcomes such as death or myocardial infarction) are usually used where possible, as statistical analysis is more straightforward and the results more meaningful.

How large was the treatment effect?

A full discussion of statistical tests is beyond the scope of this article, but we will review some of the basic outcome measures that are commonly used (see Box 2).

Consider an intervention which is designed to reduce mortality in patients with severe sepsis. The relative risk (RR) tells us how many times more likely it is that an event will occur in the treatment or experimental group, than the control group. A relative risk of 1 means that there is no difference in the outcome measure between the two groups. If the RR is less than one, the outcome is less likely in the treatment group, and conversely a $RR > 1$ means it is more likely.

Absolute risk reduction (ARR) tells us in absolute terms the difference in risk (or rates) of the outcome between treatment and control groups. An ARR of zero means the outcome is equally likely in treatment and control groups.

Relative risk reduction (RRR) tells us the reduction in risk of the outcome relative to the risk of the outcome in the control group. The control event rate (CER) is important here - consider an intervention which has a RRR of 30%. If the risk of death in the control group is 10% (i.e. CER = 0.1), then a RRR of 30% reduces the risk of death to 7% over whatever period the intervention and study were applied. However, if the CER for the intervention was low (say 0.1%) the

Box 3. Demonstration of outcome of patients in a RCT for control and intervention groups.

	Dead	Alive	Total
Treatment	a	b	a + b
Control	c	d	c + d

Control event rate (CER) = $c/(c+d)$

Experimental event rate (EER) = $a/(a+b)$

Relative risk (RR) = EER/CER

Absolute risk reduction (ARR) = $CER - EER$

Relative risk reduction (RRR) = ARR/CER

Number needed to treat (NNT) = $1/ARR$

same RRR of 30% would represent a much less meaningful benefit to patients, particularly when weighed against the cost of the intervention and the risk of adverse effects. The RRR is the most often reported outcome measure, perhaps because it provides a numerically larger estimate of treatment effect than the ARR, when the CER is low.

The *number needed to treat* (NNT) is arguably the most clinically relevant measure of outcome and represents the number of patients we need to treat with the experimental intervention, to prevent one adverse outcome. When the intervention causes more harm than the control the NNT is negative and is usually converted to a positive number and expressed a *number needed to harm* (NNH).

In the study of children who received saline boluses versus no boluses, the RR of death was 1.44 (i.e. death more likely in the saline group). In other words, children were 44% more likely to die in the saline group compared to the control group. This is a large effect given a control event rate of 7%. $ARR = (0.073 - 0.106) = -0.033$, and the $NNH = 30 (1/0.033)$.

How precise was the treatment effect?

By convention we consider a study to be positive (i.e. showing a difference between the intervention and the control) if the statistical analysis shows that we are 95% sure that the study result represents a true difference between the intervention and the control. Put another way, the study result will not be a true representation of 'the truth' 5% of the time - if 20 identical studies were conducted, 19 would agree and give this result, but one of them would show the opposite result.

The true relative risk of an intervention, applied to an entire population, can never be known, but a rigorous controlled trial can provide an estimate of the treatment effect in a sample of the population (the trial subjects) at a given point in time - a **point estimate**. The true value of the RR of the treatment lies somewhere in the range defined by the study; confidence intervals are used to describe this range. Ninety-five percent confidence intervals of the RR tell us that we can be 95% sure that the true treatment effect (or RR) is within the range quoted.

If the confidence interval is narrow the point estimate of the population RR is an accurate reflection of the true population value (provided

the results are not subject to significant bias). If the 95% confidence interval, overlaps a RR of 1.0, i.e. the value corresponding to no effect, then the results are not statistically significant. If the value corresponding to no effect (RR = 1) lies outside the 95% confidence interval, then the results are statistically significant at the 5% level (i.e. the result could occur by chance less than 5% of the time).

The calculation of confidence intervals for relative risks is complicated and beyond the scope of this article.

In our study of children who received saline boluses compared to no boluses, the RR of death was 1.44 with 95% confidence intervals of 1.09-1.90. This confidence interval does not include unity (1.0), so the results for this comparison are significant at the 5% level. A similar result was true for the comparison of albumin boluses versus no boluses.

Will the results of the study help me in caring for my patient (or are the results externally valid)?

We have established that the study demonstrates internal validity - it has been conducted rigorously and the results are probably a true representation of this population. We should now consider whether it is applicable to other patients in other clinical settings (its external validity). An excellent article by Rothwell highlights some of the pitfalls surrounding this problem.⁹ There are a number of questions we should ask ourselves, before deciding to apply the results of a study to patients in our care.

Are my patients so different from those in the study that the study results do not apply?

Ideally, we want to ask ourselves whether the patient in front of us would have met the inclusion criteria for the study, and not fulfilled the exclusion criteria; the answer is rarely a straightforward 'yes'. By their nature RCTs study treatment effects in the context of a clinical trial, and not in general clinical practice, so inevitably external validity will be less than perfect. In reality, a treatment effect will be influenced by factors such as the doctor-patient interaction, the placebo effect, doctor or patient preference etc. All of these factors are minimized in clinical trials by the use of blinded allocation of treatments, placebo

control, and the exclusion of clinicians who do not have equipoise over the intervention in question (i.e. excluding clinicians who hold a prior belief that one or other of the study interventions is superior). The net effect of these factors probably underestimates the benefits of treatment in clinical practice.

The **placebo effect** is the name given to the benefits or changes in outcome measures perceived by patients or assessors, when an inert treatment is administered. Treatments are compared with an appropriate control to ensure findings are not due to this placebo effect alone. It is more important when subjective outcome measures are being used (scores of pain, satisfaction, quality of life etc) than objective measures (mortality, heart rate etc).

The setting in which the trial was performed is clearly important. Differences between healthcare systems (and even between countries, which operate similar healthcare systems) have been shown to affect external validity. For example, trials testing the BCG vaccination for the prevention of tuberculosis, demonstrated great effectiveness in more northern countries, with far less effect in trials conducted further south. Additionally, there may be significant differences in the use of ancillary non-trial treatments – a particular treatment may be considered standard practice in one country, for a particular condition, but it may be rarely used elsewhere.

Selection of centres to conduct clinical trials has the potential to affect external validity. While it may be tempting to perform a trial in specialist intensive care units of a large metropolitan teaching hospitals, the trial results may be more generalisable if a wider variety of hospitals are included in the trial. Consider a trial of glycaemic control in a Belgian intensive care unit¹⁰ in which over 60% of the patients were post cardiac surgery. This study found a relative risk reduction in ICU mortality of 42%, in patients randomised to tight glycaemic control (blood glucose levels 4.4–6.1 mmol.L⁻¹ or 80–110 mg.dL⁻¹) compared to conventional treatment (blood glucose levels less than 11.1 mmol.L⁻¹ or 200 mg.dL⁻¹), findings which were not replicated in a medical ICU by the same author¹¹ or a large international multicentre randomised controlled trial by the ANZICS study group.¹²

Many studies exclude pregnant women, the young and the elderly for ethical or other reasons, so care must be taken when extrapolating a trial's results to these populations.

The use of 'run-in' periods can be more difficult to recognise. Patients in a placebo run-in all receive placebo to assess patient compliance with trial protocols, and those patients who are poorly compliant are excluded from analysis. Excluded patients are known to differ from recruited patients in age, social class etc. Active treatment run-ins, in which patients who are intolerant of the study intervention are excluded, produce trial data with much lower complication and treatment failure rates than may otherwise be seen, and can seriously undermine external validity.

Some clinical trials use enrichment strategies. In these trials patients are selected who are likely to respond well to treatment, or perhaps even had a previous good response to a similar drug. Although there may be a place for such trials, their external validity is clearly much reduced.

*What of our study? Over three thousand patients were randomised over two years across six centres (~0.6 patients/centre/day). The study was performed in resource-poor healthcare systems, where over half of the children presenting with severe infections had *P. falciparum* parasitaemia. Those with bacterial sepsis (only 12% had a positive blood culture) may have benefited from fluid therapy, however there are logical reasons why those with pneumonia, cerebral malaria and other causes of encephalopathy may have been harmed by fluid therapy, as they have high levels of ADH (antidiuretic hormone) resulting from their underlying disease.*

In addition, the high numbers of children with severe anaemia may be harmed by liberal fluid administration, since haemodilution in profoundly anaemic children may reduce oxygen delivery below a critical level needed for adequate organ oxygenation. The mortality rate in the control group (7.3%) was considerably lower than predicted (15%) and it is likely that this reflects the training in triage, basic life support and regular monitoring that was introduced as part of the study.

A further limitation of the generalisability of this study is that children with dehydration due to gastroenteritis were excluded, and it would be disastrous if fluid therapy were withheld from children with this form of septic illness.

Were all clinically important outcomes considered?

Surrogate outcomes are used as indirect measures of clinical outcome, but the literature contains many examples of studies in which treatments had apparently beneficial effects on surrogate markers of outcome, but subsequent RCTs, with appropriate clinical endpoints, showed the treatments to be either ineffective or harmful. A good example is the CAST trial¹³ in which anti-arrhythmic agents, such as flecainide, were administered to patients after myocardial infarction on the basis that they reduced ECG abnormalities in pilot studies. Mortality was increased in the treatment arm of this RCT.

Outcome measures should be patient-centered (i.e. provide information the patient wants), avoid the use of composite outcomes (e.g. "stroke or cardiac death" as outcomes may vary between components of the composite outcome) where possible, be measured after adequate length of follow up, and report adverse effects of treatment.

In our study, the primary (dichotomous and meaningful) endpoint was death at 48 hours. Secondary endpoints concerning adverse effects of volume overload were also considered, for example there appeared to be no statistically significant increase in pulmonary or cerebral oedema, two features that might have explained the excessive mortality caused by fluid boluses.

CONCLUSION

*This study of fluid boluses in the resuscitation of African children with severe infections appears to be methodologically sound, and has found increased mortality in the treatment arm which is statistically (and clinically) significant. It was conducted in a region with developing economies and healthcare systems in an area with a high prevalence of malaria due to *P. falciparum*. Its generalisability is limited to patients and clinicians working in similar circumstances.*

Evidence based medicine is a powerful tool, which has a clear place in modern medical practice. Obsessive adherence to EBM risks taking the art out of medicine, to the detriment of our patients care. In contrast, refusal to accept and apply the results of good quality RCTs, on the basis of insufficient external validity, is not acceptable practice either. For the foreseeable future, we must rely on EBM and an enquiring mind, tempered by some healthy skepticism and empathy with our patients, to help us find fitting strategies to guide our patients through their critical care admissions.

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Management of major trauma

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INTRODUCTION

Patients suffering from multiple injuries present enormous demands at all levels within hospitals, particularly on those attending to the patient within the first few hours of hospital admission. This article outlines a system for the management of major trauma victims in the Emergency Department.

The Advanced Trauma and Life Support (ATLS) Program, devised by the American College of Surgeons (ACS), is widely accepted as the standard for the initial care of trauma victims, whether the patient is treated in an isolated rural area or a well-resourced trauma centre. This article follows many of its recommendations, with additions from other sources.

EPIDEMIOLOGY OF TRAUMA

Every five seconds someone in the world dies as a result of an injury. Injuries kill about 5.8 million people each year; more than malaria, tuberculosis and HIV/AIDS combined.¹ Among the causes of injury are acts of violence, road traffic collisions, burns, drowning, falls and poisoning. Road traffic injuries are the leading cause of injury-related deaths worldwide.

Within the last few decades our understanding of the nature of injuries has improved and today both intentional and unintentional injuries are viewed as largely preventable events, rather than as unavoidable accidents. Injury prevention strategies are having an impact in most developed countries, where trauma is still the leading cause of death in people between the ages of 1 and 44 years. More than 90% of the world's deaths from injuries occur in low and middle income countries.²

Despite injury prevention strategies, injury-related disease burden is expected to increase dramatically by 2020, particularly in the case of road traffic injuries, interpersonal violence, war and self-inflicted injuries. By 2020, it is estimated that more than 1 in 10 people will die from road traffic injuries.³ Global trauma-related costs are estimated to exceed US\$500 billion annually. The true cost of trauma, however, can only be measured when it is realised that trauma victims tend to be society's youngest, and potentially most productive, members.

TRIMODAL DEATH DISTRIBUTION

Mortality due to injury occurs during one of three time periods or peaks.

First peak

This occurs at the time of the injury. Very few of these patients can be saved, because of overwhelming primary injury to major organs or structures such as the brain, heart or great vessels. Only prevention can significantly reduce this peak of trauma-related deaths.

Second peak

The second peak occurs within minutes to several hours following the injury. Trauma care is directed at this period because many of the causes of morbidity and mortality during this time are preventable by avoidance of secondary injury due to hypoxia, haemorrhage or any process that leads to inadequate tissue perfusion. Deaths that occur during this period are usually due to intracranial haematomas, haemopneumothorax and major haemorrhage from viscera, bones and vessels.

Third peak

This occurs several days to weeks after the initial injury and is most often due to sepsis and multiple organ dysfunction. Although this stage usually occurs in a high dependency area, improvements on initial management upon admission will reduce morbidity and mortality during this period.

PREPARATION

Ideally a designated resuscitation area should be available to receive trauma patients. Basic equipment requirements include:

- Airway equipment should be tested and placed where it is immediately accessible,
- Warmed intravenous fluids should be ready to infuse when the patient arrives,
- Specific provision should be made for children, with appropriate sizes of equipment to deal with all ages and equipment for intra-osseous fluid administration,
- Appropriate monitoring capabilities should be immediately accessible.

Summary

Trauma is a major cause of death around the world. This article gives an overview of the basics of management of patients who have suffered major trauma. Several areas of practice have evolved in the last few years, following the experience of the armed services in conflict zones.

Some sections such as management of cervical spine injury, thoracic injury and patients with major burns are dealt with in detail in other articles in this edition of *Update*.

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It may be necessary to improvise, particularly in remote areas where resources are limited.

An effective method to call for additional medical assistance should be in place, as well as a means to ensure rapid responses by laboratory and radiology personnel. Transfer agreements with trauma centers should be established and operational. Patients with multiple injuries are best treated by a well-organised and trained team, made up of members who are competent in assessing and treating the range of life-threatening injuries commonly seen. Where possible, staff should have attended an ATLS course (or equivalent such as PTC, Primary Trauma Care), although in smaller hospitals a full trauma team will not be available.

A schematic diagram of a full trauma team in their various positions is shown in Figure 1. Where there are limited resources, individuals in the team will assume more than one role and specialist resources (e.g. the surgeon) may move serially from one patient to another, dependent on the need for specialist assessment and intervention skills.

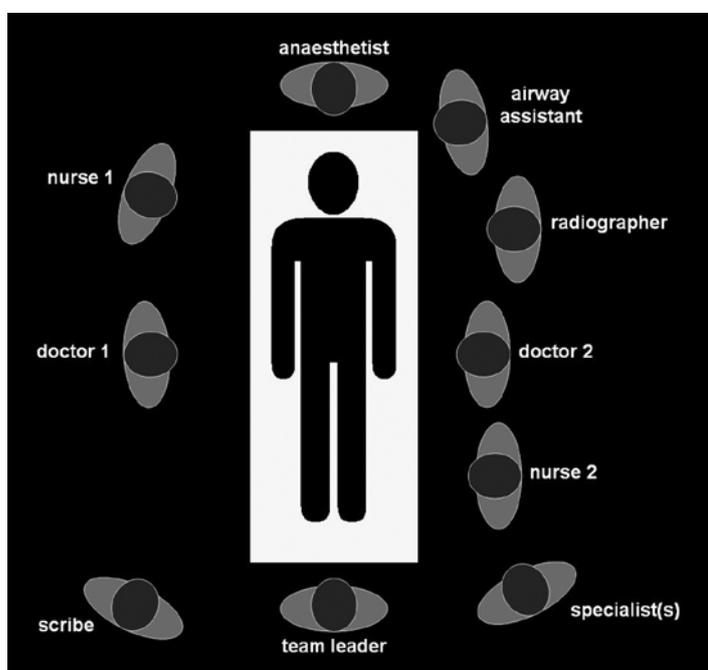


Figure 1. Schematic diagram of a trauma team and their positions around the patient.

The overall management of the patient is the responsibility of the team leader. If there are enough staff the team leader should adopt a ‘hands off’ approach, in order to maintain an overview of the resuscitation. The trauma team’s responsibility is to complete the **primary survey** and necessary resuscitation and subsequently complete the **secondary survey**, if time allows, as well as recording all diagnoses and treatments given. The team leader must ensure that this is achieved effectively and rapidly. Specific tasks are allocated to different members of the team at an early stage; in a well-practiced team this is done before the patient arrives.

Advance warning of the arrival of a severely injured patient in the emergency department enables emergency department staff to alert the trauma team, who should assemble in the resuscitation room. Each member of the team should wear gloves, a plastic apron and eye

protection. Where possible both a general surgeon and an orthopaedic surgeon should be members of the trauma team.

Objectives of the trauma team⁴

- Identify and correct life threatening injuries.
- Resuscitate the patient and stabilize vital signs.
- Determine the extent of other injuries.
- Prepare the patient for definitive care, which may mean transport to another centre.

Box 1. Trauma team roles and responsibilities. (ODP - operating department practitioner; RSI - rapid sequence induction; ED - emergency department)

Team Leader (Emergency Physician)

- Controls and manages the resuscitation.
- Makes decisions; prioritises investigations and treatment.

Anaesthetist

- Responsible for **assessment and management of the airway** and ventilation.
- Counts the initial respiratory rate.
- Administers oxygen; performs suction; inserts airway adjuncts; endotracheal intubation (RSI).
- Maintains cervical spine immobilisation and controls the log roll.
- Takes an initial history (AMPLE – see below).

Airway Assistant (ODP or ED Nurse)

- Assists in preparing equipment for advanced airway intervention.
- Assists with advanced airway intervention, e.g. applies cricoid pressure.
- This role may be undertaken by Nurse 1.

Doctor 1 (Emergency Physician or Surgeon)

- Undertakes the primary survey: **<C> + B to E**.
- Clinical findings are clearly spoken to team leader and recorded by the scribe.
- Performs procedures depending on skill level and training.

Doctor 2

- Performs procedures depending on skill level and training.

Nurse 1 (ED Nurse, ‘Airway’)

- Applies monitoring equipment and assists with procedures.
- Assists advanced airway intervention (unless ODP present).

Nurse 2 (ED Nurse, ‘Circulation’)

- Undresses patient & assists with procedures.

Scribe (ED Nurse, Paramedic, Health Care Assistant)

- Collates all information and records decisions on trauma chart.
- All team members are responsible for ensuring that their findings and decisions are correctly recorded.

Radiographer

- Xrays as directed by Team Leader.

Specialists

- Undertake secondary survey and advanced procedures (e.g. General Surgeon to undertake secondary survey of head and torso. Orthopaedic Surgeon to undertake secondary survey of limbs, pelvis and spine.)
- FAST (focused assessment with sonography for trauma) scan may be undertaken by General Surgeon, Emergency Physician or Ultrasonographer.

INITIAL ASSESSMENT AND RESUSCITATION - <C>ABC

Every trauma patient should be assessed using the same systematic method, preferably using a team approach.

An 'ABC' approach has become established across the spectrum of advanced life support programmes. Experience and evidence with combat casualties has shown that external peripheral haemorrhage is the leading cause of combat casualty death. As a result, the UK and US militaries have replaced ABC with <C>ABC, where <C> stands for **catastrophic haemorrhage control**. This is being increasingly adopted by the civilian community.

A horizontal approach to trauma management, where systems are managed simultaneously, is preferable to a vertical approach, where systems are managed in order of priority, but this is dependent on the size and skill set of the trauma team.

Box 2. An overview of trauma management

Primary survey and resuscitation

- **C**atastrophic haemorrhage control
- **A**irway and cervical spine control
- **B**reathing
- **C**irculation and haemorrhage control
- **D**isability
- **E**xposure

Secondary survey

Definitive management

PRIMARY SURVEY AND RESUSCITATION

The purpose of the primary survey is to identify immediate life threatening conditions. These should be treated as soon as they are

diagnosed, before continuing the survey. Whilst the primary survey is ongoing, any deterioration in the patient's clinical condition should be managed by reassessing from the start of the protocol, as previously undiagnosed injuries may be revealed.

Catastrophic haemorrhage control

Immediate control of obvious bleeding is of paramount importance. The use of **tourniquets** is now recommended for the management of life threatening bleeding from open extremity injuries, in the pre-surgical setting.

Pressure bandages, rather than tourniquets, should be applied in the case of minor bleeding from open wounds in extremity injuries. When uncontrolled arterial bleeding occurs from mangled extremity injuries, including penetrating or blast injuries or traumatic amputations, a tourniquet is a simple and efficient method to control haemorrhage.⁶⁻¹⁰ Tourniquets should be left in place until surgical control of bleeding is achieved, however this time-span should be kept as short as possible⁶⁻⁹

It may not be possible to staunch catastrophic haemorrhage, particularly if it is internal, for example within the abdomen or chest cavities. In these circumstances, surgery must not be delayed.

Airway and cervical spine control

The main objective, in the early management of the severely injured patient, is to provide sufficient oxygen to the tissues in order to prevent secondary organ failure and central nervous system damage.

The first priority is to ensure a clear and unobstructed airway. If the patient can answer questions appropriately, then it is unlikely that there is any immediate threat to the airway. Noisy or laboured breathing or paradoxical breathing movement (when movements of the chest and abdomen are out of phase) is evidence of obstruction, that must be corrected.

Head injury with impaired consciousness and reduced pharyngeal tone is the commonest trauma-related cause of airway obstruction. The airway may also be soiled with vomit, blood or foreign material. Blunt or penetrating injuries that obstruct the airway include maxillary, mandibular and laryngotracheal fractures and large anterior neck haematomas.

Patients who have been exposed to significant blunt trauma are at risk of unstable cervical injuries. During airway interventions, neck movement must be minimized to avoid spinal cord damage. 2-12% of major trauma victims have a cervical spine injury and 7-14% of these are unstable.¹¹

Any patient with a possible cervical spine injury should have their neck immobilized in a neutral position to prevent further damage. Immobilization of the cervical spine must be continued, until a complete clinical and radiological evaluation has ruled out injury. This can either be done manually (manual in-line stabilisation of the neck - MILS) or with a correctly sized hard cervical collar, lateral blocks (or sandbags), and straps across the forehead and chin piece of the collar (see article on page 112).

A jaw thrust may be better at relieving airway obstruction with decreased consciousness than a chin lift. If tolerated, an oropharyngeal airway may maintain an open airway, whilst exerting less force on the

vertebrae. It should never be inserted into the pharynx of a patient with an intact gag reflex, as this can cause retching or vomiting. In these circumstances a nasopharyngeal airway should be inserted, if there is no basal skull fracture.

Endotracheal intubation is indicated if airway patency remains inadequate despite the above measures, or in the presence of apnoea or loss of protective upper airway reflexes. Other indications for intubation are listed in Table 1. Orotracheal intubation is a two-person technique with in-line cervical spine immobilization.

It is important to assess the patient's airway prior to attempting intubation, in order to predict the likely difficulty. Facial hair, trauma and burns prevent effective mask application. Mechanical trismus may hinder supraglottic airway and laryngoscope insertion. Laryngoscopy becomes more difficult in the presence of airway oedema, blood or burns. MILS and cricoid pressure increase the incidence of Cormack and Lehane grade 3 laryngeal views to 20%.¹¹ Backward, upward and right pressure ('BURP') on the larynx may help if it is anteriorly placed.

Failed intubation

Failed or difficult intubation is a common problem in this setting. It is important not to waste time with repeated attempts at intubation, while the patient is desaturating. Alternative methods of securing the airway should be started as soon as the problem is recognised. Management is guided by algorithms that are discussed in a previous edition of *Update in Anaesthesia*.^{14,15}

If intubation is impossible, a laryngeal mask airway (LMA) will provide a temporary airway, but may not prevent aspiration. The intubating LMA (ILMA) may be easier to insert in the neutral position and provides the opportunity for blind intubation, although consistent success requires ongoing practice. If this fails, a cricothyroidotomy should be carried out; this is discussed in detail in a recent *Update* article.¹⁵

Table 1. Indications for intubation.

Need for airway protection	Need for ventilation or oxygenation
Unconscious Severe maxillofacial fractures Risk of aspiration <ul style="list-style-type: none"> • Blood • Stomach contents Risk of airway obstruction <ul style="list-style-type: none"> • Oedema • Neck haematoma • Laryngeal or tracheal injury • Stridor • Upper airway burns 	Unconscious No respiratory effort Inadequate respiratory effort: (tachypnoea, hypoxia, hypercarbia, cyanosis): <ul style="list-style-type: none"> • Flail chest • Pulmonary contusion • Blast injury To regulate intracranial pressure by controlling CO ₂ in severe, closed head injury To perform therapeutic and diagnostic procedures in uncooperative patients

Box 3. Tips for rapid sequence induction (RSI) and intubation

- Check the ventilator, breathing system, laryngoscopes, tracheal tubes, suction and equipment for managing a difficult airway prior to commencing RSI.
- Routine monitoring should be applied.
- Have a plan for difficult or failed intubation.
- Where cervical spine injury is possible MILS is applied by an assistant, crouched beside the intubator, holding the patient's mastoid processes firmly down on the trolley.^{12,13} MILS must simply oppose the force generated by direct laryngoscopy (which rotates the occipito-atlanto-axial complex) and must not cause traction, which could cause spinal cord injury.
- Remove the hard collar after MILS has been applied mouth opening is easier.

Breathing

Airway patency alone does not ensure adequate ventilation. Adequate gas exchange is required to maximize oxygenation and carbon dioxide elimination. Ventilation requires adequate function of the lungs, chest wall and diaphragm. Each component must be examined and evaluated rapidly. The patient's chest should be exposed and any obvious injuries noted. The respiratory rate should be measured; it is a sensitive indicator of physiological stress. Diaphragmatic (or 'paradoxical') breathing may be observed with cervical cord injury: the abdomen is seen to move in and out, rather than the chest.

The trachea should be checked for deviation and both sides of the chest assessed for expansion. The thorax must be percussed and the lung apices and axillae auscultated. The back of the chest and axillae

should not be forgotten, especially in the case of penetrating trauma, such as gunshot wounds, when an exit wound should be specifically sought. An odd number of gunshot wounds means that a wound has either been missed or that there is still a bullet in the body. The chest is examined when the patient is log-rolled off the ambulance trolley or hard board. Formal log roll and spinal examination is described in the secondary survey.

If available, a pulse oximeter is useful, as it gives an indication of the adequacy of perfusion as well as arterial oxygen saturation. High flow oxygen (6-8L.min⁻¹) should be administered to every patient. Oxygen is delivered to the spontaneously breathing patient via a Hudson mask with a non-rebreathing bag. Where ventilation is inadequate, this should be assisted by bag-valve-mask prior to RSI.

The chest Xray is part of the clinical examination in serious trauma and should be performed during the primary survey. A simple, easy, cheap and informative method of indicating the trajectories caused by penetrating injuries on chest Xrays is the application of bullet markers (for example, paper clips secured with micropore) to the wounds. Open clips can be applied to anterior wounds (forming a triangle) and closed clips to posterior wounds to help identify which is which.

Box 4. Life threatening conditions that need immediate treatment

- Tension pneumothorax
- Massive haemothorax
- Cardiac tamponade
- Flail chest with pulmonary contusion
- Open chest wound.

These conditions are described in more detail in the article on page 119.

Diagnosis of cardiac tamponade can be difficult. The classic diagnostic Beck's triad consists of venous pressure elevation, decline in arterial pressure, and muffled heart sounds. All of these signs can be easily misinterpreted in a noisy emergency department with a shocked patient. A FAST scan (Focused Assessment with Sonography for Trauma) is sensitive and specific for the evaluation of the pericardium for cardiac tamponade in penetrating trauma.¹⁶ If haemopericardium is confirmed, needle pericardiocentesis may help in the short-term, however thoracotomy is the definitive treatment.

Circulation

The first step in managing shock in injured patients is to recognise its presence. The second step is to identify the probable cause of the shock state. Treatment should be initiated simultaneously with the identification of the probable cause. The time spent between injury and operation must be minimised for patients in need of urgent surgical bleeding control.¹⁷

Recognition of shock

Profound shock, with circulatory collapse and inadequate perfusion

of the skin, kidneys and brain, is easy to recognise. However, after the airway and breathing have been assessed, careful evaluation of the patient's circulatory status is important to identify early shock.

Signs of early shock include tachycardia, with reduced capillary refill time and skin temperature. Attention must also be paid to an increased respiratory rate and narrowed pulse pressure (the difference between systolic and diastolic pressure). Relying on systolic blood pressure as the only indicator of shock leads to delayed recognition of shock. This is because compensatory mechanisms prevent the systolic blood pressure from falling until up to 30 percent of the patient's blood volume is lost, particularly in young, fit patients.

The normal heart rate varies with age. Tachycardia is present when the heart rate is greater than 160 in an infant, 140 in a preschool age child, 120 from school age to puberty, and 100 in an adult. Elderly patients may not show tachycardia because of reduced cardiac response to catecholamine stimulation, or the concurrent use of medications such as beta-adrenergic blocking agents. The ability to increase the heart rate may also be limited by the presence of a pacemaker.

Identification of the cause of shock

Shock in a trauma patient can be classified as haemorrhagic or non-haemorrhagic. Haemorrhage is the most common cause of shock after injury and accounts for up to 50% of deaths in the first 24 hours after injury.

Nearly all patients with multiple injuries have hypovolaemia. Most non-haemorrhagic shock states respond partially, or briefly, to volume resuscitation. Therefore, if signs of shock are present, treat for hypovolaemia and then reassess the patient, as it is important to identify the few patients whose shock has a different cause, such as cardiogenic, neurogenic or even septic shock. Tension pneumothorax should also be considered.

Hypovolaemia can be divided into 4 classes as shown in Table 2, with their appropriate signs. This is a useful tool for estimating the percentage of acute blood loss. The extent of traumatic haemorrhage should be assessed using a combination of mechanism of injury, patient physiology, anatomical injury pattern and the patient's response to initial resuscitation.¹⁷

Patients presenting with haemorrhagic shock and an unidentified source of bleeding should undergo further assessment of further assessment of the major sources of acute blood loss in trauma - the chest, abdominal cavity, pelvic ring and the long bones.¹⁷ If pelvic instability is suspected, a tight pelvic binder or sheet should be wrapped around the pelvis at the level of the greater trochanters, as soon as possible.

Xrays of chest and pelvis, in conjunction with FAST or diagnostic peritoneal lavage (DPL), are recommended diagnostic modalities during the primary survey.¹⁸

FAST is now the imaging modality of choice when a trained operator is available. DPL is carried out less frequently, but is considered positive if 15ml of blood is obtained immediately, or if it is not possible to read print through the backwash from 1 litre of warmed saline infused into the abdominal cavity. The backwash fluid is sent for gram stain and analysis of the red blood cell count and white blood cell count. It also

Table 2. American College of Surgeons, Advanced Trauma Life Support (ATLS) classification of blood loss, based on initial patient presentation for a 70kg male¹⁸

	Class 1	Class 2	Class 3	Class 4
Blood loss (ml)	up to 750	750-1500	1500-2000	>2000
Blood loss (% blood volume)	up to 15%	15-30%	30-40%	>40%
Pulse rate (min ⁻¹)	<100	100-120	120-140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate (min ⁻¹)	14-20	20-30	30-40	>35
Urine output (ml.h ⁻¹)	>30	20-30	5-15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

should be examined for enteric, bilious, or vegetable matter content. A positive DPL in an adult classically requires one of the following results: 10ml gross blood on initial aspiration, >500 per mm³ white blood cells, >100,000 per mm³ red blood cells, or the presence of enteric or vegetable matter.¹⁹

Patients who are haemodynamically unstable and who have significant free intraabdominal fluid should undergo laparotomy, whereas those who are haemodynamically stable and who are either suspected of having torso bleeding (clinically or FAST positive) or have a high-risk mechanism of injury, should undergo further assessment using computed tomography (CT), if readily available.¹⁷

In selected centres, readily available CT scanners may replace usual radiographic imaging techniques during the primary survey.

Initial management of haemorrhagic shock

Definitive bleeding control and prevention of the lethal triad of hypothermia, coagulopathy and acidosis are key to the management of haemorrhagic shock.

Insert two large bore (minimum 16 gauge) peripheral intravenous (IV) cannulas. Other peripheral lines, cut downs and central venous lines should be used as necessary, in accordance with the skill level of the doctor who is attending the patient. The central route is only recommended for rapid fluid resuscitation when peripheral access is not possible, and a relatively short, large bore catheter (e.g. 8.5 Fr introducer sheath) should be used. For rapid access the external jugular vein may be used. Intraosseous access is well established in children and use is growing in adults.

At the time of IV insertion, take blood for type and crossmatch and baseline haematologic studies, including a pregnancy test for all females of childbearing age.

The CRASH-2 study has shown that tranexamic acid, a fibrinolysis inhibitor, given as early as possible to bleeding trauma patients, improves mortality from bleeding.¹⁸ The dose is 1g IV over 10 minutes, followed by an infusion of 1g over 8 hours. If treatment is delayed three hours or later after injury, mortality is increased by haemorrhage.²⁰

Arterial blood gas analysis should be performed where available. Insert

an arterial cannula for blood gas sampling and invasive blood pressure monitoring if this technique is available.

Initial fluid therapy

Early treatment of injured patients has traditionally focused on aggressive resuscitation with high chloride-containing crystalloid solutions. Whilst recognizing that in many hospitals the choice of fluid is limited, we include a brief update on research on resuscitation fluids.

Resuscitation with crystalloid exacerbates each element of the lethal triad of hypothermia, coagulopathy and acidosis. Pre-hospital and early in-hospital resuscitation with crystalloids has been shown to increase morbidity and mortality in patients with penetrating torso trauma.²¹

The absence of clotting activity in both crystalloid solutions and packed red blood cells contributes to dilutional coagulopathy. High chloride content in crystalloid solutions exacerbates the acidosis of shock and prehospital fluid, maintained at room temperature, contributes to hypothermia.

The current fluid of choice is a colloid such as 6% hetastarch suspended in a balanced salt solution that contains lactate (such as Hartmann's).²² This has been shown not to exacerbate coagulopathy, even with substantial volumes, and has been shown to reduce blood loss in patients undergoing major surgery, compared with 6 per cent hetastarch suspended in 0.9% saline.²³

The goal of resuscitation is to restore organ perfusion. This is achieved by the use of resuscitation fluids to replace lost intravascular volume and is assessed on clinical grounds. If blood pressure is raised rapidly, before haemorrhage has been definitively controlled, increased bleeding may occur, due to increased hydrostatic pressure on the wound and dislodgement of blood clots.

Those involved in military trauma are trained to withhold fluid resuscitation, unless a casualty has either an impaired mental state or absent pulse, and to give only enough fluid to reverse these abnormalities. Until surgical control of haemorrhage has been achieved, target fluid resuscitation to a blood pressure that is lower than normal, but maintains a level of tissue perfusion that is adequate for short periods. This target will depend on age and coexisting morbidities.²⁴

This approach must be modified in traumatic brain injury and spinal injuries, because an adequate perfusion pressure is vital to ensure tissue oxygenation of the injured central nervous system. A mean arterial pressure of at least 90mmHg is required in patients with even slightly raised intracranial pressure.

Evaluation of fluid resuscitation and organ perfusion

The volume status of the patient is determined by observing the change in vital signs after the initial fluid bolus. Failure to improve the vital signs implies ongoing haemorrhage, and necessitates immediate surgical intervention and blood transfusion. Sensitive measurements that give valuable information regarding organ perfusion include urine output, lactate and base excess. If available, thromboelastography® (TEG®) and thromboelastometry (ROTEM®) are direct measures of coagulopathy and indicate which blood components are required. These should be monitored to estimate the extent of bleeding and shock, and the response to fluid resuscitation.

The potential patterns of response to initial fluid administration can be divided into three groups: rapid response, transient response, and minimal or no response. Vital signs and management guidelines for patient in each of these categories are outlined in Table 3.

If the patient remains unresponsive to bolus IV therapy, blood transfusion may be required. In this situation, consider the possibility of tension pneumothorax, cardiac tamponade or 'spinal shock'. Aggressive and continued volume resuscitation is not a substitute for definitive control of haemorrhage. Definitive control includes operation, angioembolization and pelvic stabilization.

Damage control surgery

Damage Control Surgery (DCS) is aimed at stopping bleeding and preventing further contamination. It is limited to the control of uncompressible haemorrhage and the insertion of vascular shunts. These are temporising procedures that are used to gain control of a rapidly deteriorating clinical situation. If damage control surgery is

required, the primary survey should be interrupted and continued postoperatively.

Damage control surgery techniques can apply to the abdomen, chest, pelvis and long bones.

Patients with major trauma are at risk of developing impaired coagulation, metabolic acidosis and hypothermia, which significantly contributes to illness and death. To prevent this lethal triad, damage control surgery is a staged process, involving five critical decision-making stages.

The first stage is patient selection and the decision to perform damage control surgery. This should take place in the Emergency Department, if not before. The second stage is the operation and the 'damage control'. The third stage takes place in the intensive care unit, where the patient is resuscitated towards normal physiology. This is followed by 'relook' surgery or a definitive surgical procedure. The final stage is definitive closure of the body cavity.

The advantage of the DCS approach is that surgeons only do the more thorough and therefore longer surgery once the patient is stable.

Hypothermia

Hypothermia may be present when the patient arrives, or it may develop quickly in the Emergency Department, if the patient is uncovered and undergoes rapid administration of room temperature fluids or refrigerated blood.

Hypothermia, defined as a core body temperature below 35°C, is associated with acidosis, hypotension and coagulopathy in severely injured patients. It is a serious complication and is an independent predictor of mortality.²⁵ Steps to prevent hypothermia, and the risk of hypothermia-induced coagulopathy, include removing wet clothing, covering the patient to avoid additional heat loss, increasing the ambient temperature, forced air warming, warm fluid therapy and, in extreme cases, extracorporeal re-warming devices. The use of a high

Table 3. American College of Surgeons, Advanced Trauma Life Support (ATLS) responses to initial fluid resuscitation¹⁸

	Rapid response	Transient response	Minimal or no response
<i>Vital Signs</i>	Return to normal	Transient improvement, recurrence of decreased blood pressure and increased heart rate	Remain abnormal
<i>Estimated blood loss</i>	Minimal (10%-20%)	Moderate and ongoing (20%-40%)	Severe (>40%)
<i>Need for more crystalloid</i>	Low	High	High
<i>Need for blood</i>	Low	Moderate to high	Immediate
<i>Blood preparation</i>	Type and crossmatch	Type-specific	Emergency blood release
<i>Need for operative intervention</i>	Possibly	Likely	Highly likely
<i>Early presence of surgeon</i>	Yes	Yes	Yes

flow fluid warmer or microwave oven to heat crystalloid fluids to 39°C is recommended. One litre of crystalloid in a 600 Watt microwave oven for 60 seconds is usually enough. Blood products, however, cannot be warmed in a microwave oven, but they can be heated by passage through IV fluid warmers.

Blood replacement

The main purpose of blood transfusion is to restore the oxygen-carrying capacity of the intravascular volume. A target haemoglobin (Hb) of 7-9g.dl⁻¹ is recommended.¹⁷ Fully crossmatched blood is preferable, although the complete crossmatching process requires about 45 minutes in most blood banks. For patients who stabilise rapidly, crossmatched blood should be obtained and made available for transfusion when indicated.

Group-confirmed blood can be issued within 10 minutes. Such blood is compatible with ABO and Rh blood types, but incompatibilities of other antibodies may exist. Group-confirmed blood is preferred for patients who are transient responders. If group-confirmed blood is unavailable, type O packed cells are indicated for patients with exsanguinating haemorrhage. To avoid sensitization and future complications, Rh-negative cells are preferred for females of childbearing age.

Coagulopathy

Severe injury and haemorrhage result in the consumption of coagulation factors and early coagulopathy. Massive transfusion, with the resultant dilution of platelets and clotting factors, along with the adverse effect of hypothermia on platelet aggregation and the clotting cascade, all contribute to coagulopathy in injured patients.

Routine practice to detect post-traumatic coagulopathy should include the measurement of international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen and platelets. INR and APTT alone should not be used to guide haemostatic therapy however.¹⁷ If available thromboelastography® (TEG®) or thromboelastometry (ROTEM®) should be performed to assist in characterising the coagulopathy and in guiding haemostatic therapy.

Consideration of early blood component therapy, including thawed fresh frozen plasma (FFP), platelets and cryoprecipitate, should be given to patients with class 4 haemorrhage.

A fibrinogen of less than 1g.L⁻¹ or a prothrombin time (PT) and APTT of >1.5 times normal, represents established haemostatic failure and is predictive of microvascular bleeding. Early infusion of FFP (15ml.kg⁻¹) should be used to prevent this occurring, if a senior clinician anticipates massive haemorrhage. Established coagulopathy will require more than 15ml.kg⁻¹ of FFP to correct.²¹ The most effective way to achieve fibrinogen replacement rapidly, is by giving fibrinogen concentrate, or cryoprecipitate if fibrinogen is unavailable.¹⁹

1:1:1 red cell:FFP:platelet regimens are reserved for the most severely traumatised patients.²¹ A minimum target platelet count of 75x10⁹.L⁻¹ is appropriate in this clinical situation.¹⁷

Calcium

Ionised calcium levels should be monitored during massive transfusion, as hypocalcaemia develops during massive transfusion, as a result of

the citrate used as an anticoagulant in blood products. It has been suggested that calcium chloride be administered during massive transfusion if ionised calcium levels are low or electrocardiographic changes suggest hypocalcaemia.¹⁷

Further management of massive haemorrhage

Once bleeding is controlled, blood pressure, acid-base status and temperature should be normalised; vasopressors should be avoided. The patient should be actively warmed. Coagulopathy should be anticipated and prevented if possible; if present, it should be treated aggressively. Following treatment for massive haemorrhage, the patient should be admitted to a critical care area for monitoring and observation, including monitoring of coagulation, haemoglobin and blood gases, together with wound drain assessment, to identify overt or covert bleeding.

Venous thromboprophylaxis

Standard venous thromboprophylaxis should be commenced as soon as possible after bleeding has been controlled, as patients rapidly develop a prothrombotic state.

Disability - rapid neurological assessment

Check the pupils for size and reaction to light and assess the Glasgow Coma Score (GCS) score rapidly. If the patient requires urgent induction of anaesthesia and intubation, remember to perform a quick neurological assessment first.

- A:** Alert
- V:** Responding to Voice
- P:** Responding to Pain
- U:** Unresponsive

A simple mnemonic for a crude but simple GCS assessment is AVPU:

Patients who score 'P' or 'U' on the AVPU scale are likely to need intubating. 'P' roughly corresponds with a GCS of 8/15.

Checking glucose levels is an important part of the primary survey, as it may reveal a potential cause for the trauma. For example, hypoglycaemia in a diabetic patient leading to a road traffic crash.

Exposure

Undress the patient completely and protect from hypothermia with warm blankets or a hot air blower.

CONSIDER NEED FOR PATIENT TRANSFER

During the primary survey and resuscitation phase the evaluating doctor often gathers enough information to decide whether to transfer the patient to another facility. This transfer process may be initiated by administrative personnel, at the direction of the examining doctor, while additional evaluation and resuscitative measures are underway. Once the decision to transfer the patient has been made, communication between the referring and receiving doctors is essential.

SECONDARY SURVEY

Secondary survey takes place following the primary survey and resuscitation, when the patient has been initially stabilised; it is a top to toe examination and should involve, as per the traditional ATLS teaching, 'fingers and tubes in every orifice'. As any clinical picture can evolve, the team should ensure their assessment is continuous and any change in the condition of the patient should result in reassessment, starting again with <C>ABC.

At this stage, if not already given during handover on the arrival of the patient, an 'AMPLE' history should be obtained as a minimum.²⁷ Emergency services, relatives, friends or other witnesses can be used for this, if the patient is unable to communicate effectively.

An AMPLE history incorporates:

Allergies,
Medication,
Past medical history,
Last meal and,
Events leading up to the point of injury.

The mechanism of injury is a vital clue to possible injuries sustained and pictures taken by Emergency Services on scene can be invaluable. In the case of a road traffic collision, factors such as position of the patient in the vehicle, restraints worn, speed of collision, vehicle rollover, passenger ejection and other casualties or fatalities are key indicators of the nature and severity of injury. Risk factors for significant injury in falls include falling from heights over 1m or 5 steps. With burns it is important to know what substance has caused the burn and the duration of exposure to that substance. It is also crucial to exclude exposure to hazardous substances, which may pose a threat to the medical team, as well as to the patient.

Head and neck

Assessment should begin with a mini neurological exam and formal GCS estimation. GCS trends are especially important in the trauma patient. If there is any suspicion of head injury, this must be assumed to be the cause of a decreased GCS, until proven otherwise. Along with respiratory rate and systolic blood pressure, the GCS helps make up the Revised Trauma Score. This is a physiological scoring system that is based on the first set of data obtained from the patient and which has shown high inter-rater reliability and accuracy in predicting mortality. Lower scores correlate with higher mortality rates and it is recommended that patients with a score of 4 or less should be managed at a designated trauma center where possible.²⁸

The head and neck should be thoroughly examined for wounds and signs of skull fractures. Beware of depressed skull fractures that may be masked by overlying haematomas, but which merit CT and neurosurgical consultation. Signs of base of skull fracture include:

- Epistaxis
- Cerebrospinal fluid (CSF) otorrhoea or rhinorrhoea (check for halo sign on gauze)
- Raccoon eyes
- Subconjunctival haemorrhage with no visible posterior limit
- Haemotympanum
- Battle's sign may be a late sign (bruising over mastoid process).

If any of the above is present, a CT head should be performed.²⁹ In the absence of CT facilities, a plain skull Xray will show skull fractures. Any open skull fracture requires antibiotics and theatre. If neurosurgery is not available, any lateralising signs that develop should be treated by performing a craniectomy following 3 burr holes.

Head injury is classified as mild (GCS 14-15), moderate (GCS 9-13) or severe (GCS 3-8). In civilian trauma, 80% of head injuries fall into the mild category, 10% into moderate and 10% are severe. A patient with GCS less than 8 requires intubation.

Prevention of secondary brain injury is described in the article on page 107.

The neck should be inspected and palpated for wounds, surgical emphysema, tracheal deviation and ruptured larynx. Distended neck veins may be hard to elicit if the trauma patient is hypovolaemic but, if present, should raise suspicion of cardiac tamponade or tension pneumothorax. A neck wound should not be explored unless in an operating theatre.

Whilst the head is held, the hard collar can be temporarily removed and the C-spine palpated for bony tenderness or deformity. If the patient's GCS is less than 15, if they are under the influence of drugs or alcohol, or if they have another distracting injury, then the C-spine cannot be cleared without imaging and the patient will have to remain immobilized.

Further clearance of cervical spine injury is described in the article on page 112.

Chest

Immediately life-threatening chest injuries should have been dealt with by this stage. This is the time to carry out a more detailed inspection, palpation, percussion and auscultation and to review the chest Xray taken during the primary survey. Potentially life threatening injuries should be considered and excluded. These are described in the article on page 119.

In paediatric trauma, it is important to remember that significant intrathoracic trauma may have been sustained, despite the absence of rib fractures or other bony injuries.

It is crucial in the recovery of patients with chest injuries to ensure they have effective analgesia, so that they can achieve adequate ventilation.

Patients with rib fractures may require intercostal nerve blocks and those with a flail chest might benefit from a thoracic epidural for the first few days. These patients are at risk of developing atelectasis and subsequent pneumonia.



Figure 2. Chest Xray of a 32-year-old male, unrestrained driver in an RTC who suffered left sided diaphragmatic rupture with respiratory compromise. He required urgent laparotomy and was intubated by RSI with a double lumen tube.

Abdomen

As mentioned previously, a haemodynamically compromised patient, who is FAST positive, requires immediate surgery. Secondary survey should then take place, once damage control surgery has been carried out. If the patient is stable after the primary survey, however, he should have a full abdominal examination carried out. If FAST or CT is not available, then continuous reassessment may be required; changing clinical signs may indicate the need for laparotomy.

A suspected pelvic fracture should already have been splinted during the primary survey, using a firmly tied sheet if nothing else is available. There is no requirement to 'spring' the pelvis. Look for obvious deformity and palpate once. The pelvis should be immobilized on any suspicion of a fracture, until it can be formally imaged; preferably using CT. Traction may be required if the leg length is unequal, especially in shear fractures. Bruises over the iliac crests, pubis, labia or scrotum indicate possible pelvic fracture.

All creases and crevices should be examined, particularly in victims of penetrating trauma. Do not forget to look at the perineum and to perform a vaginal examination if indicated.

All trauma patients should have a urinary catheter inserted, unless there is concern about urethral injury (blood at meatus, high riding prostate

on rectal examination), in which case a supra pubic catheter should be used. Urine output should be maintained at $>0.5\text{ml.kg}^{-1}.\text{hr}^{-1}$ in adults and $>1\text{ml.kg}^{-1}.\text{hr}^{-1}$ in children, unless the patient has suffered a crush injury, when at least double this output should be achieved. Output should be measured accurately using an urometer, remembering that the initial residual urine volume obtained on catheterization is not included in the measured response to resuscitation. It should be tested for blood and glucose and then discarded. Macroscopic haematuria should be investigated; this can be done initially using contrast enhanced Xrays or CT. All females of childbearing age should have a urine pregnancy test performed.

An intubated patient should have a nasogastric or orogastric tube inserted to help reduce gastric dilatation and minimise diaphragmatic splinting, thereby improving ventilation.

Indications for laparotomy in the trauma patient are largely dictated by the patient's physiology.

Limbs

Catastrophic limb haemorrhage should have been dealt with at the very start of primary survey. During the secondary survey all four limbs should be thoroughly re-examined for deformity, wounds and neurovascular status. An alert patient will be able to indicate which areas are painful on passive movements. It is important to seek signs such as swelling and crepitus in unconscious patients. Palpate the muscles and have a high index of suspicion for compartment syndrome in trauma, especially in the unconscious patient.

Compartment syndrome occurs when the pressure within an osteofascial compartment of muscle causes ischaemia and then necrosis. Common areas where compartment syndrome occurs are the lower leg, forearm, foot, hand, the gluteal region, and the thigh. The ischaemia may either be caused by an increase in compartment size, for example swelling secondary to revascularisation or by decreasing the compartment size, for example a constricting dressing.

The signs and symptoms of compartment syndrome include pain greater than expected (and this typically increases by passive stretching of involved muscles), paraesthesia in the distribution of the involved peripheral nerve, decreased sensation or functional loss of the nerves that traverse the involved compartment and tense swelling of the involved region. A palpable distal pulse is usually present in a compartment syndrome.

Intracompartmental pressure measurements may be helpful in diagnosing a suspected compartment syndrome, particularly if the patient is unconscious. Tissue pressures that are greater than 35 to 45mmHg suggest decreased capillary blood flow that results in increased muscle and nerve anoxic damage. Systemic blood pressure is important because the lower the systemic blood pressure, the lower the compartment pressure required to cause a compartment syndrome. Pressure measurement is indicated in all patients who have an altered response to pain.

Any deformities should be realigned and splinted. Ensure adequate analgesia and appropriate imaging prior to these manoeuvres. Examine pulses and document findings both before and after manipulation. If there is vascular compromise, reduction should take place before imaging. In every case, imaging should be performed after reduction.

All wounds should be cleaned and then covered loosely with iodine soaked gauze. Photographs may be taken of the wounds to prevent multiple examinations by different specialties.

It should be noted that the presence of pulses does not exclude vascular injury. It is important to suspect vascular damage based on mechanism of injury. If there is more than a 10% difference in blood pressure between the right and left limbs (comparing arm with arm and leg with leg, not arm with leg), then angiography is mandated.

Analgesic options are broad but will depend on available medications and expertise. Possibilities include IV paracetamol, non-steroidal anti-inflammatory agents, morphine, nerve blocks such as fascia-iliaca or femoral nerve blocks, sedation and Entonox® (50% oxygen and 50% nitrous oxide).

Open fractures require broad spectrum IV antibiotics and any wound should prompt consideration of tetanus prophylaxis. If there is uncertainty about whether a patient has received 3 tetanus toxoid immunizations, then a booster should be given. In addition to this, a tetanus prone wound (such as a dirty wound covered with foreign material) should be covered with tetanus immune globulin.¹⁸

Log roll

If not already performed during the primary survey, a log roll should be carried out for all trauma patients, ensuring full in-line spinal stabilisation is maintained throughout. A team of five is required for this. The anaesthetist at the head end will co-ordinate and give commands to move the patient. Three personnel will stand along one side of the patient and take charge of the shoulders and chest, pelvis and legs respectively. The patient is rolled away from the injured side where possible, taking care of lines and tubes, and the fifth team member inspects and palpates the spine and back. A rectal examination should also be performed to check anal tone, to exclude a high riding prostate, and to look for blood on the glove, that may indicate a rectal injury.

TRANSFER TO DEFINITIVE CARE

The requirement for transfer is individual to each trauma patient. Patient outcome is directly related to time elapsed between injury and definitive care.¹⁷ It is essential to be aware of the capabilities of the primary receiving hospital and of any potential secondary referral units, in order to make the initial decision to transfer. As mentioned earlier, a Revised Trauma Score of less than four is used to indicate that a patient should be managed in a major trauma centre.²⁸

Timing of transfer is largely based on the stability of the patient; damage control surgery may be required prior to transport. Other key decisions include how to transport the patient and which medical staff should accompany them. The answer to these questions will also be individual to each case and will depend partly on what transport options exist and on the skill set of available staff. Ideally an intubated patient should be accompanied by an anaesthetist, but in smaller hospitals, such a move could leave that hospital without anesthetic cover.

Once the decision is made to transfer, good communication between referring and receiving facilities is crucial. It is the responsibility of the referring doctor to initiate this and to ensure that the patient arrives

with accurate and comprehensive documentation. It is also vital to ensure that <C>ABCDE have been addressed and stabilised as far as possible, that tubes and lines have been fully secured and that the patient has adequate analgesia or sedation for the journey. An example transfer form is included in ATLS 8th edition.^{13,18}

SUMMARY

Evaluation and resuscitation of the major trauma patient requires a coordinated approach from a well-trained and rehearsed team. The process is logical; starting with <C>ABCDE (to ensure that nothing is missed) and it should involve concurrent activity from team members, with a horizontal approach to resuscitation to ensure that this happens in an expeditious and efficient fashion.

During the primary survey, life threatening injuries are treated as they are found. Once the patient is stabilised, a thorough secondary survey is carried out, which is a head to toe examination of the patient, with further investigations and injury management taking place as required. The patient is then packaged and dispatched to the most appropriate area or facility for definitive care.

It is strongly recommended that any member of staff who could be involved in the resuscitation of a trauma patient should complete an ATLS or PTC course. Details can be found at <http://www.rcseng.ac.uk/education/courses/atls.html> and www.primarytraumacare.org/

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Management of head injuries

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INTRODUCTION

Trauma is now the leading cause of death in most developed countries in the 18-40 age group and head injury is a major contributing factor. The World Health Organisation estimates that 300 people per day are killed due to trauma on Africa's roads. The most common causes of head injury are falls, road traffic accidents and assaults, with young men and children the most affected. In the UK, around one million people per year attend Emergency Departments due to head injury.

Head injury is defined by the National Institute for Clinical Excellence in the UK (NICE, www.nice.org.uk) as any trauma to the head other than superficial injuries to the face. Mild head injury makes up around 90% of all cases (GCS 13-15), moderate 5% (GCS 9-12) and severe head injury 5% (GCS ≤ 8).

Head injury is a major cause of long term disability and economic loss to society. Much of the neurological damage resulting from a head injury does not occur immediately, but in the minutes, hours and days that follow. It is for this reason that so much emphasis is placed on immediate management of head-injured patients. The primary injury is due to irreversible mechanical injury, but secondary injury which leads to cerebral ischaemia, results from raised intracranial pressure (ICP), hypotension, hypoxia, anaemia, seizures, hypoglycaemia and hyperthermia. Prevention and correct management of these complications improves outcome from head injury.

PRINCIPLES OF MANAGEMENT

The main aim of assessment and management of head-injured patients is to maintain adequate cerebral blood flow (CBF) and to avoid cerebral ischaemia and hypoxia. In patients with a head injury, the normal auto-regulation of CBF is lost and CBF is proportional to cerebral perfusion pressure (CPP), which in turn is directly determined by both the mean arterial pressure (MAP) and the intracranial pressure (ICP):

$$CPP = MAP - ICP$$

The cranium is a rigid structure with a fixed capacity, which contains 80% brain, 10% blood and 10% CSF.

These structures are all non-compressible, therefore an increase in the volume of any of these contents, unless coupled by a decrease in volume of another, results in an increase in ICP.

The main mechanisms of maintaining CPP are to ensure adequate MAP (by the use of fluids and vasopressors) and to prevent excessive rises in ICP. In normal individuals the ICP is 0-10mmHg and this is largely determined by auto-regulation of CBF (i.e. the amount of blood in the cranium). Vasoconstriction or vasodilatation of cerebral vessels occurs in response to changes in MAP, PaO₂, PaCO₂ and blood viscosity. Although these responses may be obtunded in head injury, prevention of secondary brain injury involves manipulation of these variables. An increase in PaCO₂ causes vasodilatation and an increase in CBF, which may increase ICP; a decrease in PaCO₂ causes vasoconstriction leading to decreased CBF and ICP. Thus inappropriate hyperventilation may cause ischaemia. A fall in PaO₂ causes vasodilatation with a consequent rise in ICP.

INITIAL ASSESSMENT

Patients presenting with significant head injury may have multiple injuries. The history of the mechanism of injury is useful in determining the potential extent of the head injury and is also an indication of the likelihood of other injuries. For example, the driver of a vehicle travelling at 60mph and not wearing a seatbelt raises the suspicion of both major head injury and significant extra-cranial injury.

Initial management should be guided by protocols suggested by Advanced Trauma Life Support (ATLS) or Primary Trauma Care (PTC, www.primarytraumacare.org). Injury to the cervical spine should be assumed from the start of assessment. Brain injury may be worsened by airway or circulatory compromise; use the ABC approach to identify and treat life-threatening injuries early (see article on page 95).

Once the patient has a secure airway, is adequately oxygenated and has a stable cardiovascular system, consideration should be given to transfer to a neurosurgical unit (where available). When discussing the case with the neurosurgeon, it is important to

Summary

This article describes the basic principles of management of a patient with a head injury and includes CT images of the common intracranial injuries. It should be read in conjunction with the articles on general trauma management and management of cervical spine injury.

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convey the mechanism of injury, any other injuries and the results of a brief neurological assessment. The surgeon will want to know the history, the Glasgow Coma Score (GCS) at the scene, on arrival at your hospital and the current GCS (especially the motor score), the pupillary size and reaction, and whether there are any signs suggesting a collection of blood on one side of the cranial cavity ('lateralising' signs).

THE GLASGOW COMA SCALE

The GCS is the globally accepted method of quantifying and recording the neurological status of the head-injured patient. It is also useful in determining any improvement or deterioration in neurological function and facilitates accurate communication between health professionals. The scale is made up of three sections, with a minimum score of 3 and a maximum of 15. The best score in each section should be recorded e.g. if the patient localises with the right arm but extends on the left, then the best motor score is 5/6).

The components of GCS are:

Eye opening

- Spontaneously 4
- To speech 3
- To pain 2
- None 1

Verbal response

- Orientated 5
- Confused 4
- Inappropriate 3
- Incomprehensible sounds 2
- None 1

Motor response

- Obeys commands (for movement) 6
- Purposeful movement to painful stimuli ('localises') 5
- Withdrawal from painful stimuli 4
- Abnormal (spastic) flexion, decorticate posture 3
- Extensor (rigid) response, decerebrate posture 2
- None 1

The standard painful stimulus applied to the patient should allow the differentiation of purposeful movement ('localising'), from withdrawal and abnormal flexion. Strictly speaking true localisation or purposeful movement should follow a stimulus from one site to another. Squeezing/pinching the trapezius muscle and supra-orbital pressure are preferred stimuli. Nail bed pressure and sternal rub are less reliable and not of use in patients with spinal injury. Care must also be taken when assessing motor response in those with a suspected cervical spine injury, as any response may cause the patient to attempt to move their head.

The **Blantyre Coma Score** was originally designed for treatment of children with malaria, but is useful for assessment of children with head injury:

Eye movements

- Watches or follows (e.g. the mother's face) 1
- Fails to watch or follow 0

Motor response

- Purposeful movement to painful stimuli ('localises') 2
- Withdraws from pain 1
- No response or inappropriate response 0

Verbal response

- Cries appropriately with painful stimulus, or if verbal speaks 2
- Moan or abnormal cry with painful stimulus 1
- No vocal response to painful stimulus 0

MANAGEMENT

The main aims of management of any moderate or severe head injury are initial assessment and resuscitation, deciding whether ventilatory support is necessary and establishing a diagnosis, with a CT head scan if this is available. Early contact with specialist neurosurgical units is key; they will often advise on specific therapies. Early transfer, when indicated, is also important. The Association of Anaesthetists of Great Britain and Ireland suggest a maximum time of 4 hours between injury and surgery. Throughout this process management should be equal to that in an ICU, directed at maintaining the MAP and CPP and preventing rises in ICP.

Airway

The main concern is whether the patient is able to protect their airway and therefore whether intubation is necessary. Indications for intubation include:

- GCS \leq 8
- Risk of raised ICP due to agitation (i.e. sedation required)
- Inability to control/protect the airway or loss of protective laryngeal reflexes
- A fall of 2 or more points in the motor component of the GCS
- In order to optimise oxygenation and ventilation
- Seizures
- Bleeding into mouth/airway
- Bilateral fractured mandible.

This is not an exhaustive list and clinical judgement is important. If there is doubt, it is safest to intubate and consider early extubation

rather than delay intubation and risk secondary brain injury from hypoxia.

Rapid sequence intubation is almost always required. Maintain cervical spine immobilisation during intubation, unless the cervical spine has been clinically and radiologically cleared. Avoid the temptation to use no drugs in profoundly unconscious patients; some hypnosis and analgesia is required to obtund the rise in ICP that is inevitably caused by laryngoscopy. Propofol, etomidate, benzodiazepines and barbiturates all reduce ICP and are preferentially used. Ketamine produces a rise in ICP, but may be the only induction agent available in certain countries. Opioids and depolarising neuromuscular drugs do not increase ICP. The fasciculations caused by suxamethonium may cause a transient rise in ICP. Nitrous oxide may also cause a rise in ICP via increased blood flow.

Detection of cervical spine injuries is described in the article on page 112. All patients with head injury should have plain Xrays of the cervical spine and some may require a CT scan.

Breathing

Hypoxaemia is associated with a significant increase in mortality. A drop in PaO₂ below 8kPa (about 60mmHg) causes an increase in CBF and ICP. Targets for gas exchange should be a PaO₂ greater than 13kPa (100mmHg) and a PaCO₂ in the low normal range - usually 4.5-5.0kPa (35-39mmHg). Prolonged hyperventilation is not recommended since cerebral vasoconstriction and ischaemia may result, but short bursts of hyperventilation (a few minutes) may help to control episodes of high ICP.

Circulation

The loss of the autoregulation of CBF can result in a reduction in oxygen delivery. Maintenance of the MAP and CPP is essential; resuscitation and treatment of life-threatening circulatory instability should take precedence over neurosurgical interventions. This may

include surgery for haemorrhage control.

Use fluids, and where necessary vasopressors to achieve a MAP greater than 80-90mmHg. This figure is recommended as a guide until ICP monitoring is established, and assumes that the ICP is 20mmHg and therefore ensures a CPP of at least 60-70mmHg (since CPP = MAP – ICP). Once ICP monitoring is established then treatment is targeted at maintaining CPP 60-70mmHg. Aiming for higher CPP targets has been associated with adverse cardio-respiratory outcomes.

Ideally the MAP is measured using an arterial line. A central venous catheter may be useful for monitoring and the administration of vasopressors. A urinary catheter allows monitoring of urine output and fluid balance, especially if mannitol or other diuretics are used.

MONITORING INTRACRANIAL PRESSURE

Some clinical signs are suggestive of raised ICP. These include:

- Headache
- Dizziness
- Loss of consciousness
- Confusion
- Hypertension and bradycardia (Cushing's reflex)
- Nausea
- Vomiting
- Focal weakness or paresis
- Other focal neurological signs
- Change or asymmetry pupils.

Measurement of ICP

ICP can be measured using the techniques described in Table 1.

Table 1. Measurement of ICP.

Method	Benefits	Disadvantages
Intraventricular catheter (EVD or external ventricular drain)	<ul style="list-style-type: none"> • Gold Standard method • Allows CSF drainage to lower ICP • Re-zeroing possible 	<ul style="list-style-type: none"> • Most invasive method • High infection rate • May be difficult to insert • Simultaneous CSF drainage and ICP monitoring not possible
Extradural probe	<ul style="list-style-type: none"> • Low infection rate (no penetration of dura) • Easy to insert 	<ul style="list-style-type: none"> • Limited accuracy • Relatively delicate
Subarachnoid probe	<ul style="list-style-type: none"> • Low infection rate • No brain penetration 	<ul style="list-style-type: none"> • Limited accuracy • High failure rate
Intraparenchymal probe	<ul style="list-style-type: none"> • Low infection rate 	<ul style="list-style-type: none"> • Measures local pressure
Transcranial Doppler	<ul style="list-style-type: none"> • Non invasive 	<ul style="list-style-type: none"> • Limited precision
Lumbar CSF pressure	<ul style="list-style-type: none"> • Extracranial procedure 	<ul style="list-style-type: none"> • Inaccurate reflection of ICP • May be dangerous when brain oedema present
Tympanic membrane displacement	<ul style="list-style-type: none"> • Non-invasive 	<ul style="list-style-type: none"> • Insufficient accuracy

MANAGEMENT OF RAISED ICP

Improving venous drainage from the brain

- Elevation of the head of the bed to 30°.
- Good neck alignment – head in the neutral position.
- Ensuring ties holding the endotracheal tube in place do not compress the neck veins. Alternatively tape the tube using 'trouser-legs'.
- Where possible immobilise the patient's cervical spine with sandbags and tape rather than restrictive neck collars.

Reducing cerebral oedema

- Use mannitol (an osmotic diuretic) 0.5-1g.kg⁻¹ (= 5-10ml.kg⁻¹ of 10% or 2.5-5ml.kg⁻¹ of 20% mannitol). Some units use small aliquots of hypertonic saline as an alternative.
- Use furosemide (a loop diuretic) 0.5-1mg.kg⁻¹.
- Maintain serum Na⁺ in the range 140-145mmol.L⁻¹.

Reduction of the cerebral metabolic rate for oxygen

- Close temperature regulation. Avoid hyperthermia, but do not actively induce hypothermia.
- Use of sedation and anaesthetic drugs. Ensure that the patient is appropriately sedated and has received adequate analgesia.
- If the patient has a witnessed seizure loading with an anticonvulsant, usually phenytoin 18mg.kg⁻¹, should be considered.
- In cases of intractable raised ICP, a thiopentone infusion can be used to reduce the cerebral metabolic rate to a basal level. This is identified on EEG monitoring as 'burst suppression'.

Reducing intracranial blood volume

- Consider whether the patient has suffered a new or worsening intracranial haemorrhage. Are there any new or lateralising signs? Is a repeat CT scan required?
- Hyperventilation can be used to reduce the PaCO₂ as a temporary measure, but cerebral ischaemia may result if this is prolonged (more than a few minutes).
- The final resort if ICP remains raised is to perform a decompressive craniectomy (part of the cranial bone is removed).

Reducing CSF volume

- In a neurosurgical centre, use of an external ventricular drain (EVD) allows drainage of CSF to relieve raised ICP.

TRANSFER TO NEUROSURGICAL UNIT

Where there is a regional neurosurgical service, you may need to refer a patient or obtain advice. Electronic transfer of CT images allows the neurosurgeon to see the scans straight away and reduces delay. If the patient's condition changes significantly you should seek further advice. Some patients will benefit from being transferred to a neurosurgery centre.

Full resuscitation and stabilisation of the patient and all injuries must be completed prior to transfer. A doctor with appropriate training and

experience should oversee the transfer of the patient, the goal being continuous management to the standard available in the ICU. Ideally, monitoring for transfer should include ECG, invasive blood pressure, pulse oximetry, urinary catheter/output and capnography. Pupillary size and reaction to light should also be monitored. It is useful to check an arterial blood gas prior to departure and to correlate the PaCO₂ to the end-tidal value as the end tidal value is usually 0.5 - 1kPa higher. As with all transfers, think what may go wrong and check you have the facilities to deal with it en route.

TYPES OF INJURY

Traumatic subarachnoid haemorrhage

This is the most common type of intracranial haemorrhage. Blood is seen in the CSF and subarachnoid space. It is often caused by tearing of small subarachnoid blood vessels. Vasospasm may complicate traumatic subarachnoid haemorrhage and the amount of blood is related to the patient's GCS and outcome.

Acute subdural haemorrhage (Figure 1)

This type of injury is often caused following forceful acceleration-deceleration events. Blood is seen on CT between the dura and the brain. Rapid neurosurgical intervention is often required, necessitating rapid transfer. On CT scan the border of the haematoma next to brain tissue is typically concave (i.e. curved inward) towards the midline.



Figure 1. CT scan showing large left fronto-parietal subdural haematoma (A), with midline shift and compression of the left lateral ventricle.

Epidural (extradural) haemorrhage (Figure 2)

This is seen in up to 1% of cases. Blood is seen on CT between the skull and the dura. The classical presentation is of a patient who initially has loss of consciousness and is then lucid, before deteriorating again. Extradural haemorrhages often occur in conjunction with skull fractures, particularly over the course of the middle meningeal artery.

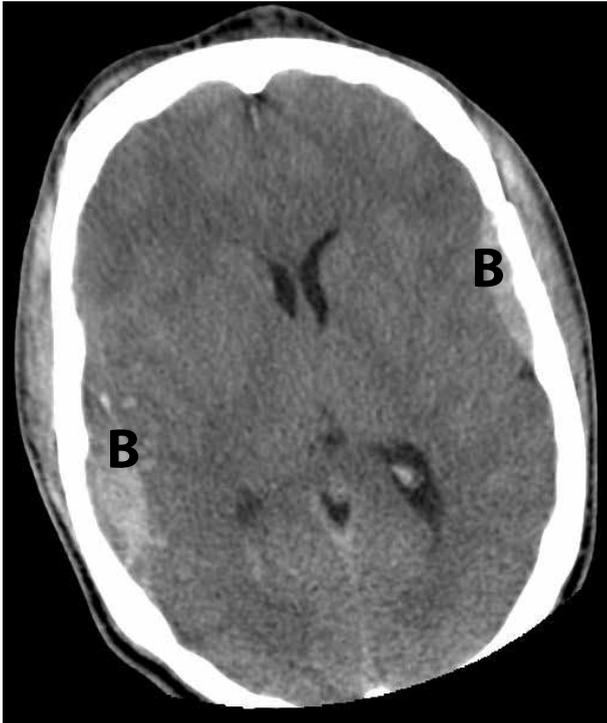


Figure 2. CT scan showing bilat extradural haematomas (B).



Figure 3. CT scan showing a fronto-parietal intracerebral haematoma (C) with surrounding oedema (D) and midline shift.

Prognosis is good if surgery is performed promptly. On CT scan the border of the haematoma next to brain tissue is typically convex towards the midline.

Intracerebral haemorrhage (Figure 3)

This is an injury deep within the brain itself, and is caused by shearing forces between the cranium and brain. It is most common around the frontal and temporal regions, with 50% of cases suffering loss of consciousness on impact.

Diffuse Axonal Injury

This is the primary lesion in around 40-50% of severe head injuries, and is secondary to shearing and tensile forces. The prognosis is linked to the clinical cause, with prolonged coma suggesting severe, irretrievable injury.

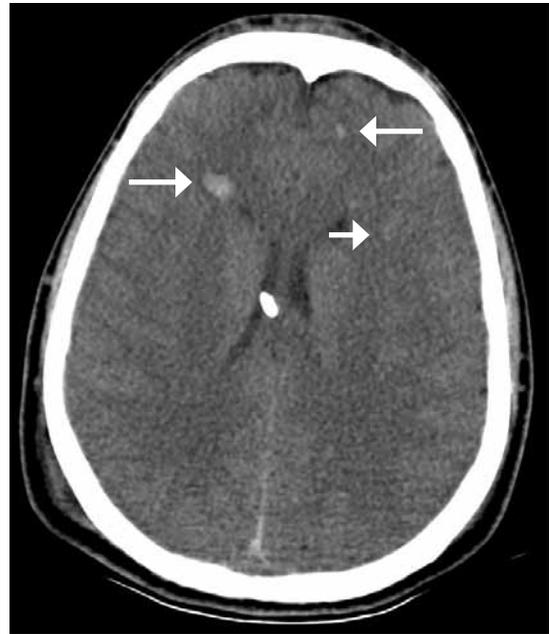


Figure 4. CT scan showing diffuse axonal injury with frontal petechial haemorrhages (arrows).

FURTHER READING

1. Recommendations for the safe transfer of patients with brain injury. The Association of Anaesthetists of Great Britain and Ireland (2006). Available at <http://www.aagbi.org/sites/default/files/braininjury.pdf>
2. NICE Guidelines. Head injury: triage, assessment, investigation and early management of head injury in infants, children and adults (2003). Available at: <http://www.nice.org.uk>
3. Primary Trauma Care. Trauma resuscitation guidelines for resource limited countries. Available at: www.primarytraumacare.org
4. Brain Trauma Foundation. Evidence based guidelines for head injury management. Available at: www.braintrauma.org

Acute cervical spine injuries in adults: initial management

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INTRODUCTION

Spinal cord injury is a catastrophic consequence of cervical spine injury and is a challenging condition to manage, with global pathophysiological changes occurring following injury. Although respiratory complications are the leading cause of morbidity and mortality the condition calls for a multisystem approach and often involves several disciplines. Correct early management of acute cervical spinal cord injuries can improve longterm outcome.

Between 2 and 5% of patients suffering from blunt polytrauma have a cervical spine injury. Cervical spine injuries tend to occur between 15 and 45 years and are seen more commonly in males (7:3). The most common level of fracture is C2 whereas dislocations occur most commonly at the C5/6 and C6/7 levels.¹

The initial management of the polytrauma patient follows the Advanced Trauma Life Support (ATLS) practice of airway and cervical spine control, breathing and circulation. Assessment of injuries takes place initially in the form of a primary survey, during which time life threatening injuries are sought. This is followed by a secondary survey, when a more detailed assessment of injuries is carried out, including spinal injuries. All polytrauma patients should be assumed to have a cervical spinal injury until proven otherwise; precautionary cervical spine immobilisation should be instigated for all patients at the scene of the injury by pre-hospital staff. By immobilising the spine immediately, major injuries can be treated at the scene, or on arrival at hospital, without the risk of disrupting an unstable cervical spine injury and causing secondary neurological injury.²

IMMOBILISATION OF THE SPINE

Until spinal injuries can be excluded or 'cleared' the spine must be immobilised and this can be achieved in a number of ways. However, all methods continue to allow varying degrees of movement. Soft cervical collars are the most inefficient and provide very little stability and therefore should not be used. Whereas the application of Gardner-Wells forceps can be considered the most effective, it is rarely a practical solution in the acute setting. Two methods are in common use,

compromising between simplicity of application and effectiveness: these are semi-rigid collars and manual in-line stabilisation (MILS). In the prehospital setting, MILS should be applied as an initial manoeuvre as the patient's airway is assessed and then, when available, a semi-rigid collar should be applied. Further stability is achieved by using sandbags or blocks on either side of the head, with two non-elastic self adhesive tapes strapped across the head and on to a rigid spinal board. Users should be aware of the disadvantages of semi-rigid collars (Table 1).

Table 1. Disadvantages of semi-rigid collar

Total immobilisation is not achieved
Increase the chances of difficult laryngoscopy
Can exacerbate cervical spinal injuries
Can cause airway obstruction
Can increase the intracranial pressure (ICP)
Increases the risk of aspiration
Increases the risk of deep vein thrombosis (DVT)
May cause significant decubitus ulcers

Laryngoscopy is more difficult with a semi-rigid collar in place. If laryngoscopy and intubation is urgently indicated the collar should be removed and MILS applied instead (Figure 1). During laryngoscopy MILS reduces cervical spine movement by up to 60%. An assistant squatting behind the patient applies MILS by placing his or her fingers on the mastoid processes and the thumbs on the temporoparietal area of the skull. The hands are then pressed against the spinal board and act to oppose movements of the head caused by the anaesthetist. Axial traction should not be applied because of the risk of exacerbating cervical spinal injuries. Until the spine is 'cleared' a log roll should be performed for any movement or transfer of the patient.^{3,4}

CLEARING THE CERVICAL SPINE

Imaging the spine does not take precedence over the treatment of life threatening conditions. Once the patient is stable, the exclusion of spinal injuries and

Summary

This review is for anaesthetists who specialise in intensive care, focusing on the first few days following injury to the cervical spine and the spinal cord. Involvement often starts in the emergency department with resuscitation of patients with polytrauma and continues with supportive care on the intensive care unit.

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ligamentous injuries requires a combination of clinical assessment and radiological investigation. Clinical clearance of cervical spine injury is difficult or impossible in patients who are unconscious (due to sedation, anaesthesia or head injury), or have distracting injuries to other parts of the body. Anaesthetists should understand the principles of clearing the cervical spine, since a proportion of patients cannot be clinically cleared for several days and prolonged cervical spine immobilisation (with its inherent risks) may be necessary.

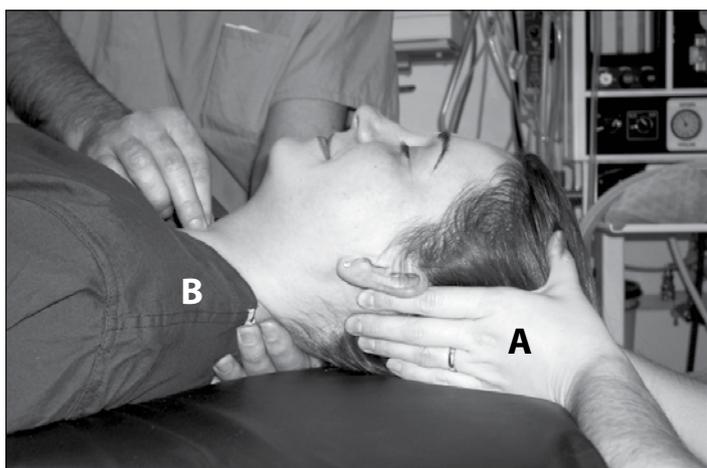


Figure 1. A - Application of manual in-line stabilisation (MILS); B - Bimanual application of cricoid pressure.

Two sets of screening clinical criteria have been proposed prior to imaging the cervical spine, in an attempt to reduce the number of unnecessary X-rays. These are the Canadian c-spine rule and the National Emergency X-radiography Utilisation Study (NEXUS) criteria. Both are sensitive tools.¹

The **NEXUS criteria** include;

- No evidence of posterior cervical tenderness
- No history of intoxication
- An alert patient
- No focal neurological deficit
- No painful distracting injuries

If all the criteria are fulfilled then the cervical spine can be cleared without the need for imaging.

The **Canadian c-spine rule** asks 3 questions;

1. *Are there any high risk factors which makes performing radiological investigation mandatory?*

- Age >65 years
- Mechanism of injury; fall >3 feet (1 metre), axial load to head e.g. diving, motor vehicle collision; >100km.h⁻¹, rollover or ejected, bicycle collision
- Parathesia of extremities.

2. *Are there any low risk factors which allow for safe assessment of range of motion?*

- simple rear end
- sitting position in Emergency Department
- ambulatory at any time
- delayed onset of neck pain
- absence of midline c-spine tenderness.

3. *Able to actively rotate neck 45° left and right?*

The NEXUS criteria have 99% sensitivity, 12.9% specificity, 99.8% negative predictive value and a 2.7% positive predictive value, whereas the Canadian c-spine rule has 100% sensitivity and 42.5% specificity. Both tests have been validated in clinical practice and have been shown to be accurate and reliable. Either test is suitable for use in everyday practice.



Figure 2. Lateral cervical spine X-ray, showing fracture-dislocation of C4 (A) on C5 (B).

If these screening tests indicate that radiological imaging is required, the strategy needed to clear the cervical spine differs depending on whether the patient is awake or unconscious. In the alert patient it is generally agreed that clearing the spine requires a 3-view plain X-ray series (lateral and AP cervical spine views with a 'peg view'), with a computerised tomogram (CT) for areas that cannot be visualised or are suspicious. If these are normal, but the patient is complaining of neck pain, a lateral cervical spine X-ray should then be performed in flexion and extension.

In the unconscious, since ligamentous injuries are difficult to exclude with accuracy using radiography, there is less agreement on the best method. Three options are available:

1. First the cervical spine is left uncleared and the spine kept immobilised until the patient is fully conscious. Inherent with this method are the complications of immobilisation for any long duration, particularly decubitus ulcers.
2. Alternatively the patient has a combination of plain Xrays and/ or CT scans to exclude bony injuries and, where available, this should followed by magnetic resonance imaging (MRI) or fluoroscopy to exclude ligamentous injuries.
3. MRI may not be available and there are considerable practical difficulties associated with its use in unconscious critically ill patients. A thin cut CT scan is an alternative, including coronal and sagittal reconstruction of the entire cervical spine. Although less sensitive than MRI for the detection of ligamentous injury, CT is more practical and the number of unstable ligamentous injuries missed is extremely small.^{1,3,5} It is worth remembering that the incidence of ligamentous injury without bony injury in blunt trauma is extremely rare.

NEUROLOGICAL ASSESSMENT

During the primary survey of resuscitation, a brief and rudimentary neurological assessment is performed using the AVPU scale (alert, verbal stimuli response, painful stimuli response or unresponsive). Following on, the secondary survey (which involves a more detailed head to toe search for injuries) includes a more thorough neurological assessment documenting both sensory and motor function, rectal tone, and reflexes. At this stage, if abnormalities are detected, a more formal neurological assessment using the ASIA (American Spinal Injury Association, see Figure 4) scoring system should be completed. An ASIA score is obtained from the essential components of the neurological assessment. It is a reliable and reproducible neurological examination which must be repeated daily to monitor for improvements or deterioration. ASIA also provide useful guides to aid standardised motor and sensory neurological examination (available at: http://www.asia-spinalinjury.org/publications/Motor_Exam_Guide.pdf and http://www.asia-spinalinjury.org/publications/Key_Sensory_Points.pdf).



Figure 3. Computed Tomography (CT) of the cervical spine. A - sagittal reconstruction showing fractures at multiple levels; B - transverse section fracture through the vertebral body of C2 to the left of the dens (arrowed); C - transverse section - comminuted fracture with displacement of the left hemi-body into the spinal canal (arrow), presumably compressing the cord; D - transverse section - midline fracture through the vertebral body (arrow), with bilateral fractures of the laminae of the vertebral arch..

Patient Name _____

Examiner Name _____ Date/Time of Exam _____



INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY



MOTOR
KEY MUSCLES
(scoring on reverse side)

	R	L	
C5	<input type="checkbox"/>	<input type="checkbox"/>	Elbow flexors
C6	<input type="checkbox"/>	<input type="checkbox"/>	Wrist extensors
C7	<input type="checkbox"/>	<input type="checkbox"/>	Elbow extensors
C8	<input type="checkbox"/>	<input type="checkbox"/>	Finger flexors (distal phalanx of middle finger)
T1	<input type="checkbox"/>	<input type="checkbox"/>	Finger abductors (little finger)

UPPER LIMB TOTAL (MAXIMUM) + =
(25) (25) (50)

Comments:

L2	<input type="checkbox"/>	<input type="checkbox"/>	Hip flexors
L3	<input type="checkbox"/>	<input type="checkbox"/>	Knee extensors
L4	<input type="checkbox"/>	<input type="checkbox"/>	Ankle dorsiflexors
L5	<input type="checkbox"/>	<input type="checkbox"/>	Long toe extensors
S1	<input type="checkbox"/>	<input type="checkbox"/>	Ankle plantar flexors

(VAC) Voluntary anal contraction (Yes/No)

LOWER LIMB TOTAL (MAXIMUM) + =
(25) (25) (50)

SENSORY
KEY SENSORY POINTS

	R	L	R	L
C2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C4	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C6	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T4	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T6	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T9	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T10	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
T11	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
L1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
L2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
L3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
L4	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
L5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
S1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
S2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
S3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
S4-5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

TOTALS: + =
(MAXIMUM) (56) (56) (56) (56)

Legend: 0 = absent, 1 = altered, 2 = normal, NT = not testable

(DAP) Deep anal pressure (yes/No)

PIN PRICK SCORE (max: 112)

LIGHT TOUCH SCORE (max: 112)

• Key Sensory Points

NEUROLOGICAL LEVEL: The most caudal segment with normal function. Sensory: R L . Motor: R L .

SINGLE NEUROLOGICAL LEVEL:

COMPLETE OR INCOMPLETE? (Incomplete = Any sensory or motor function in S4-S5)

ASIA IMPAIRMENT SCALE (AIS):

(In complete injuries only) ZONE OF PARTIAL PRESERVATION: Most caudal level with any innervation. Sensory: R L . Motor: R L .

This form may be copied freely but should not be altered without permission from the American Spinal Injury Association. REV 04/11

Figure 4. An ASIA spinal cord injury assessment chart (Available to download at: http://www.asia-spinalinjury.org/publications/59544_sc_Exam_Sheet_r4.pdf).

GENERAL MANAGEMENT

Airway management

Patients may require airway instrumentation as an emergency (for airway obstruction, respiratory failure or as part of the management of a severe head injury) or later in their management as part of anaesthesia for surgical management of other injuries.

The extent to which the injured cervical spine can be safely moved is unknown. Therefore the main aim during management of the airway, in patients with potential cervical spine injuries, is to cause the least amount of movement possible. All airway manoeuvres will produce some degree of movement of the cervical spine, including jaw thrust, chin lift and insertion of oral pharyngeal airways. Mask ventilation is known to produce more movement than direct laryngoscopy.

Most anaesthetists are comfortable with direct laryngoscopy and oral intubation and it is therefore the obvious first choice in establishing a definitive airway in the polytrauma setting. During direct laryngoscopy,

significant movement occurs at the occipito-atlanto-axial joint. Manual in-line stabilisation (MILS) is used to minimise this movement. Previous anecdotal reports of the spinal cord being damaged following direct laryngoscopy in patients with unstable cervical spine injuries were based on weak coincidental evidence.⁶ Therefore the technique of direct laryngoscopy with MILS is now an accepted safe technique for managing the airway in patients with potential cervical spine injuries. In addition the gum elastic bougie is a useful adjunct during direct laryngoscopy. It allows the anaesthetist to accept inferior views of the vocal cords thereby limiting the forces transmitted to the cervical spine and therefore movement. No particular laryngoscope blade has shown a superior benefit except the McCoy levering laryngoscope which will improve the view at laryngoscopy by up to 50% in simulated cervical spinal injuries. The McCoy is therefore an alternative to the Macintosh for those experienced in its use (Figure 5).

The laryngeal mask airway (LMA) or intubating laryngeal mask airway are both extremely useful in the failed or difficult intubation. The forces applied during insertion can cause posterior displacement of



Figure 5. The McCoy levering laryngoscope.

the cervical spine, but the movement is less than that seen in direct laryngoscopy. In the ‘can’t intubate, can’t ventilate’ scenario there should be early consideration of the surgical airway or cricothyroidotomy. These techniques can produce posterior displacement of the cervical spine, but this should not prevent the use of this life saving procedure.

Nasal intubation has formerly been included in the Advanced Trauma Life Support course airway algorithm. However, the low success rate and high incidence of epistaxis and laryngospasm has resulted in this technique losing favour. Awake fiberoptic intubation has consistently produced the least amount of movement of the cervical spine in comparative studies. However, in the acute trauma setting, blood or vomit in the airway may make the technique impossible. Further disadvantages include a relatively prolonged time to intubation, risk of aspiration and, if gagging or coughing occur, an increase in the intracranial pressure (ICP). Despite these concerns, for those anaesthetists with sufficient expertise and in the appropriately chosen patient, awake fiberoptic is an option.^{1,4}

With the recent development of video technology there has been a growth in the utilization of videolaryngoscopes. Videolaryngoscopes allow indirect laryngoscopy whereby alignment of the oral, pharyngeal and laryngeal axes is not necessary. In the elective setting they have been shown to be easy to use and master, and improve the view of the larynx compared with direct laryngoscopy, in patients with difficult airways. However this improved view does not always translate into an ease of intubation, as the endotracheal tube must be directed in some way ‘around the corner’. Intuitively one would expect videolaryngoscopes to reduce cervical spine movement during intubation as the view is achieved indirectly. However although there are studies showing a superiority of videolaryngoscopes over direct laryngoscopes, when cervical spine movement is analysed the studies are heterogeneous in their design and in their choice of scope. There are also studies which do not show any benefit. Furthermore, as has already been mentioned, blood or vomit in the airway may make the view using videolaryngoscopy inadequate. Therefore at this stage

videolaryngoscopy should not supersede direct laryngoscopy but remains an incredibly useful backup tool.

Suxamethonium is safe to use in the first 72 hours and after 9 months following the injury. In the intervening period there is a risk of suxamethonium-induced hyperkalaemia due to denervation hypersensitivity and it should be avoided.

Spinal cord injury results in important pathophysiological consequences in various systems of the body that require appropriate treatment.

Respiratory management

Respiratory failure is common and pulmonary complications are the leading cause of death. The diaphragm (C3-C5) and intercostals (T1-T11) are the main inspiratory muscles. The accessory inspiratory muscles consist of sternocleidomastoid, trapezius (both 11th cranial nerves), and the scalene muscles (C3-C8). Expiration is a passive process, but *forced* expiration requires the abdominal musculature (T6-T12). The abdominal muscles are therefore important for coughing and clearing respiratory secretions.

The severity of respiratory failure depends on the level and completeness of the injury. Complete transection of the spinal cord above C3 will cause apnoea and death, unless the patient receives immediate ventilatory support. For lesions between C3 to C5 the degree of respiratory failure is variable and the vital capacity can be reduced to 15% of normal. These patients are at risk of increasing diaphragmatic fatigue due to slowly progressive ascending injury resulting from cord oedema. This commonly results in retention of secretions and decompensation around day 4 post-injury, and intubation and ventilation is required. Where facilities are available some would electively intubate and ventilate patients in this group.

In general, the decision to intubate depends on several factors, including:^{7,8}

- loss of innervation of the diaphragm
- fatigue of innervated muscles of respiration
- failure to clear secretions
- history of aspiration
- presence of other injuries e.g. head and chest injuries
- premonitory conditions, especially respiratory disease.

Initially the intercostal muscles are flaccid, allowing in-drawing of the chest during inspiration with a consequential compromise in respiratory function. This gives the characteristic appearance of ‘paradoxical breathing’ – on inspiration the diaphragm moves down, pushing the abdominal wall out and drawing the chest wall inwards. As the muscles become spastic, respiratory function improves, allowing potential weaning of the patient from the ventilator. Paralysis of the abdominal musculature means that in the upright position the diaphragm works in a lower and less effective position and so a supine position is preferred. Abdominal binders can be used to prevent the abdominal contents from falling forward whilst being upright; they are helpful in lesions above T6. Studies have shown immediate improvements in respiratory function with their use.

Patients with high cervical spine lesions have increased bronchial secretions, possibly due to altered neuronal control of mucous glands. Nebulised N-acetylcysteine and other mucolytics reduce the viscosity of secretions and assist in keeping the airway clear.

There is evidence that spinal cord injured patients have an obstructive component, as well as a restrictive pattern of lung function, and patients with tetraplegia can be shown to have bronchial hyper-responsiveness during bronchial provocation tests. The mechanism for this includes loss of sympathetic innervation and unopposed parasympathetic nerve supply. The sympathetic nerve supply to the lung arises from the upper six thoracic segments of the spinal cord. Postganglionic fibres synapse in the middle and inferior cervical ganglia and in the upper four thoracic ganglia; from here they enter the hilum of the lung where they form plexuses around airways and vessels. In addition the restrictive lung function may be due to softening of the cartilage in large airways, a loss of lung elastin and collagen, a reduction in elastic recoil and finally excessive secretions within the airway lumen. Ipratropium and the longer acting salmeterol will improve lung function in up to 50% of tetraplegics.

Cardiovascular management

Cardiovascular instability is particularly seen with high cervical cord injuries. At the time of injury there is an initial brief period of increased sympathetic activity resulting in hypertension, an increased risk of subendocardial infarction and arrhythmias. This is followed by a more sustained period of neurogenic shock, resulting from loss of sympathetic outflow from the spinal cord, which may last up to eight weeks. This is characterised by vasodilatation and bradycardia and tends to be seen only in lesions above T6. Bradycardia is caused by loss of cardiac sympathetic afferents and unopposed vagal activity and may lead to asystole. This can be treated with atropine. In persistent and problematic bradycardia a pacemaker may need to be inserted. The loss of sympathetic innervation to the heart means that if increases in cardiac output are required, then this is best achieved by an increase in stroke volume.

The initial treatment of hypotension involves intravenous fluid administration. Once the stroke volume cannot be increased further, then vasopressors will need to be commenced using either dopamine or norepinephrine, which are both α - and β_2 -receptor agonists, providing vasoconstriction, with chronotropic and inotropic support to the heart.^{7,8}

Under normal physiological conditions spinal cord blood flow is autoregulated over a wide range of systemic blood pressures. Following trauma, autoregulation of blood flow to the cord fails and hence flow becomes directly proportional to systemic blood pressure; therefore to ensure sufficient perfusion to the cord systemic blood pressure must be maintained.

The end-point of resuscitation is controversial. There is evidence that ongoing ischaemia and secondary spinal cord damage is successfully treated by raising the mean arterial pressure to 85mmHg for up to seven days.⁹ Hence the American Association of Neurological Surgeons (AANS) recommendation of maintaining MAP to 85-90mmHg and avoiding systolic blood pressure less than 90mmHg for over 5-7 days.

Finally, spinal cord perfusion pressure can be calculated using the equation;

SCPP	=	MAP	-	ITP
(Spinal cord perfusion pressure)		(Mean arterial pressure)		(Intrathecal pressure)

i.e. the spinal cord perfusion pressure can be increased by either increasing the MAP or lowering the intrathecal pressure.

Kwon et al performed a feasibility study of intrathecal pressure monitoring and CSF drainage. Insertion of the catheter was found to be safe and without adverse sequelae. Episodes of raised ITP, and therefore potential tissue ischaemia, were found following surgical decompression, which would have otherwise gone undetected.¹⁰ Further studies are required before recommendations can be made regarding this treatment modality.

Autonomic dysreflexia

This complication does not occur during the acute phase of spinal injury, but is mentioned here for completeness. The condition can be triggered by various stimuli, noxious and non-noxious including surgery, bladder distension, bowel distension and cutaneous stimuli. It is more common in complete and higher lesions; it is rarely seen in patients with cord lesions below T10. The condition is due to massive sympathetic discharge. The symptoms may start weeks to years following the spinal injury and include paroxysmal hypertension, headaches and bradycardia. Below the lesion cutaneous vasoconstriction, piloerection and bladder spasm may be seen. Above the lesion there may be flushing, sweating, nasal congestion and conjunctival congestion. The patient may complain of blurred vision and nausea.

If left untreated complications include stroke, encephalopathy, seizures, myocardial infarction, arrhythmias and death. Management options include removal and avoidance of triggers e.g. the insertion of a urinary catheter, bowel routines and avoidance of pressure sores. If surgery is planned, consider the use of spinal anaesthesia as this reliably prevents the symptom complex. Other options include increased depth of anaesthesia and vasodilators for the treatment of hypertension and making use of orthostatic hypotension by placing patients with legs down.⁸

Venous thrombosis

The incidence of deep vein thrombosis (DVT) is 40-100% in untreated patients with a spinal injury and pulmonary embolism is one of the leading causes of death in this group of patients. Prophylaxis must be started as soon as possible although there is no consensus as to exactly when or how this should be initiated. Treatment can be divided into two clear groups, pharmacological and non-pharmacological. Unfractionated heparin 5000iu bd does not prevent DVT, whereas low molecular weight heparin, in particular enoxaparin, is effective in preventing deep vein thrombosis (DVT), but is associated with an increased risk of haemorrhage within the injured spinal cord if given acutely. Therefore mechanical compression devices and graduated elastic stockings are often applied for the first 72 hours, when the risk of DVT is low and anticoagulants considered thereafter. Prophylaxis should be continued for at least eight weeks.⁷

At 72 hours an inferior vena cava filter should be considered if the risk of bleeding is still high and anticoagulants are contraindicated.

Gastrointestinal management

Bleeding due to stress ulceration should be prevented with an H₂-receptor antagonist, such as ranitidine. Ileus and gastric distention can be treated with nasogastric suctioning and prokinetic drugs, e.g. metoclopramide or erythromycin.⁸

Following injury, the rectum and anus will be areflexic and peristalsis of the bowel is absent, causing a paralytic ileus. Bowel management should start immediately, with digital examination of the rectum and any faeces removed carefully digitally. During the period of spinal shock faeces will need to be removed digitally with the aid of suppositories. The return of bowel sounds heralds the resolution of the ileus and arrival of an *upper motor neuron bowel syndrome* or *hyperreflexic bowel*, which is characterised by increased colonic and anal tone and is associated with constipation and stool retention. Evacuating the bowel is facilitated by reflex activity initiated by a finger and or a suppository placed into the rectum. Stool consistency can be helped by using laxatives.

Pain management

Pain is a frequent complication of spinal cord injury. It can be classified into either musculoskeletal or neuropathic. Neuropathic pain tends to have a burning quality and occurs in the front of the chest, in the buttock and in the legs, whereas musculoskeletal pain has an aching quality tending to occur in the neck, shoulders and back above the level of the lesion.

Treatment of musculoskeletal pain includes paracetamol, non-steroidal anti-inflammatory drugs, opiates and muscle relaxants, such as benzodiazepines. Neuropathic pain is sensitive to anticonvulsants (gabapentin, pregabalin) and tricyclic antidepressants.

SPECIFIC TREATMENT

Different therapies have been tried, attempting to reduce the secondary neuronal injury due to cord ischaemia and inflammation. Although some have shown potential in animal studies, most have not shown significant benefit in clinical studies. Only methylprednisolone has shown any promise. Methylprednisolone 30mg.kg⁻¹ is given over 15 minutes and then 5.4mg.kg⁻¹ is infused over 23 hours. Following the second national acute spinal cord injury study (NASCIS) in 1990, giving methylprednisolone became a standard of care. However subsequent studies questioned its use, with evidence of its deleterious effects including immunosuppression, more gastro-intestinal bleeds and hyperglycaemia. The latest Cochrane review looking at this treatment modality includes 5 randomised controlled trials (3 from North America – the NASCIS trials 1-3, one Japanese trial and one French trial) where methylprednisolone had been given following spinal cord injury. The review found a significant by better recovery in motor function after methylprednisolone, if it was commenced within 8 hours.¹¹ Today methylprednisolone is a treatment option but cannot be considered a standard of care.

Oxandrolone is an oral anabolic steroid and has been shown to improve pulmonary function in patients with tetraplegia in a single

clinical study over a 4 week period.¹² However its long term effects are not known and the drug is known to cause hyperlipidaemia and abnormal liver function tests.

Indications for surgery include correction of deformity, stabilisation of the spine and decompression of the spinal cord to allow neurological recovery. Early surgical decompression has been shown to be beneficial in animal models of spinal cord injury. To date the evidence in humans is lacking, and the timing of surgical decompression remains a topic of debate and ongoing research.¹³

SUMMARY

The initial management of patients involved in blunt trauma follows the ATLS principle of airway and cervical spine control, breathing and circulation. The spine is immobilised as soon as possible to prevent secondary neurological injury. However, extrication collars should be removed and MILS applied prior to establishing a definitive airway, where this is indicated. Despite movement at the occipito-atlanto-axial joint, direct laryngoscopy with MILS is an accepted safe method to manage the airway in patients with potential cervical spine injuries. The gum elastic bougie and the McCoy laryngoscope are useful tools in this context. A high cervical spine injury is likely to result in respiratory failure and cardiovascular instability, which may require ventilatory and/or inotropic support.

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Thoracic trauma

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CASE SCENARIOS

Scenario A

The front, unrestrained passenger of a vehicle from a road traffic accident is brought into the Emergency Department. On arrival he is in PEA (pulseless electrical activity) cardiac arrest. He has obvious bilateral chest wall injuries.

- *What are the important causes of cardiac arrest in trauma?*
- *What is the immediate management if you suspected a tension pneumothorax or a cardiac tamponade?*

Scenario B

A young man presents to the Emergency Department with left sided stab wounds to his chest. His initial observations are: respiratory rate 40 per minute, saturations 88% on 15L.min⁻¹ oxygen, heart rate 110 bpm, BP 102/60mmHg.

- *What is your initial approach to this injured patient?*
- *What important diagnoses do you need to consider?*

During the primary survey you find that the young man is effectively maintaining his own airway, but his chest sounds quiet on the right side and the percussion note is dull. There is reduced chest wall movement on the affected side. The trachea appears central and

you think you can hear normal heart sounds. He is developing obvious respiratory distress.

- *Are you ready to progress onto the rest of the primary survey?*
- *What is the most likely diagnosis?*
- *What is your management?*

You decide to sedate, intubate and ventilate him. His chest Xray (below) shows a right haemothorax.



- *Which patients with a right haemothorax are likely to require a thoracotomy?*

Answers are found in the article.

Summary

Many of the injuries that require immediate attention during resuscitation following trauma, involve the chest. This article describes a systematic approach to management of these injuries, using chest Xray and CT examples to demonstrate learning points.

INCIDENCE

Thoracic trauma is responsible for 25% of all trauma deaths in the UK. Many deaths occur immediately, but a significant group can be salvaged. 85-90% of patients with thoracic trauma can be managed conservatively. Surgery is needed in 10-15% of cases.

CHEST INJURIES – GENERAL APPROACH

Full ATLS protocol should be followed, with the <C>ABCDE approach to primary and secondary survey (see article on page 95). During the B phase of the primary survey, life threatening chest injuries

should be identified and treated before moving on with the survey.

The life threatening chest injuries are:

- Tension pneumothorax
- Open pneumothorax
- Massive haemothorax
- Flail chest
- Cardiac tamponade.

Other injuries that should be identified during the secondary survey are :

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- Aortic injury
- Lung contusion
- Myocardial contusion
- Diaphragmatic rupture
- Tracheobronchial injury
- Oesophageal injury.

This article will focus on the diagnosis and treatment of the life threatening injuries that should be identified in the primary survey.

Tension pneumothorax (Figure 2)

A tension pneumothorax develops when air enters the pleural space. There is a valve-like effect of the ruptured pleura and air is forced in during inspiration and coughing, but unable to escape during expiration. The accumulated air becomes pressurised, collapsing the affected lung and then begins to push the mediastinum away from the affected side of the chest. As a result, the mediastinal structures are compressed and the major vessels kinked, decreasing venous return and therefore cardiac output.



Figure 2. Chest Xray showing left tension pneumothorax, with mediastinal shift to the right side. Generally this pathology should be recognised clinically and treatment should not be delayed for Xray imaging.

Causes of pneumothorax in trauma

- Penetrating chest trauma e.g. stab wound
- Blunt chest trauma with or without rib fractures
- Positive pressure ventilation in a patient with pre-existing simple pneumothorax (i.e. not previously under tension)
- Following insertion of a subclavian or internal jugular central venous catheter.

Clinical features

- Respiratory distress
- Tachycardia and hypotension
- Unilateral reduced or absent air entry
- Hyper-resonance to percussion on affected side
- Decreasing lung compliance
- Tracheal deviation away from affected side
- Distended neck veins.

The last two features can be difficult to identify.

Treatment

Once the diagnosis has been made clinically, treatment must not be delayed waiting for a chest radiograph. Give high flow oxygen via a face mask.

Needle thoracocentesis is indicated and then an intercostal catheter should be inserted urgently, as definitive treatment. Needle thoracocentesis is a procedure that is associated with complications and there have been case reports of haemorrhage.

Needle thoracocentesis

1. Indicated when tension pneumothorax is clinically diagnosed (do not wait for a chest Xray).
2. Clean the skin.
3. Use at least a 16G cannula (to provide adequate length). Remove the white Luer cap and the 'flash-back' chamber on which the cap sits.
4. Advance the open cannula perpendicular to the skin in the second intercostal space, mid-clavicular line of the affected side.
5. If the pneumothorax is under pressure ('tension'), a hiss of escaping air may be heard on entry into the pleural cavity - let this air escape. Remove the needle, leaving the cannula in place.
6. Leave the cannula open to air. Avoid kinking of the cannula and do not remove the cannula until an intercostal catheter has been inserted.
7. Whether or not a pneumothorax was present, you are now obliged to insert an intercostal catheter to formally treat the pneumothorax. The cannula can safely be removed after this.

Open pneumothorax

An open pneumothorax occurs when there is an associated chest wall wound. If the defect is more than 0.75 times the diameter of the trachea then, during inspiration, air is entrained directly into the chest cavity through the wound. This occurs because the hole in the chest wall provides less resistance to flow.

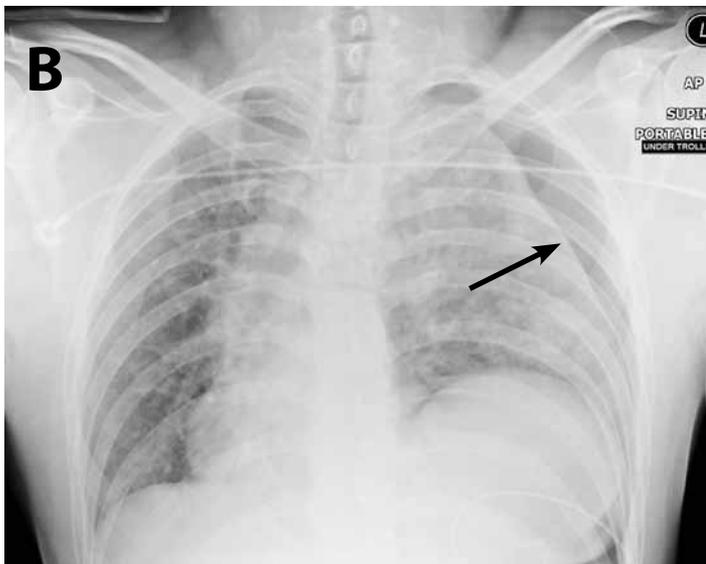
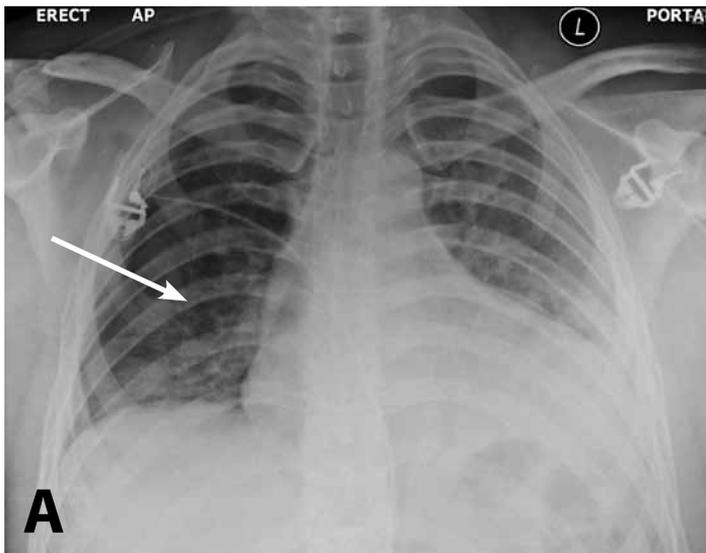


Figure 3. A - Chest Xray of a right simple pneumothorax (lung edge is arrowed); B - left pneumothorax (arrow) with likely left diaphragmatic rupture - the mediastinum is displaced to the right and so there may be an element of tension. There is also contusion of the left lung.

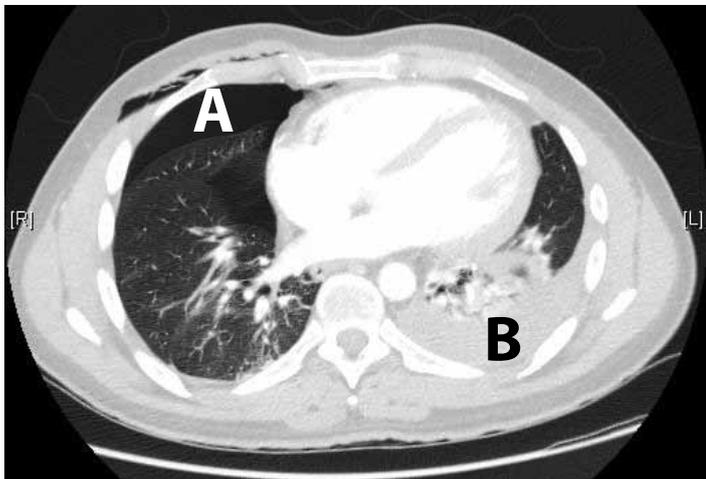


Figure 4. Chest CT scan of showing a right pneumothorax (A) and left haemothorax (B).

Clinical features

The features are those of simple pneumothorax (reduced air entry, resonant percussion note and decreased expansion), but in addition you may hear a 'sucking chest wound', as air enters the thoracic cavity during inspiration.

Treatment

1. 100% oxygen via a face mask.
2. Intubation and positive pressure ventilation is indicated when oxygenation or ventilation is inadequate.
3. Insertion of an intercostal catheter.
4. Many patients will require thoracotomy.
5. If definitive closure is delayed, a dressing can be applied to the wound and taped on 3 sides, leaving the 4th side free. An Asherman chest seal can also be used. Both act as a flap valve, allowing air to escape from the pneumothorax in expiration but not to enter during inspiration.

Massive haemothorax (Figure 5)

This is defined as blood loss of greater than 1500ml in one hemithorax. It can be associated with either blunt or penetrating chest injuries. Signs of hypovolaemic shock are often present. Management of the haemothorax and the blood loss need to occur simultaneously.

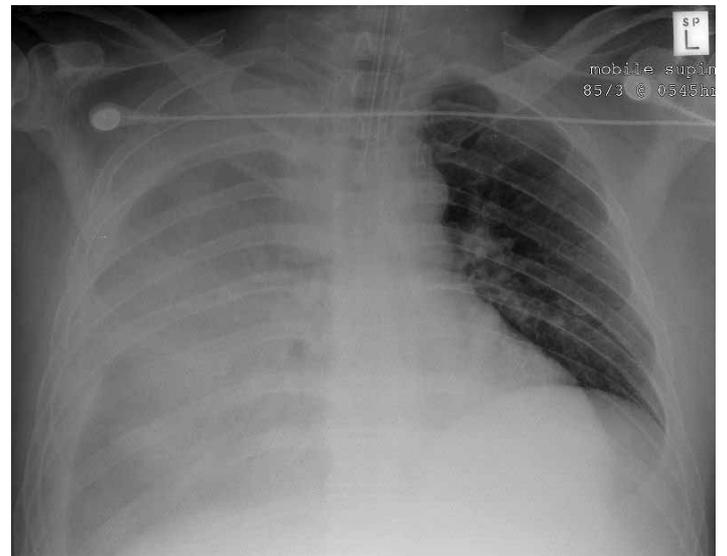


Figure 5. Right haemothorax.

Causes

- Rib fractures
- Intercostal vessel injuries
- Lung parenchymal venous injuries
- Arterial injury - less common.

Clinical features

- Evidence of overlying blunt or penetrating chest wall injury
- Reduced chest wall movement

- Quiet or absent breath sounds
- Dullness to percussion
- Tracheal deviation - rarely.

Treatment

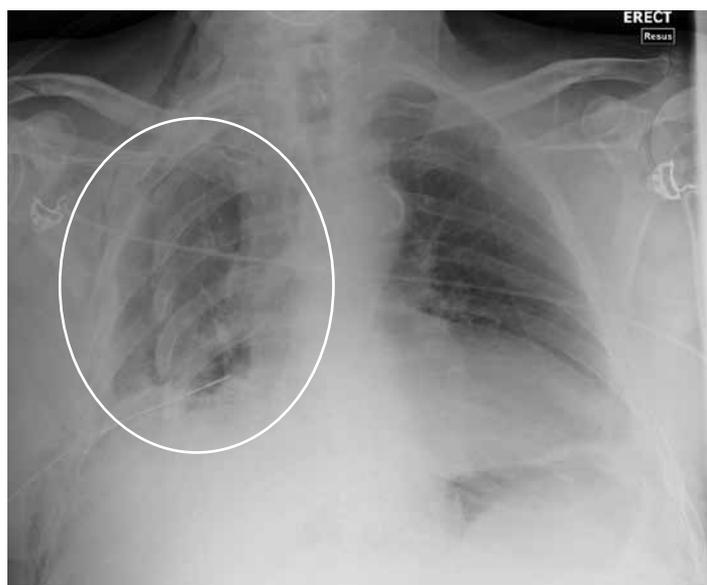
1. High flow oxygen.
2. Chest drain insertion (placed anteriorly if there is an associated pneumothorax).
3. Good IV access to allow simultaneous volume replacement
4. Thoracotomy is indicated in some patients with a massive haemothorax. Indications include:
 - immediate drainage of >1500ml of blood from one hemithorax or
 - ongoing bleeding of >250ml.h⁻¹
 - continuing requirement for blood transfusion.

Flail chest

A flail chest occurs when two or more ribs are fractured in two or more places. This results in a section of the chest wall which is able to move independently. The flail segment moves inwards during inspiration and outwards in expiration. The segment can be lateral or anterior depending on the location of the rib fractures. Flail chest can be associated with a significant lung injury underlying the fractures.

Clinical features

1. Severe chest wall pain
2. Paradoxical chest wall movement (if the patient is able to splint their chest wall due to severe pain this may not be obvious)



3. Hypoxia (from inadequate ventilation or underlying lung contusion)
4. Crepitus or palpable rib fractures
5. Rib fractures on chest Xray.

Management

1. High flow oxygen
2. Analgesia to allow adequate ventilation. Consider insertion of an epidural or paravertebral catheter, if local expertise and equipment allow.
3. Endotracheal intubation and IPPV may be needed in some cases.

Cardiac tamponade

In trauma, this is an accumulation of blood in the pericardium. It normally results from a left sided penetrating injury but can also occur in blunt trauma. As blood accumulates the ventricles cannot completely fill or contract. This leads to haemodynamic instability and PEA cardiac arrest. Presentation may be similar to a left sided tension pneumothorax.

Clinical features

1. Faint heart sounds
2. Distended neck veins
3. Hypotension
4. PEA cardiac arrest.

Management

1. If cardiac tamponade is suspected, it can be diagnosed using FAST (focused assessment sonogram in trauma) or pericardiocentesis.

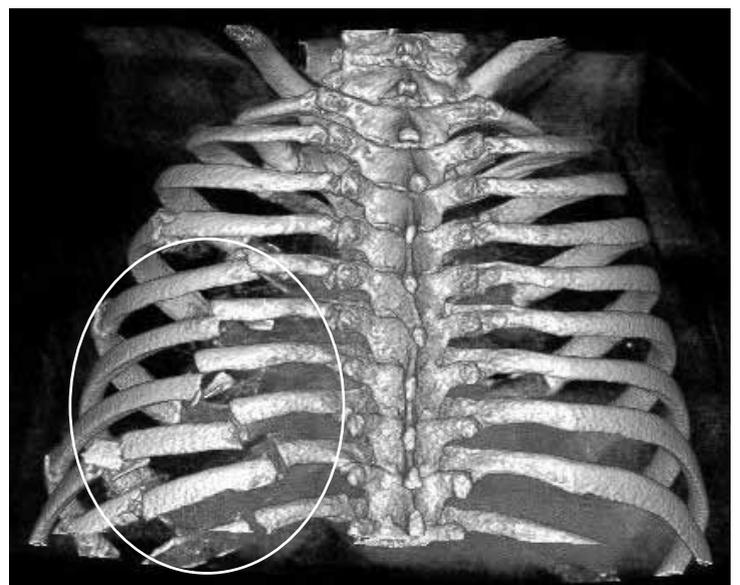


Figure 6. Flail chest resulting from multiple displaced rib fractures in two different patients, shown on A - plain chest Xray; B - 3D reconstruction of CT scan.

2. In addition, pericardiocentesis can be used to treat cardiac tamponade by aspirating blood from the pericardial sac.
3. Definitive treatment is cardiothoracic surgery.

CONCLUSIONS

This article has described five immediately life threatening chest injuries, that can be identified in the primary survey. Other chest injuries may be diagnosed during the secondary survey, as a result of

further examination and imaging. These include ruptured diaphragm, oesophageal rupture, ruptured bronchus and pulmonary contusion.

FURTHER READING

1. Advanced Trauma Life Support for Doctors, American College of Surgeons Committee on Trauma, Student Course Manual 7th Edition.
2. Advanced Paediatric Life Support – The Practical Approach 4th Edition, Advanced Life support Group.

Guideline for management of massive blood loss due to trauma

1

1. Activate hospital **trauma team** PRIOR to patient arrival
2. Team should have a **designated trauma team leader** and at least a general surgeon and anaesthesiologist
3. Receive the patient in the **emergency room** (warm environment)
4. Give **oxygen**
5. **Primary survey** <C> A (cervical spine protection) BC
6. Establish **IV access**
7. Send blood for a **group and save** (type and screen) AND crossmatch 4 units of red cells
Ensure specimens accurately labelled and hand deliver it to the blood bank
8. **Start fluid resuscitation** prior to further transport (Failure to respond to crystalloid and blood dictates the need for immediate definitive intervention)
9. **Assess injuries** and **prioritise** treatment (aortic injury, head injury)
10. **Ensure availability of specialists** based on injuries (neurosurgeon, thoracic surgeon obstetrician)
11. **Alert clinical lab, blood bank, haematologist**

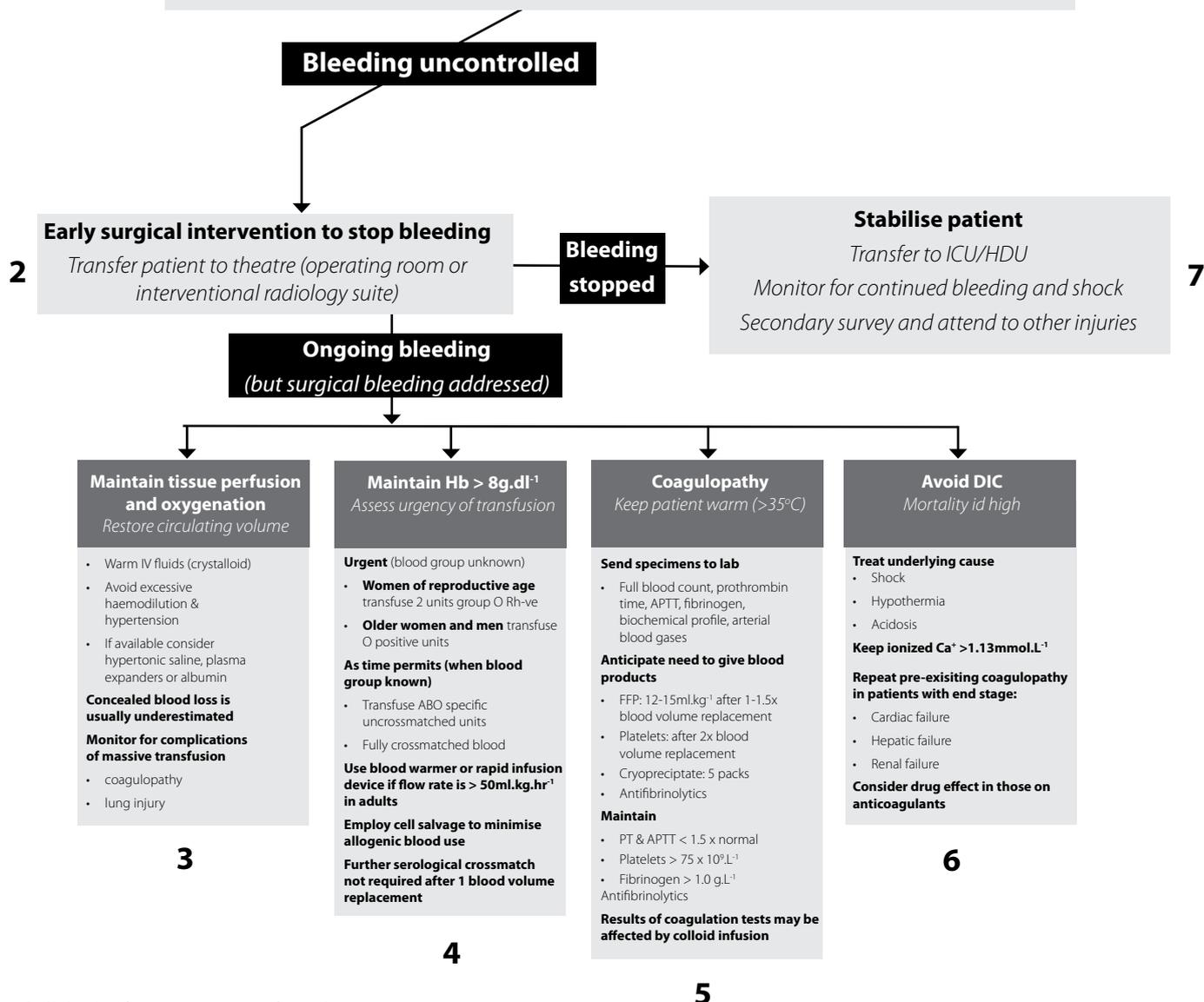


Figure 1. Guideline for management of massive blood loss.

Guideline for management of massive blood loss in trauma

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INTRODUCTION

This article is about massive blood loss. Most published guidance focuses on trauma but the advice is also relevant to other causes such as obstetric haemorrhage. Further description of the management of maternal haemorrhage is also available in a recent *Update* article.¹ As described in the article on trauma management, 'ABCDE' can be used to guide orderly assessment and treatment of any patient with major blood loss. This is increasingly expanded to <C>ABCDE, where <C> refers to catastrophic haemorrhage control. Haemorrhage is the leading cause of preventable deaths following trauma. Early recognition of major blood loss and effective action prevents shock and its consequences.

Massive blood loss is defined as the loss of one blood volume within 24 hours.

Normal blood volume is 70ml.kg⁻¹ in adults (ideal body weight), 60ml.kg⁻¹ in the elderly and 80-90ml.kg⁻¹ in children. An alternative definition of massive blood loss is loss of 50% of the blood volume within 3 hours, or a rate of loss of greater than 150ml per minute. The basic management principle is to stop the bleeding and replace the volume loss.

COMMENTARY ON ALGORITHM

The guideline presented in this article is based on template guidelines published by the British Committee for Standards in Haematology, the Adult Trauma Life Support (ATLS) group and, most recently, the Association of Anaesthetists of Great Britain and Ireland.^{2,3,4} However, most of the recommendations contained in these guidelines are based only on uncontrolled observational studies and a consensus of expert opinion.

This guideline should be modified by individual institutions based on local circumstances, including personnel, equipment and blood product availability and the time required to transport specimens and blood products. Each hospital's Transfusion Committee has a vital role in ensuring the optimum and safe use of blood components. The accompanying commentary provides key references on which the guidelines are based, but

does not constitute an exhaustive review of the topic.

Box 1 - Activate the trauma team

External haemorrhage is easily identified during the primary survey but occult blood loss may have occurred into the chest, abdomen, pelvis, retroperitoneum or long bones. Hypotension following injury must be attributed to blood loss until proven otherwise.

Simple clinical observation of the patient's level of consciousness, skin colour, respiratory rate, pulse rate and pulse pressure gives immediate information about organ perfusion (Table 1). However, the elderly, children, athletes and individuals with chronic medical conditions do not respond to blood loss in a uniform manner. The initial physiological response to blood loss in a young fit patient is vasoconstriction followed by tachycardia. Such a patient may have lost up to 30% of their blood volume with minimal or no other clinical signs of shock. Beware the patient with a normal systolic blood pressure and a raised diastolic blood pressure (therefore a low pulse pressure).

Take blood samples at the earliest opportunity as results may be affected by colloid infusion. One team member should ensure that the identity of the patient is correctly recorded on the sample and request form, and hand them to the laboratory staff in person in order to avoid unnecessary delays.

When assessing a patient with shock remember:

- There may be more than one cause for shock.
- Young healthy patients will compensate for a long period of time and then collapse quickly.
- Isolated intracranial injuries do not cause shock.
- Always be on the alert for tension pneumothorax.

Summary

- Early recognition of major blood loss and effective action is necessary to prevent shock and its consequences.
- Massive transfusion may challenge local resources.
- Effective management relies upon good communication between specialties and local guidelines.
- Successful outcome requires treatment of surgical sources of bleeding, restoration of blood volume to maintain tissue perfusion and oxygenation, and correction of coagulopathy.

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Table 1. Grading shock - estimated blood loss based on patient's clinical signs at presentation. Reproduced by kind permission of the American College of Surgeons Committee on Trauma. Modified from Table 3-1 of *Advanced Trauma Life Support for Doctors, Student Manual, 8th Edition, page 61.*

Clinical variable	Grade of shock			
	Class I	Class II	Class III	Class IV
Blood loss (ml)*	Up to 750	750-1500	1500-2000	>2000
Blood loss (% of blood volume)	Up to 15%	15%-30%	30%-40%	>40%
Pulse rate (beats.min ⁻¹)	<100	100-120	120-140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate (min ⁻¹)	14-20	20-30	30-40	>35
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Urine output (ml.hr ⁻¹)	>30	20-30	5-15	Negligible
Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

- * For a 70-kg man.
- The guidelines in this table are based on the 3:1 rule. Most patients in hemorrhagic shock require as much as 300 ml of electrolyte solution for each 100 ml of blood loss.
- A patient with a crush injury to an extremity may have hypotension that is out of proportion to his blood loss and may require fluids in excess of the 3:1 guideline.
- A patient whose on-going blood loss is being replaced by blood transfusion requires less than 3:1.
- The use of bolus therapy with careful monitoring of the patient's response may moderate these extremes.

Another member of the clinical team should be nominated to act as the co-ordinator for overall communication between clinical specialties, diagnostic laboratories and blood bank staff. If some blood components are kept in a regional centre then the transportation delay must be taken into account. The Hospital Transfusion Committee should periodically review massive transfusion episodes.

Initial fluid resuscitation should be by rapid infusion of warmed isotonic crystalloid (Hartmann's/Ringer's lactate or 0.9% saline) via large bore cannulae. The initial dose is 1 to 2 litres for adults and 20ml.kg⁻¹ for children. Volume replacement should be guided by the patient's response to initial therapy by repeated re-evaluation of ABC (see Table 2).

Box 2 - Stop the bleeding

Intravenous replacement of intravascular volume cannot succeed without definitive control of bleeding. Obvious catastrophic bleeding is addressed in Box 1 (<C>). Examples include use of compression bandages, use of limb tourniquets and application of a pelvic binder for fractured pelvis.

The goal of resuscitation is to restore organ perfusion. In some patients, if blood pressure is raised rapidly before the hemorrhage has been definitely controlled, increased bleeding may occur. Balancing the goal of organ perfusion with the risks of re-bleeding, by accepting a lower than normal blood pressure, has been called 'controlled resuscitation' or 'balanced resuscitation'. A useful concept is that of 'talking hypovolaemia', where hypotension is tolerated so long as the patient is achieving sufficient cerebral perfusion to hold a conversation. Such a strategy may buy time until surgical control of bleeding has been achieved.

Box 3 - Restore circulating volume

Prolonged hypovolaemic shock carries a high mortality rate because of progression to organ failure and disseminated intravascular coagulation (DIC). The first priority in the treatment of major blood loss is the restoration of blood volume to maintain tissue perfusion and oxygenation. Fluid resuscitation must be started when early signs and symptoms of blood loss are suspected, not when blood pressure is falling or absent.

Box 4 - Red cell transfusion

The loss of over 40% of blood volume is immediately life threatening. Red cell transfusion is usually required when 30-40% of the blood volume is lost (Table 1). Transfusion is rarely indicated when the haemoglobin concentration is greater than 10g.dl⁻¹ but is almost always indicated when it is less than 6g.dl⁻¹. However, after equilibration and redistribution of crystalloid, the haemoglobin measured may actually be higher or lower than that during the resuscitation period. In the

All transfused fluids should be warmed because hypothermia increases the risk of DIC and infection.

Table 2. Interpretation of response to initial fluid resuscitation. Reproduced by kind permission of the American College of Surgeons Committee on Trauma. Modified from Table 3-2 of *Advanced Trauma Life Support for Doctors, Student Manual, 8th Edition, page 65.*

Clinical variable	Rapid response	Transient response	Minimal or no response
Vital Signs	Return to normal	Transient improvement, recurrence of decreased blood pressure and increased heart rate	Remain abnormal
Estimated blood loss	Minimal (10%-20%)	Moderate and ongoing (20%-40%)	Severe (>40%)
Need for more crystalloid	Low	High	High
Need for blood	Low	Moderate to high	High
Blood preparation	Type and crossmatch	Type-specific	Emergency blood release (Group O -ve)
Need for operative intervention	Possibly	Likely	Highly likely

• 2000ml of isotonic solution in adults; 20ml.kg⁻¹ bolus of Ringer's lactate/Hartmann's in children.

setting of ongoing blood loss, the decision to transfuse must be based on estimation of loss and guided by bedside testing (e.g. Hemocue®) where available. In a well-compensated patient without heart disease, 6g.dl⁻¹ may be an appropriate transfusion trigger. In patients with stable heart disease and with an expected blood loss of 300ml, a haemoglobin of 8g.dl⁻¹ may be a more appropriate trigger. Older patients and those with co-morbidities, which limit the ability to raise cardiac output, should be transfused at a haemoglobin of 10g.dl⁻¹. These decisions are also influenced by the availability of blood and what may be considered to be a normal haemoglobin level in a population with endemic disease such as malaria.

Intraoperative blood salvage can be of great value in reducing the requirement for donated blood. It is contraindicated where there is wound contamination with bowel contents, urine, bone fragments or fat. This technique is dependent on having appropriate equipment and staff available, however techniques that require no specialist equipment have been described.⁶

In most blood banks completion of a full blood cross-match requires between 40 minutes to one hour. If it is urgent, **type-specific** (i.e. grouped but not cross-matched) blood can generally be provided within 10 to 15 minutes. Laboratory staff then complete the cross-match during the time taken to transport the blood and alert clinicians if there is incompatibility.

In an extreme situation it may be necessary to use group O red cells. Pre-menopausal women should receive group O Rhesus D negative red cells to avoid sensitisation and the risk of haemolytic disease of the newborn in subsequent pregnancies. However, in order to avoid severe depletion of stocks, it is acceptable to give O Rhesus D positive cells to men and post-menopausal women.

Most transfusion related morbidity is due to incorrect blood being transfused. Ensure that all staff members are familiar and up to date with local standards for checking and administering blood. Note that after replacement of one blood volume (8-10 units of red cells) further crossmatching is not required.

Remember to use a blood warmer, where available.

Remember:

- Haemoglobin values do not decrease for several hours after acute hemorrhage, when compensatory mechanisms are in place.
- Blood loss is usually underestimated or hidden.

Box 5 - Component therapy and investigations

In addition to blood grouping, where available, send samples to the laboratory as soon as possible for baseline haematology, coagulation screening, fibrinogen and serum biochemistry.

Fresh frozen plasma (FFP) and cryoprecipitate

After massive blood loss and transfusion, coagulation factor deficiency is common, because packed red cells contain no clotting factors. After blood loss of 1.5 times the patient's total blood volume, the level of fibrinogen is likely to be below 1.0g.L⁻¹ (normal range 1.8-4.0g.L⁻¹). Fibrinogen is the precursor to fibrin and therefore a key component in the coagulation cascade. A fibrinogen level of <0.5g.L⁻¹ is strongly associated with microvascular bleeding (diffuse bleeding from numerous small blood vessels which are too small for surgical methods of treatment). A decrease in other coagulation factors occurs after blood loss of twice the blood volume. Prolongation of activated partial thromboplastin time (APTT) and prothrombin time (PT) to 1.5 times the mean normal value correlates with increased bleeding and this should be corrected.

FFP contains predominantly factors 2 (fibrinogen), 7, 9, 10 and 11. When blood loss is rapid and red cells are infused rapidly, FFP infusion will be needed after approximately 4 units of packed red cells have been given. When the patient has lost one total blood volume, give 12-20ml.kg⁻¹ body weight (about 4 units of FFP in an adult). This volume of FFP will raise coagulation factor levels by about 20%. The effectiveness of FFP may be reduced due to rapid consumption in the

presence of continued bleeding. There is increasing evidence from recent military experience that supports the use of transfusion packs - i.e. giving blood and FFP and platelets in equal ratios. Balancing massive transfusion with an approximate 1:1 ratio of red blood cells to plasma, from the beginning of resuscitation, is logical in severely injured trauma patients, who develop coagulopathy as a primary event from their injury, not secondary to clotting factor dilution, hypothermia or acidosis.

Further studies of use of transfusion packs in hospital practice are needed, because patients often have comorbidities and the nature of the trauma is usually motor vehicle trauma and crush injuries, lower velocity gunshot wounds and stab wounds.

When fibrinogen levels remain low ($<1.0\text{g.L}^{-1}$), give cryoprecipitate 1-1.5 packs per 10kg body weight or about 6 packs for an adult. Cryoprecipitate contains fibrinogen, factor 8, factor 13 and von Willebrand factor (that is important for platelet function).

Platelets

Aim for the following platelet levels:

$> 75 \times 10^9\text{.L}^{-1}$	Critical level for all bleeding patients
$> 100 \times 10^9\text{.L}^{-1}$	For patients with: <ul style="list-style-type: none"> multiple high-energy trauma or, central nervous system injury or, if platelet function is abnormal (patients with end stage renal disease).

Anticipate a platelet count of $<50 \times 10^9\text{.L}^{-1}$ when about two blood volumes have been replaced by red cell transfusion.

Where platelets are available, they may not be stored locally. You may need to consider ordering them before they are needed, so that they are available when the patient's platelet level becomes critical. Where available, it is important to check these parameters frequently (at least four-hourly and after each therapeutic intervention), to monitor the need for and the efficacy of component therapy.

Investigations

Ideally, tests of coagulation and full blood count should be repeated every hour when bleeding is ongoing. Where available, base deficit and lactate can be useful in determining the presence and severity of shock. Serial measurement of these parameters can be used to observe trends, assess adequacy of resuscitative treatment and guide further therapy. If available, thromboelastography® (TEG®) or thromboelastometry (ROTEM®) should be performed to assist in characterising the coagulopathy and in guiding haemostatic therapy.

Box 6 - Shock and DIC

Shock describes an abnormality of the circulatory system leading to inadequate organ perfusion and tissue oxygenation. In trauma, the most likely cause is blood loss, but consider other causes such as cardiogenic shock, cardiac tamponade, tension pneumothorax, neurogenic shock, and septic shock.

Most patients are at risk of dilutional coagulopathy when volume replacement is with crystalloids and red cells. In addition patients suffering massive trauma are also at risk of consumptive coagulopathy and liable to develop clotting abnormalities, even in the absence of significant dilution. These patients may have clinically apparent abnormal bleeding without abnormal coagulation tests.

Patients taking anticoagulant drugs may need specific treatment. Warfarin should be reversed with a prothrombin complex concentrate and intravenous vitamin K (5-10mg). Low molecular weight heparin can be partially reversed with protamine.

Platelet dysfunction may be present in patients with renal disease and those on antiplatelet medication, such as aspirin or clopidogrel. Patients with liver disease, associated with reduced synthesis of clotting factors, may develop clinically significant coagulopathy with blood loss of less than one blood volume.

Hypocalcaemia and hypomagnesaemia often occur in massively transfused patients and will require monitoring and correction.

If accelerated fibrinolysis is suspected (particularly in multiple trauma) or identified by laboratory assay of fibrin degradation products or by the use of thromboelastography, antifibrinolytic drugs such as intravenous tranexamic acid may be used to reverse fibrinolysis. A loading dose of 1g over 10 min followed by 1g over 8 hours is recommended.

Box 7 - Stabilise the patient

When the primary injury has been addressed, the patient should be transferred to the Intensive Care Unit for further treatment. The patient should have regular clinical observations, haemoglobin levels and blood gas analysis to ensure that resuscitation is adequate and that bleeding is not continuing.

Once haemostasis is secured standard venous thromboprophylaxis should be considered as patients develop a prothrombotic state following massive blood loss.

PRE-EVENT PLANNING

1. Chose a particular approach for your institution and rehearse it before you need to use it.
2. The Hospital Transfusion Committee should periodically review massive transfusion episodes to look for points for improvement.
3. When adapting this guideline for your hospital, bear in mind the following:

Blood Bank

- Time required by the blood bank for a type and screen.
- Time required by the blood bank for crossmatch of specific units.

- Amount and type of blood locally available.
- Time required for transport from the nearest blood bank.
- Time required to thaw frozen blood components (fresh frozen plasma and cryoprecipitate).

Clinical laboratory

- Time taken to measure PT, APTT.
- Time taken to conduct a full blood count and platelet count.
- Time taken for a blood gas analysis, biochemistry profile and serum lactate measurement.

SUMMARY

- Find the source of bleeding and stop it.
- A named senior person must take responsibility for communication and documentation.
- Ensure correct blood sample ID when sending specimen to the laboratory.
- Ensure correct patient identification prior to transfusion of blood components
- Recognise your local limitations when dealing with laboratory and blood bank turnaround times for issue of blood and other components after crossmatch.
- Allow for about 30 minutes thawing time for FFP and cryoprecipitate.
- Allow for delivery time from blood centre if away from the hospital.
- The patient may have multiple antibodies following a massive transfusion. Make sure that this is clearly recorded in their notes, possibly by an ALERT sticker on the front.
- Practice this protocol to determine your actual response times.

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Rhabdomyolysis

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Summary

Rhabdomyolysis describes muscle breakdown due to a number of different pathological processes. This article describes the aetiology, clinical recognition and treatment of the condition.

INTRODUCTION

Rhabdomyolysis is the breakdown of striated muscle. There are many causes that all ultimately progress to myocyte necrosis and release of intracellular contents into the circulation. This can produce life threatening complications including hyperkalaemia and acute kidney injury (AKI).

EPIDEMIOLOGY

In the ICU setting, the most common causes of rhabdomyolysis are muscular trauma and vascular obstruction.¹ Rhabdomyolysis occurs in up to 85% of patients with traumatic injuries.² Alcohol has been implicated in the development of rhabdomyolysis in up to 20% of cases.³ About a third of all patients with rhabdomyolysis will develop AKI and it is suggested that 5-25% of all AKI results from rhabdomyolysis. Patients with severe injuries that develop rhabdomyolysis induced AKI have a mortality of approximately 20%, but this is higher if multiple organ dysfunction is present.⁴

PATHOPHYSIOLOGY

Muscle necrosis is the end-point of rhabdomyolysis.

It results from either direct sarcolemmic injury (the sarcolemma is the calcium storage system within cells), or hypoxia, causing ATP depletion and sodium-potassium pump failure. This leads to sodium influx and accumulation of free cytosolic ionized calcium, as the cell attempts to restore electrochemical neutrality via the sodium-calcium exchange mechanism.

High intracellular calcium activates calcium-dependent proteases and phospholipases, causing toxic metabolite production and cell death. Potassium, phosphate, myoglobin, creatine kinase (CK), creatinine and nucleosides (which are metabolised to urate) leak into the circulation. The subsequent inflammation and oedema leads to fluid accumulation in affected muscles and intravascular volume depletion.

AETIOLOGY

Causes of rhabdomyolysis can be classified into traumatic and non-traumatic (Table 1). The most common cause is direct trauma to the muscle, either from being crushed or from direct pressure, for example a patient lying on the floor for a long period, unable to get up.

Table 1. Causes of rhabdomyolysis.

Traumatic	Non-traumatic
<ul style="list-style-type: none">• Crush injury• Entrapment• Prolonged immobilisation• Electrical injury• Excessive muscle activity - marathon running, status epilepticus, malignant hyperpyrexia• Heat-related - heat stroke, neuroleptic malignant syndrome (NMS), hypothermia (rarely)	<ul style="list-style-type: none">• Ischaemic insult• Substance misuse - alcohol, cocaine, amphetamines, ecstasy• Drugs - statins, fibrates, antipsychotics, antidepressants• Toxins - carbon monoxide, heavy metals, snake venom• Infection - tetanus, Legionella, viral, sepsis syndrome• Electrolyte disturbance - hypokalaemia, hypo/hypernatraemia, hypocalcaemia, hyperphosphataemia, hyperosmolar non-ketotic coma, diabetic ketoacidosis, hypo/hyperthyroidism

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PRESENTATION

Clinical manifestations

The clinical presentation of rhabdomyolysis varies, depending on the aetiology and severity. It may range from an asymptomatic rise in serum CK to hypovolaemic shock with life threatening arrhythmias. Muscle pains and weakness are common and often associated with general malaise, nausea, tachycardia and confusion. Dark coloured urine may be the first indication of muscle damage.

The 'classic' triad of symptoms includes muscle pains, weakness and dark urine, but is seen in less than 10% of patients.⁴

Laboratory features

Biochemical markers confirm the diagnosis and can be used to predict prognosis. Serum CK levels are the most sensitive indicator of muscle damage, rising within the first twelve hours of injury, peaking at one to three days and declining at three to five days.⁴ A serum CK level over 5000U.L⁻¹ is associated with an incidence of AKI of over 50%.⁴ Levels are directly proportional to the extent of muscle injury. Compartment syndrome, compounding the injury, may further increase serum CK.⁵

Myoglobin is one of the significant compounds released after muscle disintegration. High circulating levels produce dark-brown discoloration of the urine, as myoglobin is filtered in the kidney. Haematuria and myoglobinuria often co-exist, particularly in the context of trauma. The absence of myoglobinuria does not exclude the diagnosis of rhabdomyolysis so clinical use is questionable.

Many metabolic derangements occur due to the rapid influx of calcium into cells. These include hyperkalaemia, hyperuricaemia, hyperphosphataemia, hypermagnesaemia and initially hypocalcaemia, as calcium concentrates in myocytes. Hyperkalaemia is an early feature; electrolytes should be measured as soon as the diagnosis is made. High anion gap metabolic acidosis may develop in severe rhabdomyolysis due to lactic acid production in ischaemic muscles.

COMPLICATIONS

Early

Severe hyperkalaemia may lead to arrhythmias and cardiac arrest, especially in association with profound hypovolaemia, hypocalcaemia and acidosis.

Early or late

Compartment syndrome may develop and is exacerbated by the presence of hypotension. Compartment pressures greater than 30mmHg are likely to cause significant muscle ischaemia and subsequent secondary rhabdomyolysis. Hepatic dysfunction occurs in approximately 25% of individuals.⁶

Late

Disseminated intravascular coagulation may occur up to 72 hours following the initial insult. Acute kidney injury is the most serious complication.⁷ The mechanism is not completely understood, but it is thought to be due to a combination of renal vasoconstriction, hypovolaemia, mechanical obstruction by intraluminal cast formation and direct cytotoxicity.

During the recovery phase, hypercalcaemia may result from accumulation in muscle and from iatrogenic administration of calcium supplementation during periods of hypocalcaemia.⁸

MANAGEMENT

Early recognition and initiation of treatment is key to the stabilisation of life threatening electrolyte disturbance and metabolic acidosis. Prompt aggressive fluid resuscitation with crystalloid is paramount and is the single most important factor in reducing the incidence of AKI. Alkalinisation of the urine with crystalloid resuscitation is considered standard. The use of bicarbonate and mannitol therapy has been used, however observational data suggest that they provide no additional clinical benefit to volume expansion with crystalloid (see below).

Initial resuscitation

As soon as the diagnosis is confirmed, intravenous access should be established and baseline measurements, including electrolytes and an arterial blood gas sample, taken. Acute hyperkalaemia should be treated with standard therapy including insulin, glucose and bicarbonate. As much as 10 litres of fluid may be sequestered into injured muscle. Intravenous crystalloid therapy with sodium chloride 0.9% should be started immediately. Fluid should be titrated to achieve a urine output of 200- 300ml.h⁻¹. There is no good evidence to show that alkaline diuresis is superior to sodium chloride 0.9%.⁹ The administration of both sodium chloride (0.9%) and isotonic sodium bicarbonate (1.26%) is an acceptable approach, that can be used to avoid a worsening hyperchloraemic metabolic acidosis. Resuscitation should ideally be guided by the use of invasive monitoring.

Intravenous mannitol can also be used, as it promotes renal blood flow and diuresis, although there is no evidence that this therapy leads to beneficial outcomes.

Rationale for bicarbonate and mannitol therapy

Alkalinisation of the urine is achieved by using 1.26% sodium bicarbonate of up to 500ml.h⁻¹, aiming for a urinary pH of greater than 6.5. This potentially prevents precipitation and degradation of myoglobin in the urinary tubules. It is also useful in the management of hyperkalaemia and acidosis, however neither therapy has been subject to randomised clinical trials. Observational data suggest that the addition of mannitol and bicarbonate have no effect on the development of acute kidney injury, need for dialysis or death. If sodium bicarbonate is used, serum bicarbonate, calcium and potassium should be closely monitored.¹⁰

Compartment syndrome

Irreversible muscle and nerve damage can occur if there is a delay in the recognition and management of compartment syndrome. Neurovascular compromise implicates the need for fasciotomy. Intracompartmental pressures consistently greater than 30mmHg, despite reductive measures, indicate a clear requirement for fasciotomy.

Renal replacement therapy

Established acute kidney injury, or the presence of refractory hyperkalaemia and acidosis, may necessitate renal replacement therapy (RRT). It is unusual for fluid overload to be an indication for RRT

in rhabdomyolysis. Haemodialysis corrects metabolic and electrolyte disturbances rapidly and efficiently. The prognosis of AKI secondary to rhabdomyolysis is good, with renal function usually returning to normal within 3 months.¹⁰

SUMMARY

Rhabdomyolysis is often encountered in the intensive care setting. Patients may have few symptoms so a high level of suspicion should be maintained. Serum CK is the most sensitive indicator of muscle injury.

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Management of burns

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INTRODUCTION

Burns are a serious public health problem throughout the world. In 2002 fire-related burns were responsible for an estimated 322,000 deaths worldwide.¹ Deaths are only part of the problem; for every person who dies, many more are left with lifelong disabilities. Over 95% of fatal fire-related burns occur in low and middle income countries.¹ The standard of burn care that is routinely available in many countries, is suboptimal due to lack of education and resources.

This article focuses on the basics of the initial management of burns patients, which can have a significant impact on the patient's outcome.

EPIDEMIOLOGY

More than two million people suffer burn injuries in India each year.² South-East Asia alone accounts for over one-half of the total number of fire-related deaths worldwide and females in this region aged 15 to 45 years account for 26% of global fire deaths.³ Burns

are the leading cause of adult deaths in the slums of Karachi, Pakistan.

Children under 5 years and the elderly have the highest fire-related burn mortality rates.¹ In the UK there are approximately 250 000 burns per year, 175 000 attend emergency departments and 13 000 are admitted to hospital. Of these, 1000 need fluid resuscitation and, on average, 300 patients die each year.²

RISK FACTORS FOR BURN INJURY²

- Open fires for cooking, heating and lighting.
- Substance abuse including alcohol and smoking.
- Low socioeconomic status, overcrowding, lack of safety measures, lack of parental supervision.
- Medical conditions such as epilepsy.
- Non accidental injury in children - the incidence of child abuse among hospitalised children for treatment of burns ranges from 5-25%.

Summary

Burns are a major cause of morbidity and mortality. This article describes the pathological process of burns and a systematic approach to their management. Initial care should follow the basic principles of trauma resuscitation, with assessment and treatment of life threatening problems of the airway, breathing and circulation. Recognition of burn severity, stopping the burning process, initiating fluid and analgesia and early surgical involvement can have a significant effect on patient outcome.

Table 1. Estimated number of deaths and mortality rates due to fire-related burns by WHO region* and income group (2002). Reproduced by kind permission of the WHO from 'A WHO plan for burn prevention and care' (2008).

Region	Africa		The Americas		South-East Asia		Europe		Eastern Mediterranean		Western Pacific		World
	low/middle	high	low/middle	low/middle	high	low/middle	high	low/middle	high	low/middle			
Number of burn deaths (thousands)	4.3	4	4	184	3	21	0.1	32	2	18		312	
Death rate (per 100 000 population)	6.1	1.2	0.8	11.6	0.7	4.5	0.9	6.4	1.2	1.2		5.0	
Proportion of global mortality due to fires (%)	13.8	1.3	1.3	59	1.0	6.7	0.02	10.3	0.6	5.8		100	

* Countries within each geographical region have been further subdivided by income level, according to the divisions developed by the World Bank

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- Violence against women related to gender inequality.
- Men at the workplace due to scalds, chemical and electrical burns.

TYPES OF BURN

Burns can be thermal, chemical, radiation and electrical. Thermal burns may be hot or cold. Hot thermal burns include contact, flame, flash, heat and scalding. With scald burns, the more viscous the liquid and the longer the contact with the skin, the greater the damage.

Chemical burns include extravasation injuries such as concentrated dextrose, calcium and sodium bicarbonate. They are more common in the elderly where veins are more friable. Alkaline burns produce liquefactive necrosis and are considered higher risk burns due to their likelihood to penetrate more deeply. Acid burns are the result of coagulation necrosis, limiting the depth and penetration of the burn.

Electrical burns produce heat injury by passing through tissue. Most problems from these burns present in patients exposed to greater than 1000V. Cardiac injury is prominent and cardiac monitoring is recommended for 4-72 hours. Visceral injuries, fractures, myoglobinuria and compartment syndromes should all be considered.

ANATOMY AND PHYSIOLOGY

The skin is a complex organ with a wide variety of functions. Loss of these barrier functions occur with a skin burn. Understanding of these alterations in skin function greatly assists in initial management.

Barrier functions

- Protection from bacterial entry (infection).
- Protection from toxin absorption.
- Fluid balance: avoiding evaporative water loss.
- Sensory (touch, pain, pressure).
- Social-interactive (visible portion skin).
- Protection from injury because of the properties of elasticity and durability.
- Regulation of body temperature to avoid hypo- or hyperthermia.

Skin structure

Epidermis

The outer, thinner layer, known as the epidermis, is composed mainly of epithelial cells. The deepest epidermal cells are immature cells that are continually dividing and migrating toward the surface. The same types of regenerating epidermal cells are found in hair follicles which are anchored in the dermis.

Dermis

The dermis is the deeper layer, responsible for skin durability and elasticity. The nerves for touch and pain, blood vessels and hair follicles are present in the dermis. The dermis is responsible for reforming the outer epidermis. So, if the outer layer is burned, the wound can heal as long as there is dermis. If the dermis is destroyed, the burn cannot heal.

PATHOLOGY

The depth of the burn is dependent on the temperature of the heat

insult, the contact time and the medium. Excess heat causes protein denaturation and cell damage. Scalds travel more rapidly into tissue than dry heat. A surface temperature of over 68°C, caused by wet heat, produces immediate tissue death. A higher temperature is required with dry heat. The thickness of the skin is important; the thinner the skin (the elderly and children) the deeper the burn. The dead tissue on the surface is known as **eschar**. Toxic agents released by inflammation cause much of the tissue damage after the burn.

A thermal burn causes coagulation of soft tissue. Areas that were marginally perfused become re-perfused, triggering a release of vasoactive substances. These chemicals cause formation of reactive oxygen species, leading to increased capillary permeability. Fluid loss results and plasma viscosity increases, with formation of micro-thrombi.

After the initial 24 hours, fluid requirements abruptly drop as the capillary permeability returns to normal. Under resuscitation in this initial 24-hour time period leads to significant morbidity from hypovolemia and shock.

Major burns cause a hypermetabolic (inflammatory) state manifested by fever, increased metabolic rate, increased minute ventilation, increased cardiac output, decreased afterload, increased gluconeogenesis and increased catabolism.

INITIAL ASSESSMENT

Early management of burns can reduce the degree of pain, the rate of infection, the degree of scarring and increase the rate of healing. Early management can substantially reduce mortality and morbidity.

Initial care of the burn, victim should follow the basic principles of trauma resuscitation, with assessment and treatment of life threatening problems of airway, breathing and circulation. Recognition of burn severity, stopping the burning process and initiating fluid and analgesia, should be the next steps.

History

The history of the burn injury can give important information about the nature and extent of the burn, and any likelihood of inhalation or other injuries. Consider the type of burn, (thermal, chemical, radiation) and the location. Other important points include a history of trauma (e.g. an explosion), past medical history, medications, allergies and the patient's tetanus immunization status. Ascertain the history early because often the paramedics are the only source of information about the event.

Medical personnel must consider abuse as a cause of burns in both children and the elderly. Components of the history that should raise suspicion of abuse include:

- Conflicting stories of how the injury was sustained.
- Injury claimed to be unwitnessed.
- Pattern of burns that suggest contact with an object e.g. cigarette burns.
- Stocking, glove, or circumferential burns.
- Burns to genitalia or perineum.

- Injury incompatible with developmental level of the child.
- Injury attributed to a sibling.
- Presence of adult male who is not child's father living in household.

Accidental scalds often show a pattern of splashing, with burns separated by patches of uninjured skin. In contrast, intentional scalds often involve the entire extremity, appearing in a circumferential pattern with a line that marks the liquid surface.

Examination and burn assessment

Burn severity is determined by:

- Burn depth,
- Burn size,
- Burn location.

In some countries the depth of a burn is classified by degrees. In the UK a different classification exists to help decide the need for surgery, guide treatment and predict outcome.

Assessment of burn depth

Simple erythema (1st degree) burn

This is confined exclusively to the outer surface and is not considered a significant burn. No barrier functions are altered. The most common form is sunburn, which heals by itself in less than a week without scarring.

Superficial partial thickness (2nd degree) burn

This involves the entire epidermis and no more than the upper third of the dermis. Rapid healing occurs in 1-2 weeks, because of the large amount of remaining skin and good blood supply. Scarring is uncommon. Initial pain is the most severe of any burn, as the nerve endings of the skin are exposed to the air. This depth of burn is at low risk for infection unless grossly contaminated.

The microvessels perfusing this area are injured, resulting in leakage of large amounts of plasma, which in turn lifts off the heat-destroyed epidermis, causing blister formation. The blisters will continue to increase in size in the post-burn period. A light pink, wet, very painful wound is seen as blisters are disrupted. Frequently, the epidermis does not lift off the dermis for 12 to 24 hours and what appears initially to be a first degree burn is actually a second degree burn.

Deep partial thickness (2nd degree) burn

Most of the skin is destroyed except for a small amount of remaining dermis. The wound looks white or charred, indicating dead tissue. Blood flow is compromised and a layer of dead dermis, or eschar, adheres to the wound surface. Pain is much less, as the nerves are destroyed by the heat. Usually, one cannot distinguish a deep dermal burn from a full thickness (third degree) burn by visualization. The presence of sensation to touch usually indicates the burn is a deep partial thickness injury.

Re-epithelialization is extremely slow, sometimes taking months. In these patients, blister formation does not characteristically occur,

Table 2. Summary of assessment of burn depth.

Degree of burn	Characteristic appearance
<i>Erythema (1st degree)</i>	Redness Reversible Tissue blanches with pressure Heals within a week
<i>Superficial partial (2nd degree)</i>	Confined to upper third of dermis Blisters, wet pink, painful Tissue blanches with pressure Heals in 10-12 days without scarring
<i>Deep partial (2nd degree)</i>	Involves majority of the inner dermal layer Dry, white, or charred skin Pain is minimal If heals, scar is severe Tissue does not blanch with pressure May heal in 2-3 months
<i>Full thickness (3rd degree)</i>	Complete destruction of both layers White, charred, dry Painless Needs to be excised and skin grafted

because the dead tissue layer is sufficiently thick and adherent to underlying viable dermis that it does not readily lift off the surface. The wound surface may be red and dry in appearance, with white areas in deeper parts. There is a marked decrease in blood flow, making the wound very prone to conversion to a deeper injury and to infection. A deep dermal burn requires 4 to 10 weeks or longer to heal. Excision and grafting is the preferred treatment.

Full thickness (3rd degree) burn

Both epidermal and dermal layers of skin are completely destroyed, leaving no cells to heal. Any significant burn will require skin grafting. A characteristic initial appearance of the avascular burn tissue is a waxy white colour. The burn wound is also painless and has a coarse non-pliable texture to touch.

Assessment of burn area

The more body surface area (BSA) involved in a burn, the greater the morbidity and mortality. Burn extent is only calculated for individuals with partial thickness or full thickness burn.

There are three ways of assessing the burn area:

Palmar area

A simple method to estimate burn extent is to use the patient's palmar surface, including fingers, to measure the burned area. An individual's palmar surface classically represents 1% of the BSA, but this is considered an over-estimate by some, who consider the palm to be 0.4% or 0.8% including the fingers.

Rule of nines (Figure 1)

A second method is to use the 'rule of nines' to estimate the extent of burn injury. The head represents a greater portion of body mass in children than it does in adults.

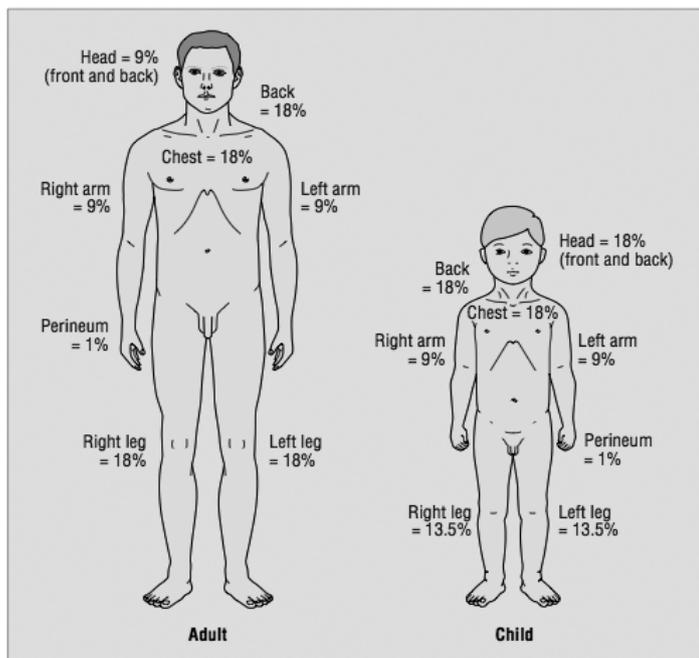


Figure 1. The 'rule of nines' (reproduced from reference 3, by kind permission from John Wiley and sons).

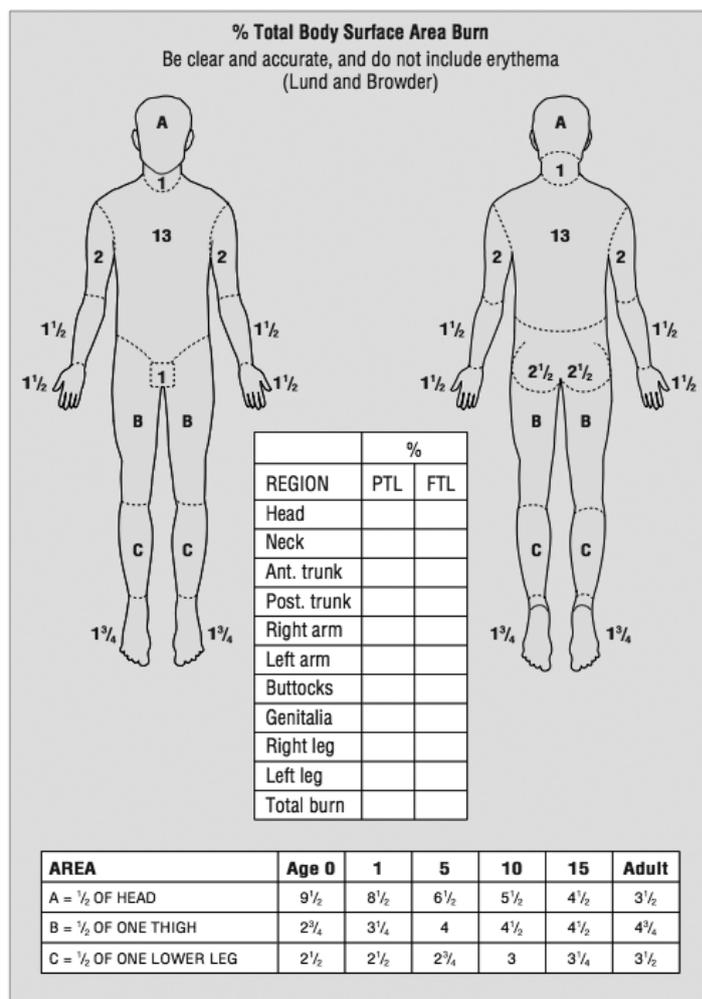


Figure 2. The Lund and Browder chart (reproduced from reference 3, by kind permission from John Wiley and sons). PTL = partial thickness, FTL = full thickness

Lund and Browder chart (Figure 2)

This is used to calculate the burn surface area (BSA). It compensates for the variation in body shape with age.

INITIAL MANAGEMENT

Immediate death is the result of coexisting trauma or airway compromise. Perform a rapid primary survey to assess the status of the patient's airway, breathing, and circulation. Immediately correct any problems found. Figure 3 summarises the goals of initial management.

Airway

During airway assessment, give careful attention to signs of airway injury. Facial or oral burns, singed facial or nasal hair, hoarse voice, carbonaceous sputum or altered mental status suggest the possibility of airway or inhalation injury. Changes in voice suggest laryngeal oedema.

If any doubt exists, secure the airway by induction of anaesthesia, paralysis using suxamethonium and endotracheal intubation. Do not cut the endotracheal tube as significant facial swelling is likely in the next 24 hours. Ventilate with an increased minute volume and 100% oxygen until carboxyhaemoglobin levels are known.

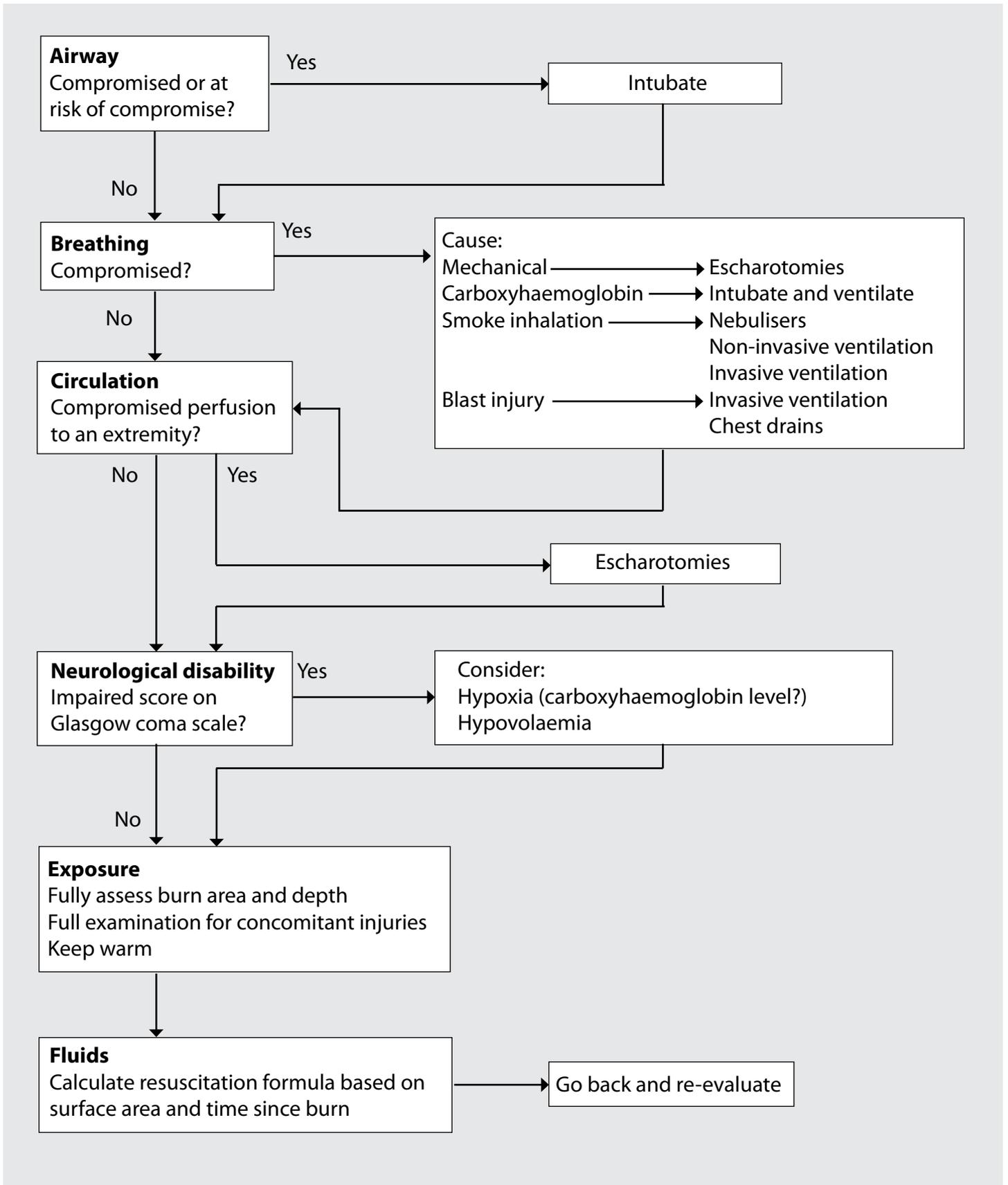


Figure 3. Algorithm of primary survey and initial management of a patient with a major burn injury (reproduced from reference 4, by kind permission from John Wiley and sons).

Breathing

Assume inhalation injury in any person whose history suggests prolonged entrapment or confinement in an enclosed area of fire. Inhalation injury may include systemic effects of carboxyhaemoglobin (COHb), hydrogen cyanide absorption, chemical pneumonitis or a combination. If present, carbon monoxide (CO) has up to 250 times the affinity for haemoglobin (Hb) than oxygen. COHb has a half life of 3-4 hours in room air, 30-40 minutes in 100% oxygen and 20 minutes in hyperbaric oxygen.

Table 3: Interpretation of carboxyhaemoglobin levels

% COHb	Effect
0.3-2%	normal non-smokers
5-6%	normal smokers
15-30%	headache, dizziness, nausea
30-40%	confusion
> 60%	convulsions, coma, death

Consider cyanide toxicity if there is a history of toxic fumes, an unexplained metabolic acidosis, raised lactate or anion gap. Cyanide is also found in smoke, especially from burning polyurethane. Plasma cyanide levels are difficult to obtain, so treatment is usually based on a high index of suspicion. For cyanide poisoning, cardiopulmonary support is usually sufficient treatment. Sodium nitrite can be used (300mg IV over 5-10 minutes) in severe cases.

If your patient's respiratory function worsens, remember that there are many toxins released from different compounds in household fires. They can all cause different degrees of mucous membrane irritation, bronchospasm, bronchorrhoea, mucous plugging and pulmonary oedema. Treatment is supportive with humidified oxygen, bronchodilators and ventilation as necessary.

Circumferential or deep chest wall burns may restrict breathing and so require escharotomy (incision of the eschar).

Circulation

Any burn greater than 15% of the total body surface area may produce shock due to hypovolemia. Fluid administration should begin immediately with warmed fluid. Intravenous cannulae may be placed through burned skin if necessary. If intravenous access is not possible, consider using intraosseous access early. Inadequate resuscitation, resulting in shock or vasoconstriction, can reduce blood flow causing the burn to become greater in size or depth and reduce healing.

With the loss of the barrier provided by intact skin, burn victims have large fluid losses due to evaporation. Remember burn victims will need generous fluid resuscitation as only 20-30% will remain in the intravascular space.

Fluid therapy for a burn victim in the acute phase can be calculated using the **Parkland formula**, as follows:

For children a **modified Parkland formula** exists, due to the influence of surface area to body weight ratio:

For the first eight hours give normal maintenance and 2ml.kg^{-1} per %BSA over eight hours.

For the subsequent 16 hours continue maintenance but add 1ml.kg^{-1} per %BSA.

Remember that a formula is only an estimate and adjustments need to be made based on the patient's status. The formula does not predict fluid resuscitation needs in electrical injuries accurately. In addition the presence of coexisting trauma may increase fluid volumes required for resuscitation.

Monitor markers of fluid status (e.g. urine output) and adjust fluids accordingly. Placement of a urinary catheter ensures accurate measurement of hourly urine output. Urine output should be maintained at $0.5\text{ml.kg}^{-1}\text{h}^{-1}$. In children, maintain urine output at $1\text{ml.kg}^{-1}\text{h}^{-1}$, a pulse of 80-180 per minute (age dependent) and a base deficit of < 2 .

Perfusion to a burnt distal extremity must be closely monitored. Pain and colour are unreliable indicators of perfusion in the presence of a burn to the area. Be aware that circumferential extremity burns can impair perfusion (escharotomy or fasciotomy may be required) and that jewellery may become tight with tissue swelling.

Disability

A low conscious level could be due to hypoxia, carbon monoxide, hydrogen cyanide, head injury or drugs. A reduced conscious level could precede the burn, if the patient has other medical conditions such as diabetes, epilepsy or cerebrovascular disease. Where available, check the patient's blood gas, COHb, blood sugar, electrolytes, alcohol level and urine toxicology. Look carefully for evidence of head injury, focal neurology or pupil asymmetry, that would suggest neurological injury.

Exposure

Remove all clothing, cool the burn with running water or saline, but avoid hypothermia. Cover the patient with dry, sterile sheets or clean clear dressing, such as 'cling film'. Take the opportunity to assess the

Fluid requirement in first 24 hours (in ml) = $4 \times (\% \text{BSA burn}) \times (\text{body weight in kg})$

Example: A man who weighs 70 kg and has a 30% BSA burn would require:

$$30 \times 70 \times 4 \text{ ml.kg}^{-1} = 8400\text{ml in the first 24 hours.}$$

One half of the calculated fluid requirement is administered in the first 8 hours, and the rest is given over the remaining 16 hours. Thus, fluids would be given at 525ml.h^{-1} for the first 8 hours, then at 262.5ml.h^{-1} for the remaining 16 hours.

depth and extent of the burn thoroughly. Clean other areas with minor burns with the use of a mild soap and gentle scrubbing.

Debridement of intact blisters is subject of debate; the intact skin serves as a barrier to infection, although the blister fluid can serve as an excellent medium for bacterial growth. Blisters that are intact, but are located in areas that have a high likelihood of rupture, may be debrided. The World Health Organization (WHO) recommends debridement of all bullae and excision of all adherent necrotic tissue.

Fluids

Intravenous fluid replacement is necessary for:

- Adults with greater than 15% body surface area burns,
- Children with greater than 10% body surface area burns.

There is no clear evidence that crystalloid or colloid is superior. Colloid has inherent risks of allergy and pruritus and there is some evidence that starches may increase renal injury.

Ongoing fluid losses are difficult to quantify. There can be significant fluid losses in soaked bandages and bed sheets. After 24-48 hours, standard maintenance fluids may be adequate. Repeated assessment of urine output, clinical signs, biochemistry and haematocrit is useful to assess the adequacy of fluid resuscitation.

Gastric feeding

Place a nasogastric or orogastric tube in those patients who are comatose, as they tend to have gastric dilatation. Start enteral feed early or add gastric protection (H_2 antagonists, proton pump inhibitors or sucralfate, as available).

The patient's energy and protein requirements will be extremely high due to the catabolism of trauma, heat loss, infection and the demands of tissue regeneration. If necessary, feed the patient through a nasogastric tube to ensure an adequate energy intake (up to 6000kcal per day). Anaemia and malnutrition prevent burn wound healing and result in failure of skin grafts. Use of eggs, peanut oil and locally available supplements are encouraged.

Head up

Nurse the patient thirty degrees head up.

Infection

A fresh burn is initially sterile but soon becomes colonised. Infection is almost inevitable and sepsis is a major cause of morbidity and mortality. Topical antimicrobials, dressing changes and prevention of cross infection (e.g. strict hand hygiene) are all important. Intravenous antibiotics are not recommended in the initial treatment of most burn patients, as it may increase the chance of colonization with more virulent and resistant organisms. They should be reserved for those patients with secondary infections. Administer tetanus immunization as appropriate.

INDICATIONS FOR PATIENT TRANSFER

The American Burn Association has developed criteria for admission to a specialist burn centre, as follows:

- Full thickness (third degree) burns over 5% BSA,

- Partial thickness (second degree) burns over 10% BSA,
- Any full-thickness or partial-thickness burn involving critical areas (e.g. face, hands, feet, genitals, perineum, skin over any major joint), as these have significant risk for functional and cosmetic problems,
- Circumferential burns of the thorax or extremities,
- Significant chemical injury, electrical burns, lightning injury, coexisting major trauma, or presence of significant pre-existing medical conditions,
- Presence of inhalation injury.

INVESTIGATIONS

Where available, consider the following:

- Full blood count, urea and electrolytes, liver function tests,
- Arterial blood gases with carboxyhemoglobin levels,
- Coagulation profile,
- Urine analysis,
- Group and save,
- Creatine phosphokinase and urine myoglobin levels in electrical injuries. The presence of myoglobin can signify muscle breakdown (rhabdomyolysis) as well as impending kidney impairment.
- Chest Xray in cases of smoke inhalation.

ANALGESIA

Opioids provide rapid pain relief that can be titrated to achieve the desired comfort level for each patient. Where available, a patient controlled analgesia pump is appropriate. Take extra care in those patients with hypoxaemia and reduced conscious level. Use regular paracetamol and, where not contraindicated, non-steroidal anti-inflammatory drugs (NSAIDs). Ketamine infusion is useful, where opioid analgesia is unavailable or inadequate. Ketamine bolus and entonox are useful for dressing changes. At later stages, oral opioids and tricyclic antidepressants, such as amitriptyline, can be useful.

SURGERY

In the initial stages after a burn, surgery is a priority to achieve debridement of affected tissues. At the same time the surgeon will usually try to achieve coverage of the burn with one or more split skin grafts, in order to minimise infection, reduce pain and allow healing. Where the area of burn exceeds the area of healthy skin, skin substitutes (either temporary or permanent) may be used to cover the burn. These include allograft (from a cadaveric donor) and xenograft (for example porcine skin).

Other potential surgery may involve:

- Full thickness skin grafts,
- Flap surgery,
- Tissue expansion
- Late allograft or xenograft.

ANAESTHESIA FOR PATIENTS WITH BURNS

- The anaesthetist may encounter the same burn patient many times throughout their hospital stay. Initial involvement may be in the emergency department including airway assessment, resuscitation, establishing IV access, analgesia, their initial trip to theatre for wound assessment, cleansing, debridement or on the many trips to theatre for grafting or reconstructive surgery.
- Airway concerns change with time. Airway oedema may be due to the initial burn, or develop as a consequence of tissue inflammation or crystalloid resuscitation. At later stages, scarring and contractures can inhibit mouth opening or limit neck movement prohibiting conventional laryngoscopy. Consideration must be given to awake fiberoptic intubation or awake tracheostomy under local anaesthetic. Each patient must be assessed on an individual basis.
- Wet burns or the presence of exudate make mask holding very difficult. Initially the pressure to the face can be painful, then the seal becomes difficult to maintain. The use of dry gauze between the patient and your gloves allows some degree of grip. The endotracheal tube should be maintained with a cord tie not tape. For nasal tubes or nasogastric tubes holder devices ('bridles' that loop behind the nasal septum) are used to secure position, especially in intensive care patients.
- It is considered safe to use suxamethonium for up to 24 hours following the burn. Following this time there is an increase in extra-junctional cholinergic ion channels, beyond the motor end plate, and therefore a risk of hyperkalaemia following depolarisation. The same proliferation of binding sites, along with changes in distribution, metabolism and excretion, increase the requirement for non-depolarising muscle relaxants.
- During wound debridement and grafting, bleeding can be extreme, especially in small children. Ensure blood is available, if needed, and that there is a current group and save specimen. The use of adrenaline (epinephrine) soaked swabs can reduce blood loss through vasoconstriction. With larger burns, monitoring can be difficult with no obvious site for ECG leads and the blood pressure cuff. Extensive washing needs thoughtful positioning and repositioning of ECG electrodes.

- Monitor the patient's temperature; with extensive exposure, debridement and general anaesthesia, heat loss may be rapid, especially in children. Burns theatres can be uncomfortably warm with high ambient temperatures. Fluids for irrigation and infusion should be warmed and external warming blankets used where possible.

PROGNOSIS

The traditional formula to predict mortality (age in years + the percentage BSA, giving a predicted percentage mortality) is no longer accurate, with mortality being significantly better with modern treatments. Prognostic factors affecting outcome include early intervention, age, total body surface area of burn, and the presence of lung injury. However, outcome clearly depends on additional comorbidities and the standard of care received.

CONCLUSIONS

Burn injuries can cause major morbidity and mortality, but good early management can dramatically improve the prognosis. Early management of burns can reduce the degree of pain, rate of infection, degree of scarring and increase the rate of healing. Anaesthetists have a key role in the multidisciplinary team involved in a burn victim's care. A full understanding of the anatomy, physiology and pathological processes is essential for this role. Initial roles include assessment and resuscitation and later roles are as the anaesthetist for debridement, dressing changes, and contracture and cosmetic surgery.

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Management of drowning

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BACKGROUND

In 2004 an estimated 388 000 people died worldwide as a result of drowning.¹ This total, taken from Global Burden of Disease figures, makes drowning the third leading cause of death from unintentional injury (after road traffic accidents and falls). It is a significant underestimate, as it includes only deaths from 'accidental drowning and submersion', excluding drowning due to cataclysms (floods), assaults, suicides, and transport accidents. Drowning is a global public health concern which results in significant morbidity and mortality.

DEFINITIONS

Over twenty different definitions relating to drowning have appeared in the medical literature, hindering attempts to implement effective surveillance and management activities. In an effort to allow more accurate comparison of available data on drowning, experts at the World Congress on Drowning, held in Amsterdam in 2002, agreed on the following definition:²

Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid. Drowning outcomes are classified as:

- death
- morbidity or
- no morbidity.

EPIDEMIOLOGY

Table 1 shows the estimated number of deaths attributed to unintentional drowning, in each WHO region in 2004.¹

Risk factors for drowning include:

Sex

Males are more likely to die or be hospitalised due to drowning than females. Overall the male rate of drowning is more than twice that of females. Studies suggest this is due to increased exposure to water and riskier behaviour such as swimming alone, drinking alcohol before swimming alone and boating.

Age

Children under 5 have the highest drowning mortality rates of any age group worldwide.

Socioeconomic status

Ethnic minority groups have higher rates of drowning mortality rates, possibly due to differences in opportunities to learn to swim.

Occupation

The occupational mortality amongst Alaskan fisherman is 116 per 100 000, with an estimated 90% of deaths due to drowning

PATHOPHYSIOLOGY

The primary physiological consequences of drowning are prolonged hypoxaemia and the resultant metabolic

Summary

Drowning is a frequent accident, that is associated with significant morbidity and mortality worldwide. Prompt resuscitation and aggressive treatment are vital to optimise patient outcome and minimise long term sequelae.

Table 1. Deaths attributable to unintentional drowning by region per year. AFR - African Region; AMR - Americas Region; EMR - Eastern Mediterranean Region; EUR - European Region; SEAR - South-East Asian Region; WPR - Western Pacific Region.¹

	World Total	AFR	AMR	EMR	EUR	SEAR	WPR
Males	262,940	46,466	18,348	21,523	27,765	63,288	85,134
Females	125,060	15,874	3,842	8,140	6,460	36,648	53,823
Total	388,000	62,340	22,190	29,663	34,224	99,935	138,957
Sex ratio (M:F)	2.1:1	2.9:1	4.8:1	2.6:1	4.3:1	1.7:1	1.6:1
Rate (per 100 000)	6.0	8.5	2.5	5.7	3.9	6.0	8.0

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acidosis.^{3,4,5} When a drowning victim's airway lies below a liquid surface, initial breath-holding is inevitably followed by a gasp which draws water into the hypopharynx and triggers laryngospasm. After a period of hypoxaemia, the laryngospasm breaks and there is a further gasp, followed by hyperventilation and aspiration of variable amounts of water. The aspiration of 1-3ml.kg⁻¹ of water results in significantly impaired gas exchange. Injury to other organs arises from the subsequent hypoxia and acidosis. In 10 to 20 percent of patients laryngospasm is maintained until cardiac arrest occurs and, in this situation, no aspiration occurs (previously referred to as *dry drowning*).

When *fresh water* is aspirated, the hypotonic solution moves rapidly across the alveolar-capillary membrane. This destroys the surfactant layer and results in alveolar collapse and decreased compliance, with marked ventilation/perfusion (V/Q) mismatching. As much as 75% of blood flow may circulate through hypoventilated lung segments. Aspiration of *salt water* causes washout of surfactant and exudation of protein rich fluid into the alveoli and pulmonary interstitium. The result is a reduction in compliance, damage to the alveolar-capillary membrane and intrapulmonary shunting. Bronchospasm may occur in both fresh and salt water drowning. There is no difference in outcome between fresh water and salt water drowning; both may result in significant submersion injuries and management is identical.

The release of inflammatory mediators may result in pulmonary hypertension, whilst pulmonary oedema occurs as a result of both negative pressure (following obstruction and laryngospasm) and hypoxic neuronal injury. The destruction of surfactant commonly results in acute respiratory distress syndrome (ARDS). Another frequent complication is ventilator associated lung injury (VALI). In a small number of patients, aspiration of stagnant water, silt, sand, sewage or vomitus may cause bronchial occlusion, pneumonia, abscess formation and inflammatory damage to the alveolar membranes.

Neurological injury is a major determinant of outcome and subsequent quality of life in drowning victims.³ As well as direct trauma, primary neurological injury occurs due to brain hypoxia and ischaemia. Secondary injury may result from multiple factors including sustained hypoxia, hypotension, acidosis, hyperglycaemia, release of excitatory neurotransmitters, seizures and cerebral oedema.

Autonomic instability is common in both severe hypoxic and severe traumatic brain injury,³ and may result in tachycardia, hypertension, diaphoresis, agitation and muscle rigidity. This encephalic/hypothalamic storm may present as a syndrome of transient left ventricular hypokinesia, dyskinesia or akinesia, manifesting as ECG changes and raised troponin levels, in the absence of obstructive coronary artery disease or myocarditis. This is also known as *Takosubo cardiomyopathy*.⁶ Rhabdomyolysis may occur, since there is extensive hypoxic muscle injury and the subsequent myoglobinaemia may precipitate acute kidney injury.⁷ Electrolyte disturbances may also occur, for example hyponatraemia is seen in children who have ingested large quantities of fresh water.

PRE-HOSPITAL CARE

Early resuscitation has been shown to play a significant role in increasing survival.^{8,9,10} Rescuers may find an individual at any stage of the drowning process and consequently a drowning victim may

require anything from simple observation to rapid and continued resuscitation. As with all emergencies, management should be aimed at ensuring adequate Airway, Breathing and Circulation, with cervical spine stabilisation if the patient is unresponsive or there is any possibility of trauma.¹¹ In the event of cardiac arrest cardiopulmonary resuscitation (CPR) should be commenced in all patients and continued during transfer to hospital, as hypothermia may make the detection of vital signs difficult in the pre-hospital setting. The adage that hypothermic patients are not dead until they are 'warm and dead' has good foundation – recovery from prolonged submergence is well documented in children and, although it is less common in adults, there are some remarkable case reports of survival.^{12,13,14}

Rescue breaths can be given whilst the patient is still in the water however chest compressions are often ineffective due to problems with buoyancy. The patient should be removed from the water at the earliest opportunity, in a supine or foetal position where possible. There is a recognised risk of circulatory collapse during or following rescue from immersion in water.⁵ While in the water there is an increase in hydrostatic pressure around the victim's legs and trunk. This results in increased venous return and pre-load with support of the cardiac output. This increased central volume is detected as relative hypervolaemia by the body and diuresis and natriuresis is triggered, depleting the victim's intravascular volume. Peripheral vasoconstriction due to the relative cold temperature exacerbates this further. Extraction from the water in the foetal position is said to protect against the circulatory collapse that occurs when this hydrostatic pressure is removed.⁵

Use of the Heimlich manoeuvre to expel water from the lungs has been shown to be ineffective and should not be attempted, as it may cause the patient to vomit and aspirate.⁴ Where available, supplemental high-flow oxygen should be given as soon as possible. Ventilation via any method may require higher pressures than expected, due to poor compliance, however, if the pre-hospital team are unable to ventilate the patient, airway obstruction should be suspected. If ventilating by reservoir bag, each breath should be just enough to make the chest wall move in order to prevent excess pressure and minimise iatrogenic lung injury.¹⁵

Traditionally, rescuers have been advised to begin re-warming as soon as possible, by removing the victim from wet clothing, before wrapping them in blankets and administering warmed fluid (where facilities allow). However, there is now good evidence that therapeutic cooling improves neurological outcome in out-of-hospital ventricular fibrillation cardiac arrest. Further research is required to determine whether this evidence can be extended to victims of drowning.

DEFINITIVE CARE

Ongoing management should focus on continuing resuscitation, correcting hypoxia and acidosis, and the treatment of concomitant injuries. Some patients – those who give a reliable history of short immersion, without significant injury, change in mental status, respiratory problems or impaired oxygenation – may be safely observed for a period and then discharged.

Airway and respiratory support

Bronchospasm may be provoked by inhalation of water and particulate

matter, and by cold-induced bronchorrhoea (increased bronchial secretions). This should be treated aggressively to avoid worsening hypoxia. The drug of choice is an inhaled beta-agonist bronchodilator, such as salbutamol. If the patient is sufficiently cooperative (and where it is available) bi-level positive airway pressure (BiPAP) may improve oxygenation. Intubation (using rapid sequence induction) and ventilation are indicated in the following situations:

- severe hypoxia and/or acidosis,
- signs of significant respiratory distress,
- inadequate respiratory effort,
- failure to protect the airway (e.g. low conscious level).

Patients with submersion injuries are at high risk of developing Acute Lung Injury (ALI) and ARDS so protective lung ventilation strategies should be used to minimise iatrogenic damage associated with mechanical ventilation.¹⁵ These include:

- Aim for SaO₂ > 88%, with pH > 7.2. Optimise PEEP.
- Tidal volume < 6ml.kg⁻¹.
(Use ideal body weight:
Males 50 + [0.91 x (height – 152.4)]cm
Females 45 + [0.91 x (height – 152.4)]cm)
- Plateau pressure < 30cmH₂O.

Advanced respiratory techniques

It may be possible to remove plugs of foreign material and vomitus using bronchoscopy, and bronchioalveolar lavage can be of use in obtaining samples for culture in cases of aspiration pneumonia. Surfactant therapy has been used in some drowning victims and has been shown to improve ventilation, oxygenation and fluid leak.^{16,17,18} The use of Extracorporeal Membrane Oxygenation (ECMO), in patients who remain hypoxic despite aggressive mechanical ventilation, has achieved dramatic effects in both adults and children.^{19,20}

Cardiovascular support

In both salt water and fresh water drowning, intravascular depletion is common due to intracompartmental fluid shifts and pulmonary oedema (as well as diuresis). Fluid resuscitation using warmed isotonic crystalloids (20ml.kg⁻¹) or colloids may be indicated. Vasoactive drugs may also be required, in particular in the presence of other traumatic disease processes such as neurogenic shock and blunt myocardial injury, or where there is underlying cardiac disease. Cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, bradycardia and asystole can occur, often due to hypothermia rather than electrolyte imbalance, and should be treated according to standard international resuscitation guidelines.

Temperature

Temperature management in patients following drowning is a topic of ongoing research and clinical interest. Traditional studies have supported vigorous rewarming of hypothermic patients to normothermia via a number of different modalities (warmed fluids,

warmed inspired air, bladder, peritoneal and pleural lavage). More recent literature suggests that mild therapeutic hypothermia is effective in improving neurological outcome and mortality rates in out-of-hospital VF cardiac arrest.²¹ Several case reports in drowning victims, who have made a full neurological recovery following coma and cardiac arrest, suggest that therapeutic hypothermia may confer neuroprotection in this setting;^{22,23} however its role is yet to be established by clinical trials.²⁴

At the World Congress on Drowning a consensus on temperature management was reached, based on the available evidence:²

“The highest priority is restoration of spontaneous circulation, subsequent to this continuous monitoring of core and/or brain (tympanic) temperatures is mandatory in the ED and intensive care unit and to the extent possible in the prehospital setting. Drowning victims with restoration of adequate spontaneous circulation, who remain comatose, should not be actively warmed to temperature values above 32-34°C. If core temperature exceeds 34°C, hypothermia should be achieved as soon as possible and sustained for 12 to 24 hours...”

The patient's cardiovascular status will dictate the method of rewarming, and so the rate at which they are rewarmed. Those who are haemodynamically unstable, or in cardiac arrest, require rapid rewarming. Cardiopulmonary bypass (CPB) techniques or veno-veno haemodialysis can achieve a temperature increase of 5-10°C.h⁻¹ and ECMO is also highly effective.²⁵ However, where such facilities are not available, then traditional techniques should be employed – meta-analysis has demonstrated the efficacy of pleural lavage when CPB is not available, or transfer to a tertiary centre not possible or would require unacceptable transfer times.²⁶

Other considerations

Appropriate treatment of hypoglycaemia, electrolyte imbalances and seizures should be initiated where necessary. The use of corticosteroids have been shown to be of no long term benefit and therefore should not be given unless otherwise indicated.²⁷ Antibiotic prophylaxis also has no proven benefit and is not recommended unless the patient was submersed in grossly contaminated water. Tetanus immunisation status should be checked and a booster, or course of treatment, should be given if necessary. Associated injuries should be identified early, as these may complicate further management.

PROGNOSIS

Drowning is a frequent accident, associated with high morbidity and mortality. There is no validated clinical scoring system to predict survival and long term neurological recovery in drowning victims. Some factors have been shown to adversely affect survival, including prolonged submersion,²⁸ delay in the initiation of effective CPR,²⁸ asystole on arrival at hospital,²⁹ fixed dilated pupils, a low Glasgow Coma Score,³⁰ and severe metabolic acidosis (pH <7.1).²⁹ Prompt resuscitation and aggressive treatment are therefore crucial to optimal survival. In cases where it is clear that submersion has been very prolonged, or there is evidence of fatal concomitant injury, life may be pronounced extinct. In all other cases, advanced life support should be implemented and continued until a full evaluation can be made as to the futility or otherwise of continued resuscitation.

SUMMARY

Early resuscitation plays a vital role increasing survival and should follow the same Airway, Breathing, Circulation approach to management as all medical emergencies. Further management should focus on correcting hypoxia and acidosis, making full use of protective lung ventilation strategies and advanced respiratory techniques, where available. Attention should also be paid to concomitant injuries.

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Management of sepsis with limited resources

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WHY IS SEPSIS IMPORTANT?

Sepsis is common, has a high mortality and its incidence is increasing. Studies in developed countries have shown that the hospital mortality for severe sepsis is between 32% and 55%.¹⁻³ Sepsis is the most common cause of death in children worldwide. Sixty percent of deaths in developing countries occur as a result of communicable disease.⁴ Although sepsis is a complex topic, early recognition, resuscitation and basic treatment can significantly improve outcome.

The aim of this review is to explain sepsis, the principles of its management and to describe the major recent advances in this field. Financial limitations make many of the more recent technological developments and expensive interventions impractical in developing countries. These techniques are described briefly for educational value, with an emphasis on how they can be incorporated into practice in a poor resource setting. The main focus is adults, but the same principles apply to children.

WHAT IS SEPSIS?

The Systemic Inflammatory Response Syndrome (SIRS) is an immune response to a variety of severe insults including infection, burns, pancreatitis, and trauma. It affects many organ systems.

Sepsis is SIRS in response to infection. Definitions are summarised in Box 1.

In sepsis, failure of the circulatory system to maintain organ perfusion results from hypovolaemia, myocardial depression and abnormal regulation of vascular tone. This, together with increased metabolic rate, causes an imbalance between tissue oxygen supply and demand, leading to global tissue hypoxia.

The interactions between infecting microorganisms and the immune, inflammatory and coagulation responses in sepsis are complex. Proinflammatory and procoagulant responses are amplified by ischaemia and hypoxia, and immunosuppression occurs in severe sepsis.⁶

RECOGNITION OF SEPSIS

Good hygiene practices and hand washing can help prevent healthcare associated infections. Identifying infections early and treating appropriately can prevent the development of sepsis. This includes good wound care and reviewing patients regularly, asking about and examining for signs of infection. Patients with early sepsis may have a significant imbalance between oxygen supply and demand, despite normal vital signs. A vigilant clinician with a high index of suspicion may notice subtle signs such as cool peripheries, sweating, altered mental state or reduced urine output, as well as tachypnoea and tachycardia.

Signs of SIRS should be picked up on routine observations. These should include temperature, heart

Box 1. Definitions of sepsis⁵

Systemic Inflammatory Response Syndrome (SIRS): Two or more of the following:

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats per minute
- Tachypnoea (respiratory rate > 20 breaths.min⁻¹) or hyperventilation (PaCO₂ < 4.25kPa)
- White blood count > 12 x 10⁹.L⁻¹, or < 4 x 10⁹.L⁻¹

Sepsis: Two or more SIRS criteria in response to infection.

Severe sepsis: Sepsis associated with hypotension or organ dysfunction or organ hypoperfusion (e.g. oliguria, altered mental status, lactic acidosis).

Septic shock: Sepsis-induced hypotension (systolic blood pressure < 90mmHg or a reduction ≥ 40mmHg from baseline) despite adequate fluid resuscitation along with signs of hypoperfusion.

Summary

Early recognition and prompt treatment of sepsis improves survival. It is vital to administer appropriate antibiotics within one hour of diagnosis and to arrange for rapid surgical source control, where indicated. Evidence suggests that 'goal-directed therapy' improves outcome. In resource poor settings this must be guided by clinical signs. Guidance using 'bundles' of care are useful, but some aspects become outdated soon after publication.

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rate, respiratory rate, blood pressure, urine output and conscious level. Low blood pressure, persistently low urine output or confusion suggests severe sepsis and a high risk of death. When dealing with children it is important to know the normal values for age, and a delayed capillary refill time (>2 seconds) can be a useful sign of shock.

Patients with abnormal vital signs should receive prompt attention - just charting observations is not enough. Nurses need to be trained to recognise abnormal signs, call for help and initiate treatment if possible. Medical Early Warning Scores (MEWS) provide an effective way of streamlining the required chain of events, to direct the appropriate level of medical expertise to sick patients⁷ (see article on page 22 of this edition of *Update*).

Early recognition and treatment of sepsis is important. Rivers' study of early goal-directed therapy in patients with septic shock demonstrated marked improvements in mortality.⁸ Several aspects of their protocol including liberal fluid therapy, inotropes and liberal blood transfusion have been studied before in intensive care patients and failed to show benefit. The difference in this study was that interventions were applied early, during the first 6 hours of admission to the emergency department. Although some of the markers of sepsis and some of the interventions may be unavailable in many countries, the underlying principle of early haemodynamic resuscitation in sepsis is critical.

The key early interventions in sepsis are assessment and management of airway, breathing and circulation to optimise oxygen delivery. Intravenous antibiotics should be started within the first hour.⁹

INITIAL MANAGEMENT

Airway

- Give oxygen.
- A patient with an obstructed airway should be managed immediately with simple airway manoeuvres and an oro- or nasopharyngeal airway if necessary. Patients with reduced conscious level should be nursed in the recovery position.
- Where facilities exist, intubation and ventilation is indicated for airway obstruction or failure to localise to pain because of a low conscious level. Some of these patients may respond to fluid resuscitation with an improvement in conscious level, and a fluid challenge is a sensible initial step before giving any anaesthetic drugs.

Breathing

All septic patients should be given as much oxygen as possible. Higher concentrations of oxygen can be achieved with two oxygen concentrators connected into to a non-rebreathing mask with a reservoir bag, or one connected to a mask and one to nasal cannulae.

Respiratory failure may require intubation and ventilation. Signs of respiratory failure include tachypnoea, dyspnoea, use of accessory muscles, poor chest expansion, poor air entry, cyanosis, low oxygen saturation and hypoxia and/or hypercapnia on arterial blood gases, if these are available. Hypercapnia may be evident clinically, causing drowsiness or a flapping tremor of the hands.

Breathing may also be helped by sitting the patient up, deep breathing,

coughing and chest physiotherapy. If available, some patients may benefit from continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV). In the short term (e.g. while preparing to intubate), assisting breathing with a bag-valve-mask or Ambubag[®] (with a PEEP valve if possible) can be helpful. Remember that unless you are assisting breathing, patients find it difficult to breathe through an Ambu-valve and a simple mask with reservoir bag will achieve more effective oxygenation. A Waters circuit is a suitable alternative.

Box 2. Checklist for intubation of critically ill patients

Monitoring:	As available: SaO ₂ , ECG, frequent BP, assistant to feel pulse
Assistants:	One or preferably two for cricoid pressure and assistance. Check they know what you expect them to do
Preoxygenation:	Deliver as much oxygen as available via bag-valve-mask or anaesthetic circuit If using an oxygen concentrator, fill a large bin liner with oxygen and use this source of 100% oxygen to preoxygenate the patient
IV access:	Large drip running freely, fluid resuscitation in progress
Equipment:	2 working laryngoscopes Endotracheal tube of correct size + 1 size smaller, cuffs checked Gum elastic bougie Guedel airway End-tidal CO ₂ monitor, if available Stethoscope to check tube position Suction switched on and within reach Tape to secure ET tube
Intubation drugs:	e.g. ketamine and suxamethonium
Resuscitation drugs:	ephedrine 30mg in 10ml (1-3ml boluses) metaraminol 10mg in 20ml (0.5-2 ml) epinephrine (adrenaline) 1mg in 10ml (0.5-1ml) atropine 0.4-0.6mg
Ventilator:	Where available, checked and set up
Other drugs:	To continue sedation and muscle relaxation if necessary.

Intubating critically ill patients has significant risks. They have little oxygen reserve and, despite full preoxygenation, will desaturate quickly. Fluid resuscitation should be started while preparing to intubate, but expect the blood pressure to drop significantly and have a vasopressor agent drawn up. Ketamine may cause less hypotension than other

induction agents. Patients who are moribund and have a depressed level of consciousness may not tolerate any sort of intravenous agent. Occasionally such patients can be intubated without sedation, using local anaesthetic agent sprayed through a cannula onto the larynx under direct laryngoscopy.

Circulation

Fluid resuscitation

Septic patients need a lot of fluid. An initial fluid bolus of 20-30ml.kg⁻¹ of crystalloid (e.g. Hartmann's solution) is appropriate - i.e. around 2 litres for a 70kg adult. Further fluid boluses can be given, assessing the response to each. In Rivers' study patients received on average 5 litres of fluid in the first 6 hours and there was no increase in the need for ventilation.⁸

The choice of fluid does not seem to be important. Hartmann's solution has some advantages over 0.9% saline, but either is acceptable. Hartmann's is more similar in composition to extracellular fluid than saline and less likely to cause a hyperchloraemic metabolic acidosis. Dextrose (glucose) is useless for resuscitation. Colloids theoretically stay in the intravascular space longer than crystalloids, however capillary permeability is increased in sepsis. The SAFE study comparing albumin and saline for resuscitation found no difference in outcome, and showed that only 1.3 times as much saline was needed to produce the same effect as albumin.¹⁰ In patients with severe sepsis fluid resuscitation with hydroxyethyl starch has been associated with higher mortality rate, compared to Hartmann's solution.¹¹

A recent study has questioned the use of fluid resuscitation in children with sepsis. This is described in detail on page 89.

Resuscitation goals

Cardiovascular parameters used to guide resuscitation include heart rate, blood pressure, peripheral perfusion (skin temperature, capillary refill), urine output and conscious level. Many clinicians believe that CVP monitoring is not useful, since right atrial pressure correlates poorly with the pressures and volumes of the left side of the heart and use of CVP measurements to guide fluid therapy remains controversial. However, and the Rivers paper used a target CVP of 8-12mmHg as part of their 'bundle' of strategies to provide 'early goal-directed therapy', which reduced the mortality from septic shock. It is not possible to say which parts of their protocol were most beneficial and ideally, to replicate the benefits of this study, a clinician should manage his patients exactly as they were managed in the study. This demonstrates the difficulties of implementing the findings of clinical studies in situations where there are insufficient resources to introduce the full package of investigations and interventions.

If a blood gas machine is available, blood taken from a central venous catheter can be analysed to give central venous oxygen saturation (ScvO₂). This may be a useful marker of oxygen delivery. A ScvO₂ of less than 70% suggests that oxygen extraction is increased due to inadequate oxygen delivery. Oxygen delivery is related to cardiac output, haemoglobin concentration and arterial oxygen saturation. It can be improved by increasing cardiac output with fluid or inotropes, by increasing oxygen carrying capacity with blood transfusion and by supplemental oxygen to increase SaO₂. Oxygen demand may be reduced by intubation, ventilation and sedation.

Some blood gas analysers or labs can measure serum lactate concentration, which is a useful if non-specific marker of tissue hypoxia. The normal lactate level is <2.5mmol.l⁻¹ in venous blood and <1mmol.l⁻¹ in arterial blood. In a recent study of patients with an infective diagnosis attending an emergency department, patients with a venous lactate level above 4mmol.l⁻¹ on admission were 12.6 times more likely to die than those with normal venous lactate level. The 28-day mortality of patients with a venous lactate above 4mmol.l⁻¹ and a systolic BP below 70mmHg on presentation was 60%.¹²

Box 3. Resuscitation goals (dictated by available resources)

Mean Arterial Pressure (MAP) > 65mmHg

Urine Output > 0.5ml.kg.⁻¹h⁻¹

Warm peripheries, capillary refill < 2 seconds

Central venous pressure (CVP) 8-12mmHg

Central venous oxygen saturation (ScvO₂) > 70%

Serum lactate < 4mmol.l⁻¹

Notes:

MAP = diastolic BP + (systolic BP - diastolic BP)

3

i.e. a MAP of 65mmHg is compatible with a BP of 85/55, 95/50 or 105/45

Several monitors can measure or calculate cardiac output and fluid status (see article in this edition of *Update*). This equipment is rarely a priority in regions with limited resources and although the monitors may add useful information there is little evidence that they improve outcome.¹³ In fact a recent trial in patients with acute lung injury (of whom 25% were septic) showed no advantage of using a pulmonary artery catheter to guide haemodynamic management over clinical assessment of circulatory effectiveness (skin colour and temperature, capillary refill), blood pressure and urine output.¹⁴ This emphasises the message that early intervention guided by clinical findings is effective in the management of sepsis.

Vasopressors and inotropes

Patients with septic shock have low blood pressure and reduced tissue perfusion, despite adequate fluid resuscitation. They may be vasodilated, or have a low cardiac output, or both. This high risk group is difficult to diagnose and treat appropriately.

Adequate fluid resuscitation is difficult to determine. A CVP of 8-12mmHg, which goes up and stays up with a fluid challenge suggests adequate filling. Alternatively generous fluid resuscitation with no further improvements in heart rate, blood pressure, or peripheral perfusion following fluid challenges is probably adequate.

Patients who are vasodilated with a high cardiac output have warm peripheries, capillary refill <2 seconds and good volume pulses. If they are hypotensive they may benefit from a vasoconstrictor such as norepinephrine (noradrenaline) to improve the perfusion pressure to organs such as the kidneys and brain, particularly if urine output

or conscious level is reduced. Vasoconstrictors used alone can reduce cardiac output and worsen tissue hypoxia, so these patients need to be observed closely with repeat assessments of peripheral perfusion. Where available, a normal lactate and $ScvO_2$ are reassuring.

Patients with low cardiac output have cool peripheries and slow capillary refill. Their systemic vascular resistance may be high or low. If cardiac output fails to improve with fluid resuscitation, an inotrope is required. Epinephrine (adrenaline) is both an inotrope and vasoconstrictor and is usually very effective. Dobutamine is an inotrope and vasodilator, which is more difficult to use, and may cause the blood pressure to drop further. It can be used together with norepinephrine, but titrating two vasoactive drugs without cardiac output monitoring is difficult.

A Cochrane review in 2004 concluded that there was not sufficient evidence to recommend one vasopressor over another.¹⁵ Despite several recent studies comparing vasoactive drugs, this remains the case. The Surviving Sepsis Guidelines (2008)⁹ recommend norepinephrine or dopamine as the first line vasopressor for septic shock. However, the SOAP study,¹⁶ a large European observational study, found that dopamine administration was an independent risk factor for ICU mortality in patients with shock (of whom 38% had septic shock). A subsequent multicentre randomised controlled trial (RCT) comparing dopamine with norepinephrine (the SOAP II trial¹⁷) found no difference in 28-day mortality. However there were more arrhythmias with dopamine and subgroup analysis found increased mortality in patients with cardiogenic shock treated with dopamine. Epinephrine

is associated with a transient lactic acidosis, tachycardia and decreased gut perfusion.^{9,18} However, a multicentre RCT (the CATS trial¹⁹) comparing norepinephrine plus dobutamine with epinephrine alone patients with septic shock found no difference in mortality, time to vasopressor withdrawal or adverse events. Vasopressin is also used in refractory septic shock, but in a randomised controlled trial low dose vasopressin did not reduce mortality, compared with norepinephrine, among patients with septic shock.²⁰

The most common reason that a patient fails to respond to vasopressors or inotropes is that they are hypovolaemic: a fluid challenge is worth trying. Given the difficulty of assessing a variable clinical picture, you may not be using the best drug, for example giving norepinephrine to someone who already has a low cardiac output. Intermittent boluses of vasopressor such metaraminol 0.25-1mg, or combined vasopressor and inotrope such as ephedrine 3-9mg or epinephrine 0.05mg may give you an idea of which type of drug the patient responds to. Of course, some patients may not respond due to the overwhelming severity of the disease. Recognising this and focusing on comfort can prevent unnecessary suffering.

Blood transfusion

Increasing haemoglobin concentration is one way of improving oxygen delivery, however blood transfusion has risks. Some observational studies have found that blood transfusions are associated with increased mortality in critically ill patients and others have not.²¹ The TRICC study showed that, in intensive care patients, a restrictive transfusion

Box 4. Use of inotropes and vasopressors

These are examples. Use whatever you are familiar with or find easiest to work out. Reliable infusion pumps should be used whenever possible. Use a central line if available, otherwise use a dilute solution via a dedicated reliable cannula in a large proximal vein.

Epinephrine and norepinephrine

- By infusion pump (via central line if possible):
 - mix 5mg in 50ml (or 4mg in 40ml)
 - start at 1-5ml.h⁻¹ and titrate according to response
 - for a 50kg person 0.1mcg.kg⁻¹.min⁻¹ = 3ml.h⁻¹
- If no infusion pumps available:
 - mix 5mg in 500ml. The infusion rate should be watched continuously.
 - Paediatric giving sets with 60drops.ml⁻¹ are helpful, start at 10-50drops.min⁻¹
 - Normal 20drops per ml⁻¹ sets can also be used - divide drops.min⁻¹ by 3
 - For example for a 50kg person:
 - with 60drops.ml⁻¹ paediatric set, 0.1mcg.kg⁻¹.min⁻¹ = 30drops.min⁻¹
 - with 20drops.ml⁻¹ set 0.1mcg.kg⁻¹.min⁻¹ = 10drops.min⁻¹

Dopamine and dobutamine

- By infusion pump:
 - mix 250mg in 50ml.
 - Start around 5mcg.kg⁻¹.min⁻¹
 - for a 50kg person 5mcg.kg⁻¹.min⁻¹ = 3 ml.h⁻¹
- These can also be used without an infusion pump as above.

strategy aiming for haemoglobin of 7-9g.dl⁻¹ was at least as effective and possibly superior to a liberal transfusion strategy aiming for Hb 10-12g.dl⁻¹.²³ However, only 5% of the patients in this study had a primary diagnosis of sepsis, average lactate concentration was less than 2mmol.L⁻¹, and patients were enrolled up to 72 hours into their ICU stay. This is a different population to that studied in Rivers' trial of early goal directed therapy (see Box 5). The Rivers protocol included transfusion to a haemoglobin >10g.dl⁻¹ if a ScvO₂ above 70% was not achieved by other means. Overall, 68% of patients were transfused in the intervention group (64% before 6h) versus 45% in the control group (19% before 6h). It is not possible to say which parts of their protocol were most beneficial, and transfusion practice in intensive care remains controversial.

Crucially, most clinicians working in resource-poor areas will be unable to measure ScvO₂ and implement this strategy of treatment. In addition the risks of transfusion are greater, although a WHO initiative is improving blood transfusion services in many countries. Elsewhere screening for blood-borne disease, antibodies and cross-matching may be less thorough and limited resources should be reserved for those with the greatest need and greatest chance of survival.

Antibiotics and source control

Intravenous antibiotics in adequate dosage should be given as early as possible, after taking blood cultures. Giving effective antibiotics within the first hour has been associated with increased survival in septic shock.^{24,25} Lack of appropriate antibiotics in poor resource settings

is a major obstacle to providing effective treatment for patients with sepsis. Choice of antibiotics depends on the likely source of infection, should be broad spectrum and take into account local resistant organisms. Even where the choice appears limited a logical approach will provide effective cover; for example antibiotics such as ampicillin, gentamicin and metronidazole provide excellent cover for abdominal sepsis. Discussion with a microbiologist is helpful. Samples can be sent for gram stain if available rapidly. Further samples including wound swabs, urine, sputum or tracheal aspirate, and CSF should be taken for culture as appropriate, ideally before giving antibiotics.

Detailed history and examination should try to determine the source of infection. Investigations such as chest X-ray, ultrasound and CT scan may be helpful.

Surgeons should be involved at an early stage if surgical drainage or debridement may be required. These patients are high risk for anaesthesia, and a short period of resuscitation is appropriate, but they will die without control of the source of sepsis.

FURTHER MANAGEMENT

Mechanical ventilation

Sepsis may cause acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). This is inflammation of the lungs with increased vascular permeability characterised by bilateral infiltrates on chest X-ray, not caused by cardiac failure. The definition has recently been updated (see page 183).

Box 5. Early goal-directed therapy

Many recommendations in this review and in the Surviving Sepsis Guidelines⁹ are based on Rivers' trial of early goal-directed therapy (EGDT) in severe sepsis and septic shock.⁸ This was a randomised controlled trial of 263 patients with septic shock, presenting to a US emergency department. The study showed that a protocol of goal-directed therapy during the first 6 hours of admission, aimed at achieving a balance between oxygen delivery and oxygen demand, reduced hospital mortality from 46% in the control group to 30% in the experimental group.

Enrolled patients met SIRS criteria (above) and had systolic BP < 90mmHg after 20-30ml.kg⁻¹ of crystalloid, or serum lactate > 4. The control group received standard therapy to achieve CVP 8-12mmHg, MAP > 65mmHg, urine output > 0.5ml.kg⁻¹.h⁻¹. The experimental group protocol aimed for the same targets plus ScvO₂ > 70%:

- They were given 500ml crystalloid every 30 minutes until CVP 8-12,
- If MAP < 65mmHg they received norepinephrine (if MAP >90mmHg vasodilators),
- If ScvO₂ < 70% they were transfused to Hb >10g.dl⁻¹,
- Then, if ScvO₂ < 70%, they received dobutamine (stopped if MAP < 65 or HR > 120)
- Then, if ScvO₂ < 70% still, they were intubated and ventilated

During the first 6 hours the EGDT group received more fluid (5 litres vs. 3.5 litres), more blood transfusion (64% vs. 18.5%), and more dobutamine (13.7% vs. 0.8%). Use of vasopressors and ventilation was similar between the groups. Volume resuscitation alone was sufficient to correct ScvO₂ in 36%, transfusion in an additional 50% and inotropes in 13.7%. During the period 7-72 hours after admission the EGDT group required less fluid, less transfusion, less vasopressors and less ventilation. They had lower lactate levels, less acidosis and less severe organ dysfunction.

We can conclude that this protocol, applied early with frequent review, to patients with severe sepsis can reduce mortality. ScvO₂ is probably a useful resuscitation goal, however it is not possible to say exactly which aspects of this protocol were most beneficial. This was a small, single-centre, unblinded study with a high control group mortality. Three multi-centre trials (ProCESS, ARISE and ProMISE) are currently in progress to see whether these findings can be replicated in other settings.²³

Low tidal volume ventilation

Mechanical ventilation of patients with ARDS should avoid high airway pressures and high tidal volumes. The ARDSnet study of 861 patients is the foremost randomised controlled trial comparing ventilation strategies.²⁷ Ventilation with tidal volumes of 6ml.kg⁻¹ and plateau pressures of <30cmH₂O compared to ventilation with tidal volumes of 12ml.kg⁻¹ and plateau pressures <50cmH₂O reduced mortality and increased ventilator-free days. This study used a protocol based on volume controlled ventilation. However, pressure control ventilation or spontaneous modes are likely to be better tolerated in patients who are not deeply sedated or paralysed. The targets of pressure <30cmH₂O and tidal volume 6ml.kg⁻¹ are probably more important than the ventilation mode.

Permitting modest hypercapnia to allow lower tidal volumes and airway pressures is likely to be safe. This is limited if the patient has a metabolic acidosis (pH <7.20).⁹

PEEP

Positive end expiratory pressure (PEEP) prevents lung collapse and can improve oxygenation. A further study comparing high PEEP with low PEEP combined with the ARDSnet ventilatory strategy, showed no difference in survival.²⁷ More recent trials of high PEEP have not shown a mortality benefit, but did improve secondary endpoints such as oxygenation, duration of ventilation and use of rescue therapies.^{28,29} Increasing PEEP according to FiO₂ as in the original ARDSnet study seems reasonable (see page 195).

Semi-recumbent positioning

Nursing ventilated patients in the semi-recumbent position (45 degrees, head up) has been shown to reduce the incidence of ventilator-associated pneumonia.³⁰ Patients may need to be laid flat if hypotensive. Non-invasive ventilation,³¹ subglottic drainage and use of heat and moisture exchange filters, instead of heated water humidification, may also reduce the incidence of ventilator-associated pneumonia.³²

Ventilatory weaning protocols

A protocol for weaning patients from mechanical ventilation is helpful. Once a patient is improving and meets certain criteria, daily spontaneous breathing trials, breathing through the endotracheal tube with oxygen delivered via a T-piece, reduce the duration of mechanical ventilation.³³ Combining daily spontaneous breathing trials (using a T-piece or low level of pressure support) with a spontaneous awakening trial in which sedation (but not analgesia) is stopped, can reduce duration of ventilation and mortality.³⁴

Activated protein C

Recombinant activated protein C was shown in one trial to reduce mortality in severe sepsis.³⁵ Subsequent trials have failed to show benefit and it has now been withdrawn.

Steroids in sepsis

Patients on long term steroid therapy or with known adrenocortical insufficiency require steroid replacement during critical illness. Many studies have looked at treatment of septic patients with corticosteroids and this remains controversial.

One multicentre RCT showed an improvement in ICU mortality in patients with vasopressor-unresponsive septic shock and relative adrenal insufficiency, when they were given hydrocortisone 50mg 6 hourly and fludrocortisone.³⁶ These patients were hypotensive despite fluids and vasopressors and the effect was only seen in non-responders to the ACTH test (blood cortisol level failed to rise appropriately in response to a dose of synthetic adrenocorticotrophic hormone, ACTH). Two meta-analyses have shown reduction in mortality, but only in studies of low dose, long duration steroid therapy.^{37,38} The subsequent CORTICUS study, a large multicentre RCT comparing hydrocortisone to placebo in septic shock, showed faster shock reversal but no mortality benefit with steroids. This study included all patients with septic shock, including those who did respond to vasopressors, and use of the ACTH test did not predict benefits.³⁹

The 2008 Surviving Sepsis Guidelines suggest giving low dose hydrocortisone only to patients who respond poorly to fluids and vasopressors, without using an ACTH test.⁹

Nutrition and stress ulcer prophylaxis

Evidence based guidelines recommend that intensive care patients, who are not expected to be taking a full oral diet within 3 days, should receive enteral nutrition via a feeding tube.⁴⁰ There is no difference in the efficacy of jejunal versus gastric feeding, but they recommend jejunal feeding where this is easily carried out (for example placed during laparotomy) and for patients who do not tolerate gastric feeding. Gastric emptying is frequently the rate-determining step so, where available, motility agents such as erythromycin and metoclopramide may be helpful in patients with feed intolerance and high gastric residual volumes. If available and affordable, parenteral nutrition may be considered in patients who cannot be fed sufficient enterally.^{40,41} Use of an evidence based algorithm for nutritional support in Canadian intensive care units was associated with more days of enteral nutrition and improved clinical outcomes.⁴² It is advisable that all ICUs use an enteral feeding protocol, describing gradual introduction of feed to a predetermined goal, with regular aspiration of gastric residual volume.

Laparotomy and peritonitis is not a contraindication to enteral feeding and several studies have shown benefits of early nasojejunal feeding in these patients.^{43,44} Most studies have used specially designed feeds given by infusion, but these are often not available in developing countries. The above studies used nasojejunal feed prepared in hospital kitchens (and include the recipes). Patients are often given liquidized food, soup, milk etc. by nasogastric tube but it is not easy to meet calorific and nutritional requirements without detailed calculations and, ideally, advice from a dietician.

The enteral route can also be useful for electrolyte replacement, particularly where IV potassium is not available. Hypokalaemia can worsen ileus and oral rehydration solution by mouth or nasogastric tube may help prevent this.

The Surviving Sepsis Guidelines⁹ recommend stress ulcer prophylaxis with ranitidine, but this can potentially increase the risk of ventilator associated pneumonia and should be stopped when no longer required. The extent to which enteral feeding protects against stress ulcers is not known.

Blood glucose control

Tight glucose control was widely adopted following Van Den Berghe's study in 2001, showing improvements in ICU mortality in patients with blood glucose levels kept at 4.4-6.1mmol.L⁻¹ versus 10.0-11.1mmol.L⁻¹.⁴⁵ 62% of these patients had undergone cardiac surgery. Their subsequent study in medical ICU patients,⁴⁶ showed that intensive insulin therapy improved some markers of morbidity but not mortality, and 19% of patients in the treatment group developed hypoglycaemia.⁴⁷ The insulin arm of the VISEP trial (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) was stopped due to an unacceptably high incidence of hypoglycaemia in the treatment group (12%).⁴⁸ The recent NICE-SUGAR trial compared intensive (4.5-6.0mmol.L⁻¹) with conventional (<10mmol.L⁻¹) glucose control. They found a much lower incidence of severe hypoglycaemia and lower mortality in the conventional control group.⁴⁹ As a result most ICUs now aim for blood glucose less than 10mmol.L⁻¹.

Septic patients are at risk of both hypo- and hyperglycaemia, whether or not they are treated with glucose and insulin. Blood glucose should be checked in all sick patients, but close monitoring of blood glucose is more difficult in areas with limited resources. Four to six-hourly subcutaneous insulin, adjusted according to blood glucose, is an alternative to intravenous sliding scales where no infusion pumps are available, but still requires frequent blood glucose monitoring.

Analgesia, sedation and neuromuscular blockade

Untreated pain in septic patients increases oxygen demand, causing tachycardia and distress. The safest way to give analgesia is to titrate doses of intravenous opioid, repeated until pain has improved. Small doses of ketamine (0.2mg.kg⁻¹) can be a useful co-analgesic, but larger doses may cause disorientation. Regular paracetamol should be given. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in septic patients – the risks of renal failure and peptic ulceration will be increased.

Sedation of unintubated septic patients is potentially dangerous. Confusion and agitation may be caused by hypoxia, reduced brain perfusion or intracranial pathology, which may be worsened by sedation. Mental state may improve with resuscitation and provides an important marker of organ perfusion. Ketamine is relatively safe, but may worsen confusion and agitation. Benzodiazepines may cause respiratory depression, particularly if combined with opiates. In patients who are unmanageable and at risk of harming themselves, anaesthesia, intubation, ventilation and continued sedation may be the only safe option. Where available, haloperidol is a useful drug in confused patients.

In ventilated patients, sedation may be given by intermittent bolus or by continuous infusion, according to a protocol with sedation goals.⁹ Daily lightening of sedation (a '*sedation hold*') allows assessment of neurological function and reduces the duration of mechanical ventilation and ICU length of stay.⁵⁰ Daily sedation holds, paired with a spontaneous breathing trial, reduce length of stay and 1-year mortality.³⁴

Neuromuscular blockers should be avoided if at all possible due to the risk of prolonged muscle weakness (critical illness polyneuropathy), but are indicated in the acute phase of ARDS to facilitate a lung

protective ventilation strategy. Use of muscle relaxants without adequate continuous sedation is unacceptable.

Both chemical and physical restraint have risks.⁵¹ In one observational study in European ICUs, both prolonged sedation and physical restraint without sedation were associated with post-traumatic stress disorder.⁵² Physical restraint may be preferable to chemical sedation in some situations, but should be carefully and selectively employed. It should only be used if patients are not competent to make decisions, and pain and other causes of agitation have been addressed. It is important to keep trying to communicate with the patient. Restraints must not hurt the patient; for example 'boxing gloves' can be made out of bandages.

Renal support

Septic patients are at high risk of renal failure but renal support is unlikely to be available in resource-poor areas. The risk of renal failure can be reduced by early fluid resuscitation, maintaining renal perfusion pressure and cardiac output (with inotropes if necessary), and avoiding nephrotoxic drugs (e.g. NSAIDs, gentamicin). There is no evidence for using low dose dopamine for renal protection. Lactic acidosis should be treated by optimising the circulation, not with sodium bicarbonate.⁹

If available, renal replacement therapy (RRT) can be with either continuous veno-venous haemofiltration (CVVH) or intermittent haemodialysis.⁹ Continuous RRT may provide better haemodynamic stability and control of fluid balance but does not improve survival.⁵³ In some trials higher intensity of renal support improved outcome (CVVH ultrafiltration rates of 35ml.kg⁻¹.h⁻¹ and 45ml.kg⁻¹.h⁻¹ were similar and better than 20ml.kg⁻¹.h⁻¹)⁵⁴ but more recent larger trials have not confirmed this (no difference between 20ml.kg⁻¹.h⁻¹ and 35ml.kg⁻¹.h⁻¹ or 40ml.kg⁻¹.h⁻¹).^{55,56}

Peritoneal dialysis is appropriate but is contraindicated in patients who have intra-abdominal infection (see article on page 223)

Prophylaxis against deep vein thrombosis (DVT)

All ICU patients should receive DVT prophylaxis with either unfractionated or low molecular weight heparin, unless contraindicated (thrombocytopenia, coagulopathy, active bleeding). Graduated compression stockings may also be used for very high risk patients or if heparin is not given.^{9,57}

Sepsis 'bundles'

Sepsis bundles are clinical guidelines that combine therapies, aiming to improve outcome by promoting the use of effective therapies and improving the process of care.⁵⁸ A recent meta-analysis found that sepsis bundles were associated with improvements in survival.²³

The 'Sepsis Six' is a one-hour bundle developed in the UK to facilitate early, simple interventions in the emergency department or on the wards.⁵⁹

Several of the therapies included in these bundles are no longer recommended as a result of recent trials (such as steroids, activated protein C, tight glucose control). Only early antibiotic use has been proven to be beneficial. In the meta-analysis,²³ antibiotic use was consistently and significantly improved across all studies, but there

was a lack of consistency in the effect of bundled care on all the other bundle components analysed.

Many hospitals in developing countries do not have the resources to implement sepsis guidelines and bundles.⁶⁰ A study of intensive care units in Asia found that compliance with sepsis bundles was poor and mortality rates were high.⁶¹ Participating units were relatively well resourced and all able to measure central venous pressure, arterial blood gases and blood cultures. Compliance with bundle targets for blood cultures, antibiotics and central venous pressure independently

predicted decreased mortality. They suggest that achieving a CVP >8mmHg is a marker of aggressive fluid resuscitation, which is likely to be beneficial without necessarily measuring CVP.

Grouping therapies into bundles and providing education in their use is likely to improve the care of septic patients, but these therapies must be achievable and evidence based. In developing countries this could include giving oxygen and recording basic observations, fluid resuscitation, and early administration of antibiotics after blood cultures have been taken.

CASE EXAMPLE: Post-partum sepsis^{62,63}

A 25-year-old woman is admitted to your district hospital with vomiting, diarrhoea and abdominal pain 4 days after delivering her second child at home. She is afebrile with a heart rate of 130min⁻¹ and a blood pressure of 140/95mmHg. She is seen by a junior surgeon who finds a soft abdomen, diagnoses gastroenteritis and treats her with oral rehydration solution.

Her temperature rises to 39.5°C overnight and the next morning she is drowsy and confused. You are asked if she can be admitted to the critical care unit.

How are you going to assess and treat her?

Assess airway, breathing and circulation.

She is responding to voice with confused speech. Her respiratory rate is 35min⁻¹, your saturation monitor is not picking up a signal. Her heart rate is 140min⁻¹ and blood pressure 70/40mmHg. She is pale and peripherally cold with a capillary refill time of 5 seconds. The nurses don't know when she last passed urine.

She has septic shock: Give oxygen, fluid resuscitation and IV antibiotics.

You give oxygen 5L.min⁻¹ from an oxygen concentrator, insert two 14G cannulae and start fluid resuscitation with Hartmann's solution as fast as possible, then move her to recovery or the ICU. Further history from her mother reveals that her waters broke 2 days before delivery. Her delivery was uncomplicated, with no excessive bleeding and the placenta appeared intact. She has foul-smelling vaginal discharge and a tender uterus. You suspect genital tract sepsis, so start amoxicillin 2g 6 hourly, metronidazole 500mg 8 hourly and gentamicin 5mg.kg⁻¹ once (with further doses every 24 hours if renal function is normal).

What investigations do you want to do?

Blood cultures should be taken before giving antibiotics, but this is not available in your hospital. You take vaginal swabs for gram stain and culture and send urine for culture as soon as possible. You perform **a thorough physical examination**, looking for other sources of sepsis and take a more complete history. You ask an obstetrician to confirm your diagnosis, do a pelvic ultrasound to look for retained products and to assess whether there is an indication for surgery. You send blood for **full blood count, malaria screen, urea and electrolytes** and check **blood glucose. Arterial blood gases, lactate, coagulation screen and CRP** are not available. You would like a **chest Xray** to look for air under the diaphragm or signs of infection, but this is not available in the evenings.

How are you going to monitor her?

- Frequent nursing observations (minimum hourly): respiratory rate, oxygen saturation, heart rate, blood pressure, ECG, urine output, conscious level, pain score, temperature, blood glucose (4-hourly if stable).
- Frequent medical / anaesthetic review with goal-directed therapy.

After one hour she has had 2 litres of Hartmann's. Observations are: RR 25, SaO₂ 100% on 5L.min⁻¹ O₂, HR 130, BP 80/40, capillary refill 2s. She is drowsy but now orientated and complaining of abdominal pain. A catheter was inserted, draining a small amount of dark urine. Her temperature is 39°C.

What are you going to do now?

Give more fluid, assessing the response to each bolus.

You give 250ml of Gelofusine, and paracetamol for pain. HR improves to 120, capillary refill <2s with warm peripheries, BP is unchanged. After another 250ml there is no further change. She passes 15ml of urine in 1 hour. Her pain improves.

Some results come back: Hb 12g.dl⁻¹, white cell count (WCC) 30x10⁹.L⁻¹, platelets 90x10⁹.L⁻¹. Na 150mmol.L⁻¹, K 4.0mmol.L⁻¹, Cl 110mmol.L⁻¹, bicarbonate 15mmol.L⁻¹, urea 10mmol.L⁻¹, creatinine 80mcmol.L⁻¹, glucose 6mmol.L⁻¹. Gram stain of the vaginal swab shows gram positive cocci and gram negative bacilli.

What do you think of these results?

The high WCC is consistent with infection (it may also be low in severe sepsis). Low platelets occur in severe sepsis and may indicate disseminated intravascular coagulation. The haemoglobin is relatively high for a woman who has just had a baby, which may reflect dehydration, consistent with the slightly raised sodium and urea. The low bicarbonate and raised anion gap suggest a metabolic acidosis, probably lactic acidosis. This may be part of the reason for her tachypnoea. Gram stain shows mixed organisms for which she is on appropriate broad spectrum antibiotics. If culture shows group A streptococcal infection you could consider adding benzylpenicillin. Renal function will have to be watched closely while on gentamicin.

What are you going to do now?

Septic shock unresponsive to fluid: start vasopressor, continue goal-directed therapy.

She has now had 40ml.kg⁻¹ of fluid, with no further improvement with the last bolus. She remains hypotensive with a low urine output. A central venous catheter would be helpful but is not available. You start norepinephrine (epinephrine would be your second choice), 5mg in 500ml through a paediatric (60drops.ml⁻¹) giving set at 30drops.min⁻¹ via a separate cannula in her antecubital fossa. BP improves to 130/70 and HR to 110, capillary refill <2s. Urine output is 100ml the next hour. You explain to the nurses how to titrate the noradrenaline aiming for a BP > 100/50, urine output >30ml.h⁻¹, capillary refill <2s. You tell them to call you if these goals are not met, heart rate or respiratory rate increase, saturation or conscious level are reduced. You prescribe maintenance fluids at 125ml.h⁻¹ and analgesia.

You have a busy night: frequent fluid boluses are required for decreased urine output, reduced blood pressure or cool peripheries. Oxygen saturations drift down when she is sleeping, but they improve with sitting her up in bed and deep breathing. The next morning, after 5 litres of fluid, she is beginning to improve and the noradrenaline is gradually turned off. You ask for chest physiotherapy, encourage oral fluids and diet, and recheck blood tests.

She continues to improve, IV antibiotics are continued for 48h after the fever settles, and she is eventually discharged home.

How can you improve treatment of sepsis in future?

Early recognition and management of sepsis on the wards needs to be improved. The diagnosis may not be obvious and patients may not always have a fever, but recognising when a patient is sick is vital. This may include teaching sessions for doctors and nurses, organisational change to allow more frequent observations and improve staffing levels, and resources such as sphygmomanometers and saturation monitors.

You could discuss additional hospital and critical care resources such as blood culture and arterial blood gas analysis, central venous catheters and CVP monitoring. However, early recognition and timely simple interventions are the key to survival.

SUMMARY

Early recognition and treatment of sepsis can significantly reduce mortality. Limitations on resources make implementation of the findings of clinical trials problematic. However, the most important interventions of aggressive fluid resuscitation, oxygen and early antibiotics, with frequent review to adjust treatment, can be achieved in any hospital.

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Abdominal compartment syndrome

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Summary

Abdominal compartment syndrome (ACS) is a condition associated with significant morbidity and mortality. This article includes a case summary of a patient who developed ACS, after which the pathophysiology, diagnosis and management of this important condition are discussed.

CASE HISTORY

A 26-year-old previously fit and well man was a pedestrian involved in a road traffic accident. His injuries included rib fractures, a ruptured spleen and an unstable pelvic fracture. He was admitted to the intensive care unit following external fixation of his pelvis, laparotomy and splenectomy. Estimated blood loss was over 4 litres, which was replaced with a combination of blood, fresh frozen plasma and platelets. At the end of the case the patient had a metabolic acidosis, a mild coagulopathy, mild anaemia and was hypothermic. In view of these findings the patient remained ventilated.

Overnight the coagulopathy, anaemia and hypothermia were corrected. However his ventilatory requirements increased, with peak inspiratory pressure rising from 22 to 38cmH₂O in order to maintain acceptable tidal volumes. His abdomen was noted to be tense and distended. In addition his base excess remained greater than -8 and his urine output remained less than 0.5ml.kg⁻¹.h⁻¹ despite fluid resuscitation.

Abdominal compartment syndrome was confirmed by measurement of his intra-abdominal pressure. This was measured via an intra-vesical catheter (see below), giving a reading of 28cmH₂O. Following discussion with the surgical team he was taken for decompressive laparotomy (laparostomy). On opening the abdomen, peak inspiratory pressures fell immediately. No active bleeding was found but large intra-abdominal and retro-peritoneal haematomas were identified. The intra-abdominal haematoma was evacuated. Primary abdominal closure was not possible. Temporary closure was achieved using part of a sterile opened intravenous fluid bag, stitched into the defect in the abdominal wall.

The patient was then returned to the ICU, still ventilated, but requiring greatly reduced ventilatory support. On day 7 he underwent closure of his abdominal wound. Two days later he underwent internal fixation of his pelvic fractures and was discharged home two weeks later.

DEFINITIONS

The potential adverse consequences of raised intra-abdominal pressure (IAP) have been recognised for many years.¹ However the term abdominal compartment syndrome (ACS) was not coined until 1984, when Kron et al published

a series of post-operative patients in whom they measured IAP.² Recently the definitions of intra-abdominal hypertension (IAH) and ACS have been standardised.³

Intra-abdominal hypertension (IAH) is defined as an intra-abdominal pressure of 12mmHg or more.

Abdominal compartment syndrome (ACS) is defined as an intra-abdominal pressure (IAP) above 20mmHg with evidence of organ dysfunction or failure.

ACS is further classified as primary, secondary or recurrent.

Primary ACS is associated with conditions within the abdomino-pelvic region.

Secondary ACS includes conditions that do not originate within the abdomen, such as sepsis and capillary leak, major burns or other conditions that require massive fluid resuscitation.

Recurrent ACS is a condition in which ACS recurs after treatment of primary or secondary ACS.

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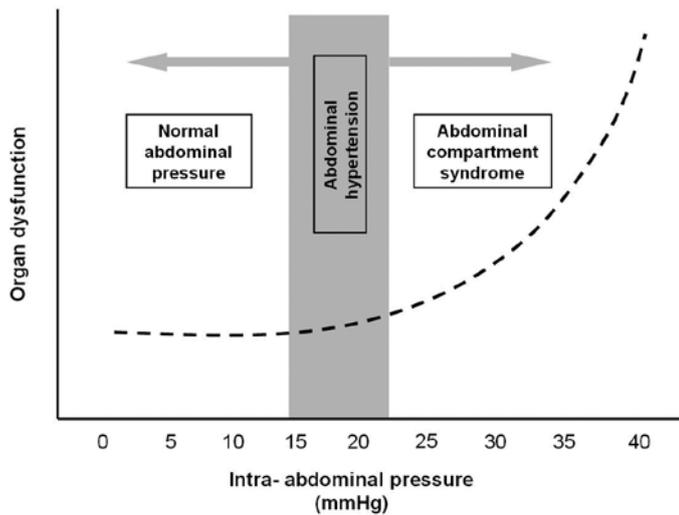


Figure 1. The relationship between intra-abdominal pressure and organ dysfunction.

PATHOPHYSIOLOGY

Intra-abdominal pressure reflects the relationship between intra-abdominal volume and abdominal compliance, and has a direct relationship with intra-thoracic pressure. The relationship between abdominal pressure and volume is non-linear. Abdominal compliance is affected by speed of increase in abdominal volume, as evidenced by the slight changes in IAP that occur during pregnancy. Normal IAP is estimated to be around 6mmHg. Chronic IAH can occur in some obese patients and patients with a large volume of ascites.

The causes of acutely raised IAP are often multifactorial.

Common causes of raised IAP are:

- Trauma and intra-abdominal or retroperitoneal haemorrhage
- Abdominal surgery (including laparoscopy intraoperatively)
- Peritonitis
- Repair of large incisional hernias
- Massive fluid resuscitation (>5 litres per 24 hours).

Small changes in IAP are usually well tolerated but as IAH worsens, it will eventually affect regional blood flow and impair tissue perfusion. This is often related to the systemic inflammatory response and multiorgan failure and the organs involved include the renal, cardiovascular, respiratory, gut, central nervous and immune systems. These will be discussed in turn.

Renal effects of ACS

Impairment of renal function seen in ACS is caused by an increase in renal vascular resistance, caused by renal vein compression. Reduction in cardiac output may be another causative factor. The exact IAP required to cause renal impairment is not known but some authors suggest a level of above 15mmHg. Impaired urine output has been noted in 65% of acutely injured patients with an IAP over 25mmHg and in 100% of those with an IAP above 35mmHg.⁴ Co-morbidities affecting renal function clearly have an additive effect. In addition to controlling IAH, maintaining cardiovascular filling pressures are important to limit renal dysfunction.

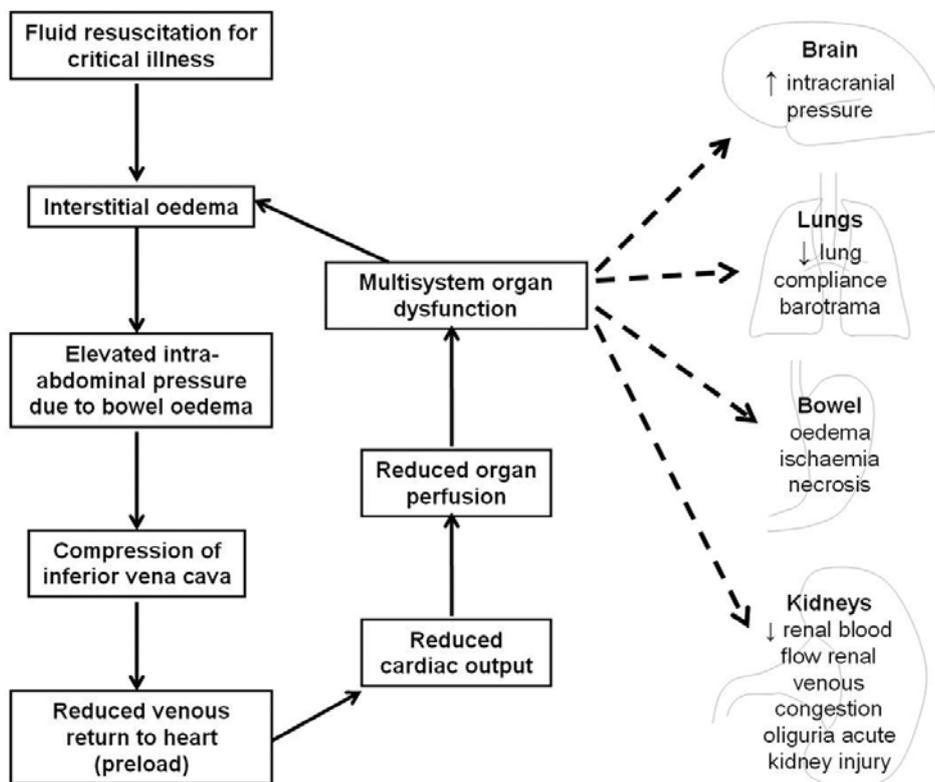


Figure 2. Overview of the effects of raised abdominal pressure on organ function.

Cardiovascular effects of ACS

Increased IAP reduces cardiac output by decreasing preload (compression of the inferior vena cava and hepatic vein) and by decreasing left ventricular compliance, secondary to increased intra-thoracic pressures. Increased intra-thoracic pressure results in increased central venous, right atrial and pulmonary wedge pressures, despite the decreased cardiac output. Significantly, monitoring these pressures could give the impression of over-filling when the patient may be hypovolaemic.

Respiratory effects of ACS

The effects of IAH on respiration are largely mechanical. Diaphragmatic elevation and splinting causes a reduction in ventilation by decreased thoracic volume and decreased lung compliance. Compressive atelectasis eventually results in increased ventilation-perfusion mismatch and hypoxia. If the patient is breathing spontaneously they will develop rapid shallow breathing. In the ventilated patient it will become increasingly difficult to achieve adequate ventilation. Patients are likely to become hypoxic with a rising CO_2 .

Other effects of ACS

Other potential adverse effects of IAH include visceral hypoperfusion with secondary bacterial translocation, impaired abdominal wound healing, worsening of raised intra-cerebral pressure in trauma patients and possibly an increased cytokine response.⁵

DIAGNOSIS OF ACS

Clinical examination alone is insensitive for the detection of IAH. Early detection requires proactive measurement of intra-abdominal pressure in patients at risk.

Indications for considering monitoring IAP include:⁶

- Any patient whose abdomen appears clinically to be distended and firm and who has a poor urine output, low BP and difficulty with ventilation.
- Patients with open or blunt abdominal trauma.
- Patients with burns and massive fluid resuscitation.

MEASUREMENT OF IAP

The standard measurement technique of IAP is by use of a Foley bladder catheter. Fifty millilitres of saline should be instilled into the bladder. Intra-vesical pressure can then be estimated by measuring the vertical height of the column of fluid when the catheter tubing is held vertical and the patient is supine. Alternatively, the collection tubing from the catheter is clamped after instilling saline into the bladder and then intra-vesical pressure can be measured via a needle inserted aseptically into the aspiration port, proximal to the clamp, which is then attached to a pressure manometer or transducer. The level of the pubic symphysis is taken as zero for both these techniques.

MANAGEMENT OF ACS

The definitive treatment of ACS is to achieve a maintained reduction in IAP. Aggressive non-operative intensive care support is critical to prevent the complications of ACS. This involves careful management of cardiovascular and respiratory impairment, maintenance of



Figure 3. A; Equipment for measurement of intra-abdominal pressure. This consists of a length of clear tubing with 1cm markings connected between the end of the catheter and the tube leading to the collection bag. B; After instillation of 50ml sterile water into the bladder, the vertical height of fluid within the tubing is measured from a set point (either the symphysis pubis or the greater trochanter of the femur, as here). This intravesical pressure is an accurate estimate of the intra-abdominal pressure.

intravascular volume, whilst avoiding over generous fluid resuscitation and possibly commencement of renal replacement therapy, if facilities are available. Mechanical ventilation with deep sedation and muscle relaxation is usually required unless abdominal decompression can be undertaken. Simple measures to decrease IAP such as nasogastric decompression and avoidance of constipation must not be overlooked. In some circumstances abdominal collections may be able to be drained percutaneously.

There is little consensus on the precise indications for and timing of surgical decompression. It is more important to correct pathophysiological abnormalities than to achieve a particular IAP.⁶ At present there are no absolute guidelines and all patients with increasing IAP and deteriorating organ function should be considered for decompression. This point is illustrated by the case history above, where surgical abdominal decompression was performed because of deteriorating renal function and compromised ventilation. Prompt intervention is beneficial – early surgical decompression may be associated with reversal of organ deterioration in 80% of patients, but despite this the mean survival rate is only 53%.⁷ With increasing awareness of this condition, surgical decompression for abdominal compartment syndrome is increasingly undertaken and would appear to have a beneficial effect on organ function. However no randomised studies have been undertaken to demonstrate its effect on patient mortality.

As anaesthetists, if the surgeon is struggling to achieve closure and you suspect that the intra-abdominal pressure is high, consider measuring the IAP during abdominal closure or, at least, before the patient is transferred from theatre. The anaesthetist has an important role in preventing a surgeon from closing an abdomen under excessive pressure.

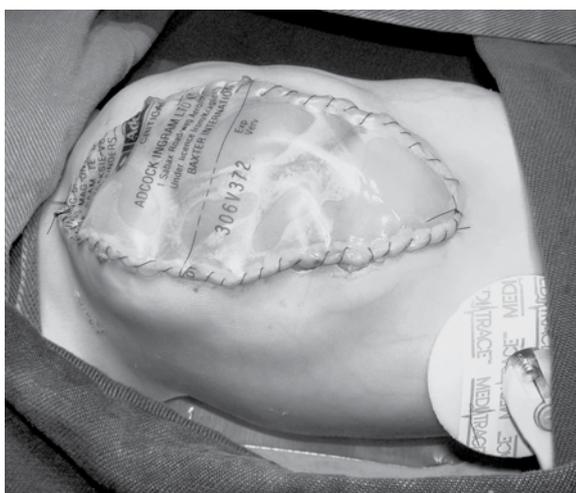


Figure 4. Closure of a neonate's abdomen with a Bogota bag, after surgery to correct gastroschisis.

Anaesthetising a patient for abdominal decompression can be hazardous. It may be difficult to achieve adequate ventilation when transferring to the theatre. When the abdomen is decompressed there may be a sudden fall in blood pressure (despite a rise in cardiac output) and intravenous fluid resuscitation is likely to be required. The immediate increase in lung compliance can lead to hyperventilation, so ideally end-tidal CO₂ or blood gases should be monitored.

CONCLUSION

ACS is a syndrome associated with high morbidity and mortality. IAP monitoring should be used in at risk patients. This can be simply and reliably estimated by use of saline instilled in a bladder catheter. As there are no current guidelines regarding the role for and timing of decompressive laparotomy, each case will require individual assessment and discussion between the intensive care and surgical teams.

FURTHER READING

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'Bugs and drugs' in the Intensive Care Unit

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Summary

This article is a basic introduction to the common organisms that cause infections in critically ill patients. Diagnosis and appropriate use of antibiotics is described. Pathogenicity of different organisms varies around the world and so the advice must be used in light of local microbiological practice.

INTRODUCTION

Infection remains one of the most important threats for patients admitted to an Intensive Care Unit (ICU). A global point-prevalence study conducted in ICU in 2007 revealed that 51% of adult ICU patients were infected and 71% were receiving antibiotics.¹ In this cohort of 13796 patients, infection was independently associated with an increased risk of hospital mortality. Bacteria most commonly cause infections in ICU patients, but fungal and viral pathogens are also important considerations in this group. There are many factors that leave ICU patients at risk of infections. In this article, we provide a basic introduction to the common organisms encountered in an ICU setting, diagnosis of infections caused by them and an overview of the antimicrobials used to treat them.

RISK FACTORS FOR ACQUIRING INFECTION IN ICU²**Nutritional status**

Poor nutrition suppresses host defences. In addition, procedures to correct nutritional status, such as parenteral nutrition or nasogastric tubes in turn increase the risk of infections, due to damaged integrity of the normal barriers and aspiration.

Glucocorticosteroids

Steroids hamper neutrophil responses and their ability to arrive at inflammatory sites. They decrease their adherence and chemotactic activity. Steroids also reduce phagocytosis and intracellular killing of microorganisms. The lack of functioning neutrophils leaves the host susceptible to serious infections.

Figure 1.

Defect / condition	Pathogen
Damaged skin / vascular access devices	Coagulase negative Staphylococci, Staphylococcus aureus, Enteric Gram negative bacilli, Pseudomonas
Total parenteral nutrition	Blood stream infections due to Candida species
Gastrointestinal tract mucosal barrier injury	Translocation of gut organisms (Gram negative bacilli, Enterococci, Candida, anaerobes) into the blood stream, colonisation and toxin production by Clostridium difficile

Physical barriers (Figure 1)

Micro-organisms normally present on the skin can get easy access to the bloodstream due to insertion of vascular access devices. Broad-spectrum antibiotics can disrupt the ecology of the gastro-intestinal tract, predisposing to colonisation by hospital acquired pathogens and fungi.

Underlying medical conditions

Clearance of respiratory secretions is impaired in smokers and the airways of smokers are prone to colonisation with virulent encapsulated microorganisms. The increased risk of infections in diabetic patients is well recognised.

GRAM POSITIVE BACTERIA

Gram staining divides bacteria into Gram positive and Gram negative, based on the structure of their cell walls, staining properties and the antibiotics they are susceptible to. Some common bacterial pathogens encountered in ICU are:

Staphylococcus aureus

- Gram positive coccus, occurring in clusters.
- Possesses the enzyme coagulase, which causes plasma to clot and distinguishes it from the coagulase negative *Staphylococci*.
- Part of the normal flora in the nose, throat, perineum, axillae, groin, hairline, etc in almost one third of the population. A 'screen' is usually requested from these sites.
- Responsible for skin and soft tissue infections like boils, abscesses, impetigo, furuncles, carbuncles, etc.

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- Can cause deep-seated infections such as those involving bone and joints, infective endocarditis (especially in intravenous drug users), pyomyositis, prosthetic device related infections.
- Capable of producing several exotoxins, some of which can cause food poisoning, Toxic shock syndrome or *Staphylococcal* scalded skin syndrome.
- Over 90% are resistant to penicillin, however flucloxacillin covers meticillin sensitive strains (MSSA).
- Cefoxitin or oxacillin is used in the lab for screening for meticillin resistance as these antibiotics are more stable than meticillin.

MRSA – Meticillin resistant *Staphylococcus aureus*

- Meticillin resistance is due to the *mecA* gene which encodes for an altered penicillin binding protein, PBP2', consequently altering the structure of the cell wall.
- Classically used to be hospital acquired, but community acquired strains are increasingly common, known as *CA-MRSA*.
- Disease spectrum is similar to MSSA.
- Risk factors for acquiring MRSA include – old age, residence in nursing homes, previous hospital admission, prior use of antibiotics.
- Meticillin resistance renders the strain resistant to all beta lactam antibiotics.
- Glycopeptides such as vancomycin or teicoplanin are the treatment of choice for MRSA and should be included in the empirical treatment for all patients with known risk factors for acquiring MRSA, until such an infection can be ruled out.
- In the UK, it is mandatory for the laboratory to report MRSA bacteraemia to the Department of Health.

Glycopeptide resistant *Staphylococcus aureus*

- First case in USA in 2002, possibly due to the transfer of *vanA* gene from *Enterococcus faecalis*, conferring resistance to vancomycin.³
- *Staphylococcal* strains with minimum inhibitory concentration (MIC) >2mg.L⁻¹ for vancomycin are considered resistant,⁴ MIC determination being more reliable than disc diffusion.

Minimum Inhibitory Concentration (MIC) = antimicrobial concentration required to kill 90% of bacteria

Panton-Valentine Leucocidin (PVL) producing *Staphylococcus aureus*

- PVL is a toxin produced by <2% strains of *Staphylococcus aureus*.
- This is a pore forming toxin that destroys leucocytes and can be produced by meticillin sensitive or meticillin resistant strains.
- Usually responsible for skin and soft tissue infections like boils and abscesses in healthy young adults.
- Clinical spectrum extends to severe life threatening infections such as necrotising pneumonia, necrotising fasciitis or purpura fulminans (mimicking meningococcal sepsis).

- PVL staphylococcal necrotising pneumonia is associated with high mortality - the typical presentation is in a previously fit young adult with recent flu-like illness with a high temperature (>39°C), tachycardia, hypotension, marked leucopenia (due to the nature of the toxin) and multi-lobular alveolar infiltrates on chest Xray that often cavitate.⁵

Coagulase negative *Staphylococci*

- Includes several species, prominently *Staphylococcus epidermidis* and *Staphylococcus saprophyticus* (a urinary pathogen).
- Part of the normal skin flora.
- Commonly cause infections related to prosthetic devices such as catheters, orthopaedic implants, shunts etc.
- Capable of producing a biofilm which hides the organisms from the host immune system and makes antibiotic penetration difficult.
- Meticillin resistance is common in coagulase negative *Staphylococci*.
- Some organisms in this group, such as *Staphylococcus lugdunensis* and *Staphylococcus intermedius*, can cause severe infections.

Beta haemolytic *Streptococci*

- Gram positive cocci that occur in chains.
- So called because of the beta or complete clearing they produce around their colonies growing on blood agar.
- Classified into groups – A, B, C, D, F, G etc based on cell wall antigens.

Group A *Streptococci*

- Also known as *Streptococcus pyogenes*.
- Common cause of sore throat and skin infections like erysipelas, but can cause severe invasive infections like toxic shock syndrome, necrotising fasciitis and puerperal sepsis.
- Invasive Group A Streptococcal infections are increasing in incidence⁶ and are associated with a mortality of up to 25%.
- Always sensitive to penicillin.

Group B *Streptococci*

- Common cause of neonatal infections and infections in diabetic patients.

Group C and G *Streptococci*

- Responsible for sore throat and skin and soft tissue infections, similar to Group A *Streptococci*.
- Lymphoedema is a risk factor for recurrent infections with Group G *Streptococci*.

Alpha haemolytic *Streptococci*

- Produce greenish discoloration around the growth on blood agar, due to the partial haemolysis of red blood cells in the agar (alpha haemolysis).
- Commonest example is *Streptococcus pneumoniae* (*Pneumococcus*).

Streptococcus pneumoniae (Pneumococcus)

- Common cause of community acquired pneumonia and can cause other serious infections like meningitis.
- Part of the normal upper respiratory tract flora.
- Increased risk of empyema following pneumococcal pneumonia.
- Severe pneumococcal pneumonia in an otherwise healthy adult is an AIDS defining illness.
- Penicillin resistance is rising - oxacillin discs are used in the laboratory, along with penicillin E test to determine MIC to penicillin.
- Ceftriaxone or vancomycin is the treatment of choice for serious infections caused by drug resistant *Pneumococci*.

Viridans (oral) Streptococci

- Cause dental caries and can cause infective endocarditis and bacteraemia in immunosuppressed patients.

Enterococci

- As their name suggests, they are part of the normal bowel flora.
- Cause intra-abdominal and pelvic infections and can cause bacteraemia and infective endocarditis.
- Intrinsically resistant to cephalosporins and ciprofloxacin.
- Common species are *Enterococcus faecalis* and *E. faecium*.
- Some species like *E. gallinarum* and *E. casseliflavus* are intrinsically resistant to glycopeptides, such as vancomycin.

Glycopeptide Resistant Enterococci (VRE – Vancomycin Resistant Enterococcus)

- Most commonly *E. faecium*.
- Organisms with intrinsically low virulence.
- Cause opportunistic infections, especially in immunosuppressed patients.
- Risk factors include prior hospitalisation, stay in specialist units – renal / ICU / haemato-oncology, prior use of antibiotics, especially glycopeptides.

Clostridium difficile

- Gram positive bacillus.
- Most important cause of hospital acquired diarrhoea – ranging from mild to severe life threatening pseudomembranous colitis.
- Risk factors – elderly population, prior use of antibiotics (sometimes even a single dose of an antibiotic can serve as a trigger), history of hospitalisation in the past.
- Stool frequency is a less reliable indicator of severity, severe infections are characterised by white cell count >15, serum creatinine > 50% increase above baseline, temperature > 38.5°C or evidence of severe colitis on examination or radiologically.⁷
- Mnemonic protocol – SIGHT:⁷

- Suspect when no clear cause for diarrhoea,
 - Isolate patients with diarrhoea,
 - Gloves and apron to be used in this environment,
 - Hand-washing is crucial as the organism, especially the spore state, is resistant to alcohol based disinfectants,
 - Test the stool for toxin.
- Treatment consists of stopping all unwanted antibiotics and commencing either oral metronidazole or oral vancomycin, depending on the severity of infection. *C. difficile* infection is the only indication oral vancomycin, as it is not absorbed systemically.

GRAM NEGATIVE BACTERIA

Coliforms

- This is the generalised term for enteric Gram negative bacilli such as *E. coli* and *Klebsiella*.
- They cause intra-abdominal and pelvic infections, urinary tract infections, opportunistic infections, such as catheter related blood stream infections, and ventilator associated pneumonia.

Extended spectrum beta lactamases (ESBLs)

- Enzymes produced by coliforms like *E. coli* and *Klebsiella*, that render the organisms resistant to all penicillins and cephalosporins.
- Predisposing factors include old age, prior use of antibiotics and prior hospitalisation.
- Infections range from simple urinary tract infections to bacteraemia and pneumonia.
- Organisms carrying the ESBL are more likely to be resistant to other classes of antibiotics like aminoglycosides, quinolones and trimethoprim, thus limiting treatment options. Treatment of choice is carbapenems.
- Eradication of colonisation is difficult.

New Delhi metallo-beta lactamases (NDMs)

- Enzyme rendering resistance to broad spectrum antibiotics like carbapenems, usually produced by *E. coli* and *Klebsiella*.
- First isolated from a patient who had travelled through New Delhi, where he was hospitalised.
- Risk factors are hospital admission / medical tourism in the Indian subcontinent.
- Infections can be mild or life threatening.
- Treatment options are very limited. Colistin and tigecycline may be used in some cases depending on the antimicrobial susceptibility testing results.

*Pseudomonas*⁸

- Gram negative bacillus, ubiquitous in soil, water and moist environments.

- Successful opportunistic pathogen.
- Disease spectrum includes community acquired infections like otitis externa, folliculitis associated with jacuzzis and hospital acquired infections such as blood stream infections, surgical wound infections and pneumonias.
- Important pathogen and coloniser in patients with cystic fibrosis.
- Antimicrobial susceptibility testing of isolates in the laboratory is crucial and susceptibility to anti-pseudomonal agents cannot be assumed, as it can acquire resistance to antibiotics rapidly on treatment.

Acinetobacter⁸

- Gram negative short bacillus and a nosocomial and opportunistic pathogen.
- Multi-resistant strains such as OXA-23 clone 1 and SE clone are seen in the UK, particularly in London and south-east England.
- Cross infection occurs through equipment or colonised health-care workers and the organism is extremely difficult to eradicate from established environments.

VIRUSES

These are organisms containing DNA or RNA, but never both. Viruses depend on the host cell machinery for replication. The clinical spectrum varies with the class of virus. In an ICU setting, one needs to be aware that bacterial super-infections of primary viral infections can occur, for example, *Staphylococcal* or *Streptococcal* pneumonia after infection with influenza virus.

FUNGI

These are eukaryotes with a cell wall containing ergosterol, that is different from that of a bacterial cell. They can be either yeasts (e.g. *Candida*) or moulds (e.g. *Aspergillus*, *Zygomycetes*). Fungal spores are ubiquitous in the environment. Fungi are opportunistic pathogens capable of causing life threatening systemic infections in immunosuppressed patients. Fungal infection should be suspected in patients who fail to improve on anti-bacterial agents, particularly where no bacterial organism has been isolated.

DIAGNOSIS OF INFECTION

The type of sample submitted to the microbiology laboratory for the diagnosis of infection depends on the site of infection. The significance of mentioning all relevant information on the laboratory request forms cannot be over-emphasised. The information provided acts as a trigger for the laboratory staff to carry out any additional tests on the sample as required.

Gram stain

This is a quick and useful method of screening the sample for bacterial pathogens. A high number of organisms (almost up to 10⁵ per ml of the sample) is required for a Gram stain to be positive.

Culture

This is a 'gold standard' test that involves growing organisms on appropriate culture media. Once the organism grows, an antimicrobial susceptibility test can be performed. Bacteria usually take 24 to 48 hours to grow in cultures.

Blood culture

The sensitivity of this investigation depends on the volume of blood cultured - 20ml blood collected in two bottles (aerobic and anaerobic) is the minimum volume, except in neonates and children, where smaller volumes are collected in paediatric bottles. In septic patients blood should be cultured even in the absence of fever.

When line sepsis is suspected, blood cultures should be drawn through the line as well as peripherally and the bottles and request forms should be labelled accordingly. Proper skin antisepsis is crucial to avoid contaminated blood cultures.

Antimicrobial susceptibility testing

This is a key investigation in the management of infections and can be done once an organism grows in culture. It is usually done by the disc diffusion method. The sample is spread uniformly across an agar plate and discs of filter paper containing various antimicrobial agents are placed on the agar. The agent diffuses into the agar, reaching higher concentrations nearest to the disc. The bacteria fail to grow where the level of antimicrobial agent is above the effective concentration. The results reported as susceptible, resistant or intermediate.

Serology

Serological tests usually detect the IgG or IgM antibody response to infections. It is a useful habit to collect a serum sample from an infected patient as a baseline. Serological tests are extremely useful to diagnose infections caused by organisms that cannot be grown in culture, such as viruses, *Chlamydia*, *Mycoplasma*, *Bartonella* and *Brucella*.

Polymerase chain reaction (PCR)

This is a rapid molecular diagnostic method for pathogens that do not easily grow in culture. It cannot distinguish between live and dead organisms as it detects DNA, and it cannot determine antimicrobial susceptibility. PCR on cerebrospinal fluid for Herpes simplex virus (HSV) is useful in the diagnosis of HSV encephalitis.

Urinary antigen testing

This test may be available for pathogens such as *Streptococcus pneumoniae*, *Legionella* and *Histoplasma*. It is based on the secretion of capsular antigens of organisms in urine.

Other blood tests

White cell count, differential count, liver and renal function tests and C reactive protein are very useful for the day-to-day management of ICU patients. Procalcitonin (PCT) is a new measurable molecule that is induced by severe bacterial or fungal infection and severe sepsis. It can distinguish between bacterial infections from viral infections.⁹

ANTIMICROBIAL DRUGS

The choice of antimicrobial agent should be made after thorough consideration of:

Host factors	underlying medical conditions allergies renal function liver function age weight interactions with other medications risk factors for acquiring resistant organisms (e.g. MRSA)
Organism factors	likely susceptibility local resistance patterns for organisms
Factors related to the antimicrobials themselves	appropriate route of administration appropriate dose, depending on severity of infection

In critically ill patients, antimicrobial concentrations in plasma may fluctuate, resulting in either over-exposure (for example in renal impairment) or under-exposure (for example oedema, effusions, IV fluid therapy).¹⁰ Therapeutic drug monitoring is an important technique to monitor these effects. Once culture and antimicrobial susceptibility results are available, de-escalation from the empirical antimicrobials should be considered. When in doubt, the advice of clinical microbiology colleagues should be sought. The tables on the following pages attempt to give an overview of the different classes of antibiotics, their mechanism of action and spectrum of activity.⁸

Practices promoting optimisation of antimicrobial use in ICU setting¹²

- Adequate empirical treatment of infections based on causative agents,
- Awareness of local pathogens and their antimicrobial susceptibilities,
- Removal of infected foreign bodies,
- Drainage of pus at any site, e.g. empyema, abscess, etc,

- Therapeutic drug monitoring,
- De-escalation based on microbiology and clinical outcomes.

Conclusion

Sepsis is both a major cause of admission to ICU and also a frequent complication of the therapies offered there. This article has given an overview of the more common infective agents, and also describes bacteria that are increasingly causing issues with antibiotic resistance. Choice of antibiotic must be guided by local prevalence, but may also be limited by availability in low income settings. It is very useful to establish regular contact with a clinical microbiologist, in order to gain current and appropriate advice.

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Antibiotic	Mechanism of action	Spectrum of activity											Comments				
		MSSA	MRSA	Beta haemolytic Streptococci	Viridans Streptococci	Enterococci	Streptococcus pneumoniae	Coliforms	Pseudomonas	Acinetobacter	ESBLs	NDMs		Anaerobes			
Penicillins	Inhibition of cell wall synthesis																
Benzylpenicillin		*	x	✓	☑		☼	x	x	x	x	x	☑				TDK
Amoxicillin / Ampicillin		*	x	✓	☑	\$	☼	x	x	x	x	x	☑	x	x	x	
Flucloxacillin	✓ **	x	✓														Anti-staphylococcal
Coamoxiclavulanate (Augmentin)	✓	x	✓			\$	☼					☑	x	x	x	✓	Beta-lactamase stable penicillin
Piperacillin – tazobactam (Tazocin)	✓	x	✓				☼					☑	x	x	x	✓	Beta-lactamase stable penicillin, anti-pseudomonal
Ampicillin-sulbactam																	

Key:	
✓	sensitive
x	resistant
*	>90% MSSA are resistant to penicillin
☉	treatment of choice in susceptible strains
☑	determined by antimicrobial susceptibility
☼	covers penicillin sensitive isolates only
\$	<i>E. faecalis</i> is susceptible
**	flucloxacillin is much more effective than vancomycin or teicoplanin to treat MSSA
MSSA	Meticillin Sensitive <i>Staphylococcus aureus</i>
MRSA	Meticillin Resistant <i>Staphylococcus aureus</i>
NDM	New Delhi Metallo-beta-lactamase
ESBL	Extended Spectrum Beta-lactamase
TDK	time dependent killing, antibiotic effective due to the extensive amount of time it binds to the organism

Antibiotic	Mechanism of action	Spectrum of activity										Comments			
		MSSA	MRSA	Beta haemolytic Streptococci	Viridans Streptococci	Enterococci	Streptococcus pneumoniae	Coliforms	Pseudomonas	Acinetobacter	ESBLs		NDMs	Anaerobes	
Cephalosporins 1st generation Cefradine Cephalexin	Inhibition of cell wall synthesis	✓	x	✓			⊕	☑	x	x	x	x	x	x	TDK, Use in minor penicillin allergy (rash) Predominant GP action
		✓	x	✓		x	⊕	☑	x	x	x	x	x	x	Enhanced GN + GP action
		✓	x	✓		x	◆	☑	⊙	x	x	x	x	x	Predominantly GN action
Carbapenems	Inhibition of cell wall synthesis			✓											TDK, Use in minor penicillin allergy (rash)
		✓	x	✓		§		✓	✓	✓	✓	✓	✓	✓	Better GP cover
		✓	x	✓		§		✓	✓	✓	✓	✓	✓	✓	Better GN cover
Ertapenem		x	✓												

Key:	
GP	Gram positive
GN	Gram negative
✓	sensitive
x	resistant
⊕	covers penicillin sensitive isolates only
◆	treatment of choice for penicillin resistant strains causing serious infections
⊙	only ceftazidime in this group has anti pseudomonal activity
§	<i>E. faecalis</i> is susceptible
✦	meropenem has better activity against <i>Pseudomonas</i> than imipenem
TDK	time dependent killing, antibiotic effective due to the extensive amount of time it binds to the organism

Antibiotic	Mechanism of action	Spectrum of activity											Comments			
		MSSA	MRSA	Beta haemolytic Streptococci	Viridans Streptococci	Enterococci	Streptococcus pneumoniae	Coliforms	Pseudomonas	Acinetobacter	ESBLs	NDMs		Anaerobes		
Glycopeptides e.g. Vancomycin, Teicoplanin	Inhibition of cell wall synthesis	√**	✓			◆	◆			x	x	x	x	x	x	TDK, Oral vancomycin is used to treat <i>C. difficile</i> infection
Amino-glycosides e.g. Gentamicin	Inhibit protein synthesis (30S subunit)	✓	☑			❖				☑	☑	☑	☑	☑	x	CDK, Often combined with penicillins, do not penetrate acid pH (pus)
Macrolides e.g. Erythromycin, Clarithromycin	Inhibit protein synthesis (50S subunit)	MLS _B	MLS _B	MLS _B					MLS _B	x	x	x	x	x	x	TDK
Lincosamides e.g. Clindamycin	Inhibition of cell wall synthesis	MLS _B	MLS _B	MLS _B					MLS _B	x	x	x	x	x	✓	TDK

Key:

✓	sensitive	CDK	concentration dependent killing, high concentration at binding site which kills the organism
x	resistant	VRE	vancomycin resistant <i>Enterococci</i>
☑	determined by antimicrobial susceptibility	MLSB	stands for macrolide, lincosamide, streptogramin type B antibiotics. Bacteria with inducible resistance to erythromycin become resistant to other MLSB agents in the presence of erythromycin. Detected in the lab in <i>Staphylococci</i> by the 'D' test 1. Avoid using clindamycin for <i>Staphylococci</i> and <i>Streptococci</i> that are resistant to erythromycin.
◆	<i>E. faecium</i> is susceptible provided not glycopeptide resistant (VRE)		
❖	treatment of choice for penicillin resistant strains causing serious infections		
**	lab should look for high level gentamicin susceptibility		
	flucloxacillin is much more effective than vancomycin or teicoplanin to treat MSSA		

Antibiotic	Mechanism of action	Spectrum of activity											Comments			
		MSSA	MRSA	Beta haemolytic Streptococci	Viridans Streptococci	Enterococci	Streptococcus pneumoniae	Coliforms	Pseudomonas	Acinetobacter	ESBLs	NDMs		Anaerobes		
Tetracyclines e.g. Doxycycline	Inhibit protein synthesis (30S subunit)	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	Cover atypicals such as <i>Chlamydia</i>
Glycylcycline e.g. Tigecycline		✓	✓	✓	✓	✓*	✓	✓	✓	✓	✓	✓	✓	✓	✓	Related to tetracyclines
Quinolones e.g. Ciprofloxacin, Levofloxacin	Inhibit nucleic acid synthesis	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	CDK, Resistance common with ESBLs
Nitroimidazoles e.g. Metronidazole	Prodrug, acts on protein, nucleic acid	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	Used to treat <i>C. difficile</i> infection
Trimethoprim	Inhibits bacterial DHFR	✓	✓													Used to treat PCP
Oxazolidinones e.g. Linezolid	Inhibits protein synthesis	✓	✓	✓	✓	✓*	✓	✓	✓	✓	✓	✓	✓	✓	✓	Bacteriostatic for gram positive organisms
Chloramphenicol	Inhibits protein synthesis															Use determined by sensitivity testing. Good CSF penetration - alternative for meningitis in penicillin allergic patients. May cause dose-dependent bone marrow suppression.

Key:

- DHFR dihydrofolate reductase,
- PCP *Pneumocystis jirovecii* pneumonia
- * also covers remcomycin resistant *Enterococcus* (VRE)

Inotropes and vasopressors in critical care

Hannah Dodwell and Bruce McCormick

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INTRODUCTION

Shock is present in many patients requiring admission to the intensive care unit. Shock is a clinical syndrome characterised by inadequate tissue perfusion, leading to organ dysfunction. Hypotension is usually present, but is not essential to diagnose shock. Other features include raised lactate levels and increased or decreased mixed venous or central venous saturations (SvO_2), depending on the underlying pathology. Shock has a high mortality.

Shock can be classified as: hypovolaemic, distributive, obstructive and cardiogenic. Patients with all types of shock are admitted to critical care units and inotropes and vasopressors play an important role in their treatment.

Inotropes are endogenous or synthetic agents that elevate the cardiac output by increasing the force of contraction of the heart's ventricles (inotropy). Most are also positive chronotropes, increasing the heart rate.

Vasopressors (again endogenous or synthetic) cause arterial vasoconstriction, tending to elevate the patient's blood pressure. The cardiac output may be increased or decreased.

CARDIOVASCULAR EFFECTS OF INOTROPES AND VASOPRESSORS

Before considering how the different inotropes and vasopressors work, it is useful to revise the relevant physiology of the cardiovascular system. More detail on this is available in a previous *Update* article.¹

Oxygen delivery (DO_2) to tissues is dependent upon cardiac output (CO) and the oxygen content of the arterial blood reaching the tissues (CaO_2):

$$DO_2 \text{ (ml.min}^{-1}\text{)} = CO \text{ (L.min}^{-1}\text{)} \times [CaO_2 \text{ (ml.dl}^{-1}\text{)} \times 10^*]$$

(*Note: the factor of 10 converts the oxygen content from ml per dl to ml per litre)

Cardiac output is the product of heart rate (HR) and stroke volume (SV):

$$CO = HR \times SV$$

Cardiac index is the cardiac output defined by the patient's body surface area.

Stroke volume is the volume of blood ejected from the left ventricle with each contraction and is determined by the preload, afterload and contractility of the ventricle.

The cardiovascular system controls blood pressure and so ensures adequate tissue perfusion by a combination of systems:

- The autonomic nervous system
- Peripheral and central baroreceptors
- The renin-angiotensin-aldosterone system.

There are many important neurotransmitters, hormones, local mediators and receptors involved - inotropes and vasopressors target these sites to exert their effects (see Table 1).

Vasopressors (norepinephrine, phenylephrine, metaraminol and high dose epinephrine) largely work by stimulating alpha-1 adrenergic receptors, causing peripheral vasoconstriction, increasing SVR and elevating the blood pressure. Increasing SVR, raises the left ventricular afterload and so cardiac output may fall, despite an increase in blood pressure. Venoconstriction may contribute by increasing preload and elevating the cardiac output.

CLASSIFICATION OF SHOCK

Shock can have many underlying causes that can be classified as follows.

Hypovolaemic shock

This is most commonly caused by haemorrhage and dehydration.

Haemodynamic parameters

- Low cardiac output with compensatory vasoconstriction causing high systemic vascular resistance.
- Low central venous pressures.
- Likely to improve with intravenous fluid boluses.

Clinical features

- The patient may be hypotensive, tachycardic and peripherally cold due to vasoconstriction.

Summary

This article describes the way in which vasoactive drugs are used in critically ill patients. Typical clinical scenarios are used to demonstrate why we choose certain drugs in certain conditions. The safety aspects of running infusions of highly potent drugs are considered.

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Table 1. Commonly used vasoactive drugs.

	Naturally occurring	Synthetic
Catecholamines	Epinephrine (adrenaline) Norepinephrine (noradrenaline) Dopamine	Dobutamine Dopexamine Isoprenaline
Phosphodiesterase (PDE) type 3 inhibitors		Milrinone Enoximone
Increasing ionised calcium		Calcium gluconate / calcium chloride
Increasing sensitivity to calcium		Levosimendan
Na ⁺ /K ⁺ ATPase inhibitor		Digoxin
Increasing intracellular concentrations of cyclic AMP	Glucagon	
Vasopressin		

- The American College of Surgeons Advanced Trauma Life Support classification of haemorrhagic shock severity is useful to assess the severity of shock, in terms of the estimated circulating volume loss (Table 2).²

Distributive shock

This includes septic shock and anaphylaxis. Increased levels of inflammatory mediators cause peripheral vasodilatation; this is sometimes termed relative hypovolaemia, meaning that no fluid has been lost, in contrast to the absolute hypovolaemia of hypovolaemic shock. In addition, capillary beds become more permeable and fluid is lost from the intravascular space into the interstitium.

Haemodynamic parameters

- Initially compensation occurs as a supranormal cardiac output is achieved by a rise in heart rate.
- Cardiac output may fall in the later stages of septic shock due to the presence of a circulating myocardial depressant factor. At this

stage there may be little response seen in haemodynamic parameters on administration of intravenous fluid boluses.

- Note that smaller children show a different response to sepsis, with compensation predominantly manifesting as profound vasoconstriction, often with a low or inappropriately normal cardiac output. This necessitates a different approach to resuscitation in paediatric septic shock.

Clinical features

- Usually includes tachycardia with bounding pulses. The patient may be flushed and be warm to touch.
- Hypotension and pyrexia (or hypothermia) may be present.

Obstructive shock

This follows obstruction of a critical part of the cardiovascular system, for example an embolus in a pulmonary artery or cardiac tamponade.

Haemodynamic parameters

- Low cardiac output, high systemic vascular resistance, high central venous pressures.

Table 2. The American College of Surgeons Advanced Trauma Life Support classification of haemorrhagic shock severity.²

Severity of hypovolaemia	Class 1	Class 2	Class 3	Class 4
Blood loss	< 750ml (0-15%)*	750 – 1500ml (15-30%)	1500 – 2000 (30-40%)	> 2000 (> 40%)
Pulse rate (per minute)	< 100	> 100	> 120	> 140
Blood pressure	Normal	Normal**	Decreased	Decreased
Pulse pressure (mm Hg)	Normal	Decreased	Decreased	Decreased
Respiratory rate (per minute)	14–20	20–30	30–40	> 40
Urine output (ml.h ⁻¹)	> 30	20–30	5–15	Anuric
Central nervous system	+/- slightly anxious	Mildly anxious	Confused	Lethargic

* note that normal blood volume is estimated as about 5000ml for a 70kg patient (~70ml.kg⁻¹)

** Vasoconstriction may cause a rise in the diastolic blood pressure with a normal systolic blood pressure (e.g. 120/90mmHg). This is a useful sign as decompensation is imminent.

- Unlikely to respond to fluid boluses.
- An echocardiogram is very helpful to determine the nature of the obstruction.

Clinical features

Hypotension, vasoconstriction, raised JVP and pulsus paradoxus may be seen.

Cardiogenic shock

This results from failure of the heart to pump blood into the systemic circulation effectively. This can be caused by a myocardial (e.g. myocardial infarction) or valvular defect (e.g. aortic stenosis). The problem may lie within the right or left side of the heart, or both (global).

Haemodynamic parameters

- Cardiogenic shock is defined by a cardiac index less $2.2\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ and a low SvO_2 despite adequate preload and associated with signs of hypoperfusion.
- An echocardiogram is extremely useful in making this diagnosis.

Clinical features

Hypotension, vasoconstriction and raised JVP.

MANAGEMENT

For all types of shock, an initial rapid assessment using an ABCDE approach, with prompt treatment, is paramount. Where available, transfer to a critical care setting for invasive monitoring and organ support may be necessary and, unless fluid therapy is rapidly effective, this may include the use of inotropes and vasopressors.

Inotropes and vasopressors

Use of inotropes and vasopressors depends upon local availability and local protocols. A recently survey of 263 African healthcare workers regarding the availability of inotropic drugs at their workplace showed that, while the majority had a reliable supply of epinephrine, only half always had norepinephrine and just over one third had access to dobutamine.³ Around one quarter to one third of respondents never had access to these drugs.

The main mechanism by which inotropes improve tissue perfusion is by increasing cardiac contractility by increasing intracellular calcium. This can be facilitated by:

- *Increasing cyclic AMP (cAMP)*
This is a second messenger which causes increased calcium ion mobilisation.
- *Inhibition of phosphodiesterase (PDE) type 3*
This is normally responsible for breakdown of cAMP, therefore inhibiting PDE 3 increases cAMP levels.
- *Directly increasing the amount of ionised calcium available in plasma.*
- *Increasing myocardial cell sensitivity to calcium.*
- *Inhibition of Na^+/K^+ ATPase*
This causes slowing of the heart rate which allows further

diastolic filling, thus increasing stroke volume. It also increases calcium availability.

- *Others mechanisms*
Glucagon, for example, stimulates adenylate cyclase, increasing calcium flux into myocardial muscle.

PRACTICAL USE OF INOTROPES AND VASOPRESSORS

The following clinical scenarios demonstrate how to use different inotropes and vasopressor in common clinical situations. In all cases basic resuscitation (guided by an ABC approach) should be the highest priority and in some cases other treatments should precede administration of vasoactive drugs (for example prompt administration of antibiotics in septic shock). Appropriate monitoring should be in place and, where available, this will include invasive blood pressure measurement and a monitor of cardiac output.

Mean arterial pressure is a useful target, with 65mmHg commonly used as an estimated adequate value. This should tailored to the response (e.g. urine output), and may need to be higher in patients with pre-existing hypertension. Other special situations are outlined within the scenarios.

It is also important to remember that patients may present with more than one type of shock, and each case must be assessed and managed on an individual basis. Further information, including doses, for each drug is found in Box 1 at the end of the article..

SCENARIO 1

A 56-year-old female presents with community-acquired right upper lobe pneumonia. She has a heart rate of 140bpm, a BP of 75/30mmHg, she is oliguric and has a temperature of 38.7°C. She feels warm to touch with a bounding pulse.

Interpretation

This patient has met the criteria of systemic inflammatory response syndrome (see page 145). The cause is infective and so she has sepsis. Her haemodynamic profile is profound vasodilatation and increased capillary leakage.

Management

She should be treated according to the 'Surviving Sepsis' care bundle, that involves taking blood cultures, giving appropriate antibiotics and administering a fluid bolus of $20\text{ml}\cdot\text{kg}^{-1}$ of crystalloid.⁴

If she remains hypotensive after 'adequate' fluid resuscitation, she has septic shock, and administration of a vasopressor agent is indicated. Norepinephrine is the drug of choice,⁵ although dopamine and epinephrine are popular worldwide. An infusion of vasopressin may be added if high doses of norepinephrine fail to achieve a target blood pressure. Steroids (hydrocortisone 50mg 6 hourly) are indicated for patients on high or rapidly escalating doses of vasopressor drugs.

Cardiac output may fall due to a circulating myocardial depressant factor. This may be present from the outset or develop later in the course of the illness. This may be evident clinically or using

cardiac output measurement. Inadequate oxygen delivery is indicated by a high or rising arterial lactate level or a low $S_{cv}O_2$ level (see Figure 1). At this point supplementation of the cardiac output, using an inotrope is appropriate, typically dobutamine, but dopamine and epinephrine are alternatives. The other way to improve oxygen delivery is to increase the haemoglobin level (and so oxygen content of blood) by transfusion.

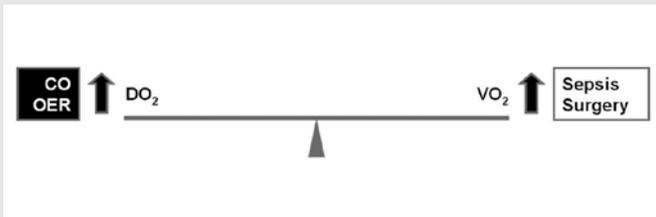


Figure 1. Organs depend on adequate delivery of oxygen (DO_2) for their oxygen consumption (VO_2). VO_2 is increased by stresses such as sepsis or surgery. DO_2 can be improved by increasing cardiac output (CO) and then, if delivery is inadequate, by the organ increasing its oxygen extraction ratio (OER). At this point delivery becomes supply-dependant - if supply falls, anaerobic metabolism increases and lactate rises. Increased OER causes venous desaturation, and so a low $S_{cv}O_2$ indicates impaired oxygen delivery.

Notes on vasoactive drugs used in sepsis

Norepinephrine (noradrenaline)

- Noradrenaline is predominantly a vasopressor agent, acting on α_1 adrenoceptors, causing peripheral vasoconstriction. It does have some β_1 -agonist effects causing positive inotropic effects.
- Restoration of blood pressure may stimulate the baroreceptor reflex causing compensatory bradycardia.
- Noradrenaline may exhibit tachyphylaxis (i.e. it becomes less potent with prolonged therapy).

Dopamine

- Dopamine acts at α_1 , and D1 (dopamine) receptors.
- Lower doses tending to have β_1 effects and stimulate endogenous noradrenaline production.
- Higher doses elicit effects at α_1 adrenoceptors and have a role in low cardiac output states, particularly in children.
- There is no evidence that dopamine a significant reno-protective role.
- Side effects include gastric stasis, arrhythmias (making it inferior to norepinephrine in this setting⁵) and anaphylaxis due to sodium metabisulphite.

Vasopressin

- This is an endogenous peptide (also known as antidiuretic hormone), usually produced in the hypothalamus. It is released in response to increased plasma osmolality and has its effects at V1, V2, V3 and OTR (oxytocin-type) receptors.

- V1 receptors are found on vascular smooth muscle of the systemic, splanchnic, renal, and coronary circulations. V2 receptors are located in the distal tubule and collecting ducts of the kidney and, when stimulated, increase water reabsorption.
- Vasopressin levels fall dramatically in septic shock and it was postulated that replacing it would improve survival in patients with septic shock. However, a large randomised controlled trial failed to show any difference in survival between treatment with vasopressin compared to noradrenaline⁶ and it is used as a catecholamine-sparing agent in septic patients on high or escalating doses of catecholamines.
- It may have a role in renal resuscitation for patients with impending acute kidney injury.
- Side effects include myocardial ischaemia at high dose, reduced splanchnic circulation and skin necrosis.

Epinephrine (adrenaline)

- Adrenaline stimulates both α - and β -adrenoceptors, with different effects depending on the dose administered.
- At low dose, there are mostly β effects; increased inotropy and chronotropy and also bronchodilatation.
- At high dose, alpha effects predominate, resulting in peripheral vasoconstriction.
- Side effects include lactic acidosis. One of its constituents (sodium metabisulphite) can cause allergic-type reactions, including anaphylaxis and life-threatening asthmatic episodes in susceptible individuals.

SCENARIO 2

A 62-year-old man presents to the Emergency Department after being stung by a wasp. He has a widespread rash, is hypotensive, tachycardic and finding it difficult to breathe. On auscultation of his chest he has widespread wheeze.

Interpretation

This patient has anaphylaxis, an IgE mediated type 1 hypersensitivity reaction. Exposure to an allergen causes widespread mast cell degranulation, resulting in the release of vasoactive substances such as histamine, prostaglandins and tryptase. These cause the clinical picture of vasodilatation, increased capillary permeability and bronchospasm.

Management

Immediate management involves an ABC approach and may necessitate tracheal intubation. Epinephrine should be administered as soon as possible in repeated boluses of 50 micrograms intravenously or 500 micrograms intramuscularly. Intravenous chlorphenamine 10mg and hydrocortisone 200mg should be administered early. Nebulised salbutamol may help

bronchodilatation. Serum tryptase levels should be taken as per published recommendations.⁷

If the patient remains cardiovascularly unstable, an epinephrine or norepinephrine infusion should be considered.

SCENARIO 3

A 70-year-old man presents with an acute anterior myocardial infarction. He has received immediate conservative treatment for this from the medical team, but has become tachycardic, hypotensive, peripherally cold due to vasoconstriction and is oliguric.

Interpretation

This patient is likely to have cardiogenic shock. After initial ABC assessment, where available, invasive arterial monitoring will be helpful.

Several drugs are available to help augment cardiac output and blood pressure. Dobutamine, levosimendan and milrinone all increase contractility and cause vasodilatation, which reduce the afterload to the heart.

Dobutamine is the first line inotropic agent in many countries, however it does increase myocardial oxygen consumption. In contrast to its use in sepsis (where a vasopressor is usually also required) it can often be infused as a sole agent in patients with pure cardiogenic shock

Levosimendan is a relatively new drug which does not increase myocardial oxygen consumption.

The patient's haemodynamic performance after acute myocardial infarction is dictated by a number of factors:

- Site of the infarct - a predominantly left ventricular infarct is likely to cause left ventricle impairment, with pulmonary oedema and low cardiac output. A blockage of the right coronary circulation may predominantly affect the right ventricle, causing right ventricular failure, with pulmonary oedema less likely, but still a low cardiac output state.
- Coronary intervention - emergency angioplasty or stent insertion may prevent, reduce or reverse myocardial damage and is offered in many well-resourced centres.

Remember that an acute deterioration should prompt a thorough reassessment of the patient:

- **Pulmonary oedema may indicate sudden onset of severe mitral regurgitation (MR) following infarction and rupture of a papillary muscle - listen for the pan-systolic murmur of MR.**
- **Sudden loss of cardiac output or reduced blood pressure, may be due to cardiac tamponade due to ventricular rupture after MI or coronary graft leak after grafting. Echocardiography is useful to confirm or exclude tamponade.**

Notes on vasoactive drugs used in cardiogenic shock

Dobutamine

- This is a potent β_1 -agonist. It also causes some β_2 -mediated vasodilatation, but this is usually counteracted by α -mediated vasoconstriction.
- It is useful in low cardiac output states.
- It is less arrhythmogenic than isoprenaline and dopamine.

Milrinone

- Milrinone is a PDE-3 inhibitor, with use limited to specialist cardiac centres. It is useful in promotion of diastolic function in patients with poorly compliant ventricles.

Levosimendan

- Levosimendan has some benefits when compared to placebo and dobutamine in reducing mortality in acute decompensated heart failure.
- At low doses it causes an improvement in microcirculation in severe septic shock, however its use in this role remains controversial.
- It is an 'inodilator' that works by increasing troponin C sensitivity to calcium. In the heart this causes positive inotropy, while causing vasodilatation of both the peripheral and coronary circulations. Use is generally restricted to a 24-hour infusion - because of its relatively long half-life the benefits on myocardial function persist for several days.
- As it improves myocardial contractility but not oxygen demand, it can help prevent cardiac ischaemia.
- Side effects include hypotension due to vasodilatation.

SCENARIO 4

An elderly patient on the medical ward is hypotensive, bradycardic and confused. His ECG shows complete heart block with ST depression in the inferior leads.

Interpretation

This patient has complete block with adverse signs.

Management

Follow the Advanced Life Support (ALS) algorithm (see page 178). After initial assessment using an ABC approach, atropine 500mcg should be administered intravenously, repeated up to a dose of 3mg. If this fails, isoprenaline 5mcg.min⁻¹ IV or epinephrine 2-10mcg.min⁻¹ IV can be given as a bridge to transvenous pacing. Dopamine may also be considered.

Notes on vasoactive drugs used in bradycardia/complete heart block

Isoprenaline

- This is a β -adrenoceptor agonist that is used in the

management of bradyarrhythmias as a bridge to transvenous or permanent pacing.

- It has a greater chronotropic than inotropic effect.
- Side effects include angina in patients with ischaemic heart disease secondary to coronary artery hypoperfusion.

SCENARIO 5

A 23-year-old girl is brought to the Emergency Department. She is hypotensive, bradycardic and says she has taken an overdose of her father's atenolol.

Management

Beta blocker overdose is treated according to the ALS algorithm for bradycardia (page 180). However, a glucagon infusion is also used to counteract the effects of beta blockers.

Glucagon

- This is an endogenous hormone released from pancreatic alpha cells, important in blood glucose homeostasis.
- It is positively inotropic and chronotropic. It acts by increasing intracellular concentrations of cyclic AMP, resulting in an increase in calcium influx. It is also useful in calcium channel blocker overdose.

SCENARIO 6

You are asked to review a 22-year-old male motorcyclist who was involved in vehicle accident 12 hours ago. He was stable on presentation, but complained of left upper quadrant pain and was admitted to the surgical ward for observation. His heart rate is now 105bpm, his blood pressure is 125/92, he has cool hands and feet and he is extremely anxious.

Interpretation

This man has deteriorated, with hypovolaemia due to haemorrhage the most likely cause. Although his systolic blood pressure is maintained, the raised diastolic blood pressure (and lowered pulse pressure) indicates that he is maintaining his blood pressure by vasoconstriction. He has class 2 shock indicating that he has lost up to about 1500ml of blood. As a young fit man, his physiological compensation masks the fact that he is close to profound haemodynamic decompensation.

Management

We should check his airway and breathing, administer high flow oxygen, check his intravenous access and administer intravenous fluids. His haemoglobin level should be measured (although this may only fall after appropriate administration of fluid) and crossmatch 4-6 units of blood. At present there is no need for vasopressors or inotropes. Full examination shows that he is markedly tender in his abdomen, in the left upper quadrant. It is likely that he has lacerated his spleen and the surgical team should be called to assess him immediately.

Excessive fluid resuscitation may increase mortality, since full restoration of normal blood pressure may further exacerbate bleeding. It is recommended that in the short term a target mean arterial pressure of 40mmHg is appropriate or that palpation of central pulses is an acceptable end point.⁸ The concept of *talking hypovolaemia* describes resuscitation end points that target cerebral perfusion, rather than a certain blood pressure.

This man should respond well to fluid administration, but probably needs an exploratory laparotomy. Inotropes and vasopressors are not likely to be needed and if fluid therapy is insufficient, other causes of hypotension should be sought (e.g. myocardial contusion causing cardiogenic shock, anaphylaxis to an administered drug).

SAFETY ASPECTS

Vasoactive drugs are life saving therapies but also highly potent agents that should be administered by nursing and medical staff with appropriate experience and training. Preparation and checking of calculations, dosages and dilutions should be undertaken by two members of staff. A major limitation to use in poor resource settings is the unavailability of reliable infusion devices. Where available, syringe pumps are used to infuse high concentration solutions. More dilute preparations may be infused from a bag of fluid, but this should always be via an infusion device, where available. There is a significant risk of inadvertent infusion of high doses of the agent, if the infusion is run without an infusion device.

The half-life of catecholamines is 1-2 minutes and so patients receiving high doses of these drugs will tolerate interruption of delivery of the agent during syringe changes poorly. 'Double pumping' may be used - two infusions are run together into a two-way tap; the new infusion is increased as the old infusion is weaned off.

Ensure that the infusion line is clamped as the syringe is loaded into the driver, as the agent may inadvertently be administered during this process.

Most agents must be administered through a central vein, although dobutamine is generally well tolerated via a peripheral vein in adults and children.

SUMMARY

Shock is a common cause of admission to critical care units and can occur for a variety of reasons.

Inotropes are used to manipulate critically ill patients' physiology, to maintain tissue perfusion and prevent end organ damage. Most inotropes work by increasing intracellular calcium and therefore myocardial contractility. Inotropes should be used in appropriately monitored and adequately fluid resuscitated patients. In all cases, it is essential that the underlying cause of the clinical presentation is sought and addressed as soon as possible.

Box 1. Doses of commonly used inotropes and vasopressors

This chart is for example only. Doses quoted are adult doses. Please refer to local policies and check all doses prior to administration. Remember that the patient should be adequately fluid resuscitated and monitored, before starting inotropes and vasopressors. Most inotropes require central venous access for their administration and should be given through pumps to ensure accuracy.

Epinephrine (adrenaline)	
Preparation	Available as 1 in 10 000 or 1 in 1 000 dilution in ampoules or pre-filled syringes. For infusion: 1 ampoule contains 5mg of epinephrine in 5ml to be diluted in 5% dextrose to total 50ml (100mcg.ml ⁻¹)
Administration	Intravenous or intramuscular injection or infusion Cardiac arrest: 1mg (10ml of 1 in 10 000) Anaphylaxis: 50mcg bolus IV, 500mcg bolus IM
Infusion	0.01-0.15mcg.kg.min ⁻¹ increasing as required. Start at 1-5ml.h ⁻¹ and titrated according to effect
Norepinephrine (noradrenaline)	
Preparation:	1 ampoule contains 4mg of norepinephrine tartrate in 4ml to be diluted in 5% dextrose to total 40ml (100mcg.ml ⁻¹)
Administration	Intravenous infusion 0.05-0.5mcg.kg.min ⁻¹ . Start at 1-5ml.h ⁻¹ and titrated according to effect
Dopamine	
Preparation	200mg (40mg.ml ⁻¹) or 800mg (160mg.ml ⁻¹) in 5ml water with the additive sodium metabisulphite. Dilute to 50ml in 5% dextrose
Administration	Either low dose (<10mcg.kg.min ⁻¹) or high dose (>10mcg.kg.min ⁻¹) depending on desired effect
Vasopressin	
Preparation	20 units in 1ml glass vial. To be diluted with 5% dextrose
Administration	Surviving Sepsis Bundle recommends infusion of 0.03units.min ⁻¹
Dobutamine	
Preparation	250mg dobutamine in 5ml ampoule. To be diluted in either 50ml or 500ml 5% dextrose to give a 5000mcg.ml ⁻¹ or 500mcg.ml ⁻¹ dilution respectively
Administration	2.5-10mcg.kg.min ⁻¹ , higher rate if required
Milrinone	
Preparation	1mg.ml ⁻¹ in 10, 20 and 50ml vials. To be diluted in either 0.9% saline or 5% dextrose to give a 200mcg.ml ⁻¹ dilution
Administration	A loading dose of 50 mcg.kg ⁻¹ over 10mins is administered intravenously, followed by an infusion at 0.3-0.75mcg.kg.min ⁻¹
Isoprenaline	
Preparation	Isoprenaline hydrochloride 1mg in 5ml ampoule, dilute up to 50ml in 5% dextrose (20mcg.ml ⁻¹) or up to 500ml in 5% dextrose (2mcg.ml ⁻¹)
Administration	At a cardiac arrest or peri-arrest situation, infusion at 5mcg.min ⁻¹ Reduce to 0.02-0.2mcg.kg.min ⁻¹ . Reduce rate or stop infusion once the heart rate > 80bpm
Levosimendan	
Presentation	2.5mg.ml ⁻¹ solution, diluted in 5% dextrose for infusion
Administration	Initial IV bolus of 12 mcg.kg ⁻¹ over 10 minutes, followed by an infusion of 1mcg.kg.min ⁻¹ , which can be reduced to 0.05 or increased to 0.2 mcg.kg.min ⁻¹ for 24 hours
Glucagon	
Preparation	1mg of freeze-dried glucagon per ampoule . Dilute 25mg in 25ml 5% dextrose (1mg.ml ⁻¹)
Dose	An IV loading dose of 50-150 mcg.kg ⁻¹ is administered, then 0.8-1.6 mcg.kg.min ⁻¹ infusion

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Management of cardiac arrest - review of the 2010 European Resuscitation Guidelines

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INTRODUCTION

The European Resuscitation Council (ERC) has an established 5-year cycle for updating its Cardiopulmonary Resuscitation (CPR) guidelines. The most recent update was published in October 2010, following the International Consensus on CPR Science with Treatment Recommendations (CoSTR).¹

The focus of these latest guidelines is to consolidate and fine tune the major changes introduced in the 2005 update. Emphasis is again placed upon early, uninterrupted and high quality chest compressions, while modifications to management algorithms have been kept to a minimum.

ADULT BASIC LIFE SUPPORT (BLS)

The BLS algorithm remains unchanged from the 2005

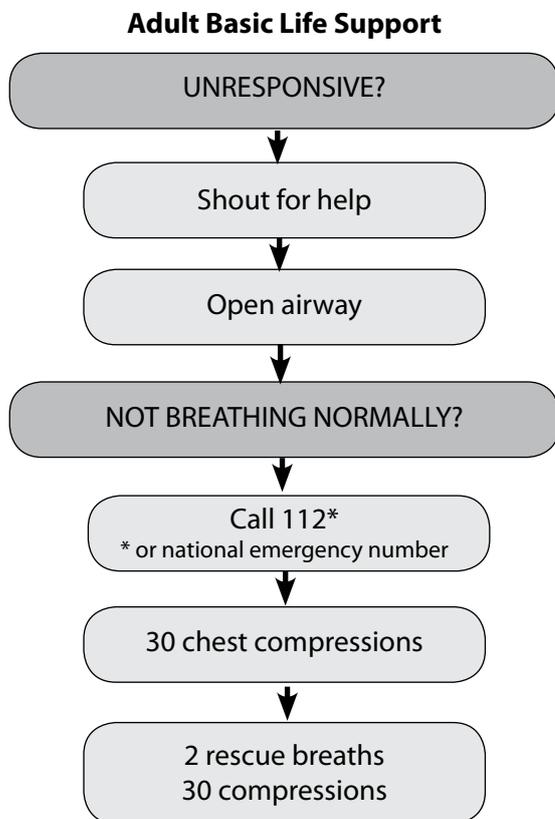


Figure 1. Adult Basic Life Support algorithm. Reproduced by kind permission of the European Resuscitation Council.

guidelines, with high quality external chest compressions (ECC) the key feature. Compressions should be at least 5cm deep and allow full recoil of the chest wall. ECC should be performed at a rate of 100 compressions per minute with a compression:ventilation ratio of 30:2.

ADULT ADVANCED LIFE SUPPORT (ALS)

Initial assessment and CPR

As before, the ALS algorithm starts with an initial assessment and commencement of CPR, followed by a division between the management of shockable (VF and pulseless VT) and non-shockable (asystole and pulseless electrical activity, PEA) rhythms.

The ALS guidelines have been changed to minimise interruptions to external chest compressions, as even brief interruptions in CPR can reduce the efficacy of subsequent defibrillation attempts. The team leader should monitor the quality of CPR and regularly rotate providers, ideally every two minutes.

There is no longer a recommendation that out of hospital cardiac arrest should be managed with two minutes of CPR prior to an attempt at defibrillation.

Defibrillation

- VF/VT is the first monitored rhythm in 25% of cardiac arrests, regardless of location. Having confirmed cardiac arrest, CPR should be continued during the location of a defibrillator and the application of adhesive pads or paddles.
- Chest compressions can be paused briefly to allow analysis of the underlying cardiac rhythm. As soon as the rhythm is identified CPR should resume.
- For shockable rhythms chest compressions should continue during charging of the defibrillator, with the adhesive pads or paddles in position on the chest. Defibrillation energy levels are unchanged from previous guidelines, 360J monophasic or 150 – 360J biphasic.
- When the defibrillator is charged chest compressions should stop and the shock delivered after a rapid safety check. Chest compressions must then immediately be resumed. Chest compressions should be interrupted for no more than 5 seconds.

Summary

This article describes the new changes to the most recent European Resuscitation Council guidance. There is increasing emphasis on maintenance of uninterrupted chest compressions. Atropine is no longer recommended for either adult or paediatric arrest.

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- Up to 3 quick, successive, ‘stacked’ shocks can be considered in VF/VT that occurs during cardiac catheterisation, immediately after cardiac surgery or in a witnessed, monitored arrest, with the patient already connected to a defibrillator.
- The precordial thump is rarely effective and now only recommended in witnessed, monitored arrests when no defibrillator is immediately available.

Drugs

Epinephrine (adrenaline) remains the vasopressor of choice in cardiac arrest. The dose is unchanged from previous guidelines at 1 mg (10ml of 1:10,000 solution), though the timing of administration has been revised.

- In VF/pulseless VT, epinephrine 1mg should be given immediately after the third shock, when chest compressions have resumed.
- In PEA/asystole epinephrine 1mg should be given as soon as IV access is obtained
- Epinephrine doses should be repeated every 3-5 minutes.

Amiodarone remains the antiarrhythmic agent of choice for VF/VT. A 300mg bolus injection should be administered after the third shock. A further bolus of 150mg may be administered for refractory VF/VT. Lidocaine 1mg.kg⁻¹ can be used if amiodarone is not available, but they should not be administered together.

The use of atropine in cardiac arrest is no longer recommended. Asystole in adults is generally a result of myocardial injury, rather than excessive vagal tone, and no evidence of benefit from atropine has been found in either asystole or PEA.

Administration of drugs via the endotracheal tube (ETT) is no longer recommended. Recent improvements in intraosseous access devices have led to this now being the alternative access of choice in cases of difficult peripheral venous cannulation.

Airway management

There is reduced emphasis on early intubation for airway management. This aims to minimise interruptions in chest compressions, and also recognizes the high failure rate of endotracheal intubation by non-expert operators. Supraglottic airway devices (SADs) are easier to insert than ETTs and do not require the interruption of chest compressions. No single SAD has been established as first choice, but successful use of the classic laryngeal mask airway (cLMA), the laryngeal tube and the I-gel have all been reported.

Endotracheal intubation should only be attempted by experienced operators, who can perform direct laryngoscopy without interrupting chest compressions. A brief pause in compressions may be required to pass the ETT through the vocal cords, but this must last no longer than ten seconds.

Waveform capnography should be used to confirm correct placement of an endotracheal tube, in conjunction with auscultation of both lung fields. Capnography also allows an assessment of the adequacy of CPR, which should ideally maintain an end-tidal CO₂ (ETCO₂) above 2kPa (15mmHg). Capnography may also give an indication of

the return of a spontaneous circulation, manifesting as a significant increase in ETCO₂.²

Ultrasound imaging

Where available, a 10 second echocardiogram, via a sub-xiphoid view, can be performed when chest compressions are paused for a rhythm check. This may aid diagnosis of the underlying, potentially reversible cause of cardiac arrest, such as pulmonary embolism, cardiac tamponade or hypovolaemia.

Absence of cardiac motion on echocardiogram during cardiac arrest has been shown to be highly predictive of unsuccessful resuscitation.³

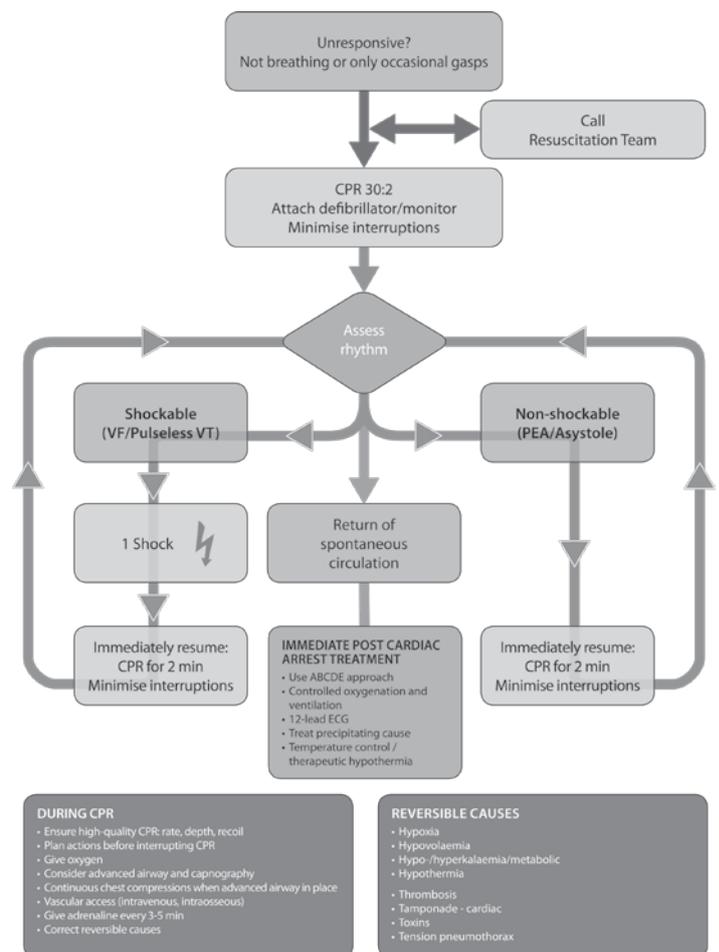


Figure 2. Advanced Life Support algorithm. Reproduced by kind permission of the European Resuscitation Council.

Periarrest arrhythmias

The algorithms for the management of tachycardic and bradycardic arrhythmias are largely unchanged from 2005. Both now share the same initial assessment of adverse clinical signs, specifically shock, syncope, myocardial ischaemia and heart failure. The subsequent recommended pharmacological and electrical therapies are unchanged.

Post resuscitation care

Post arrest brain injury, myocardial dysfunction and the systemic reperfusion response combine with the residual underlying cause of

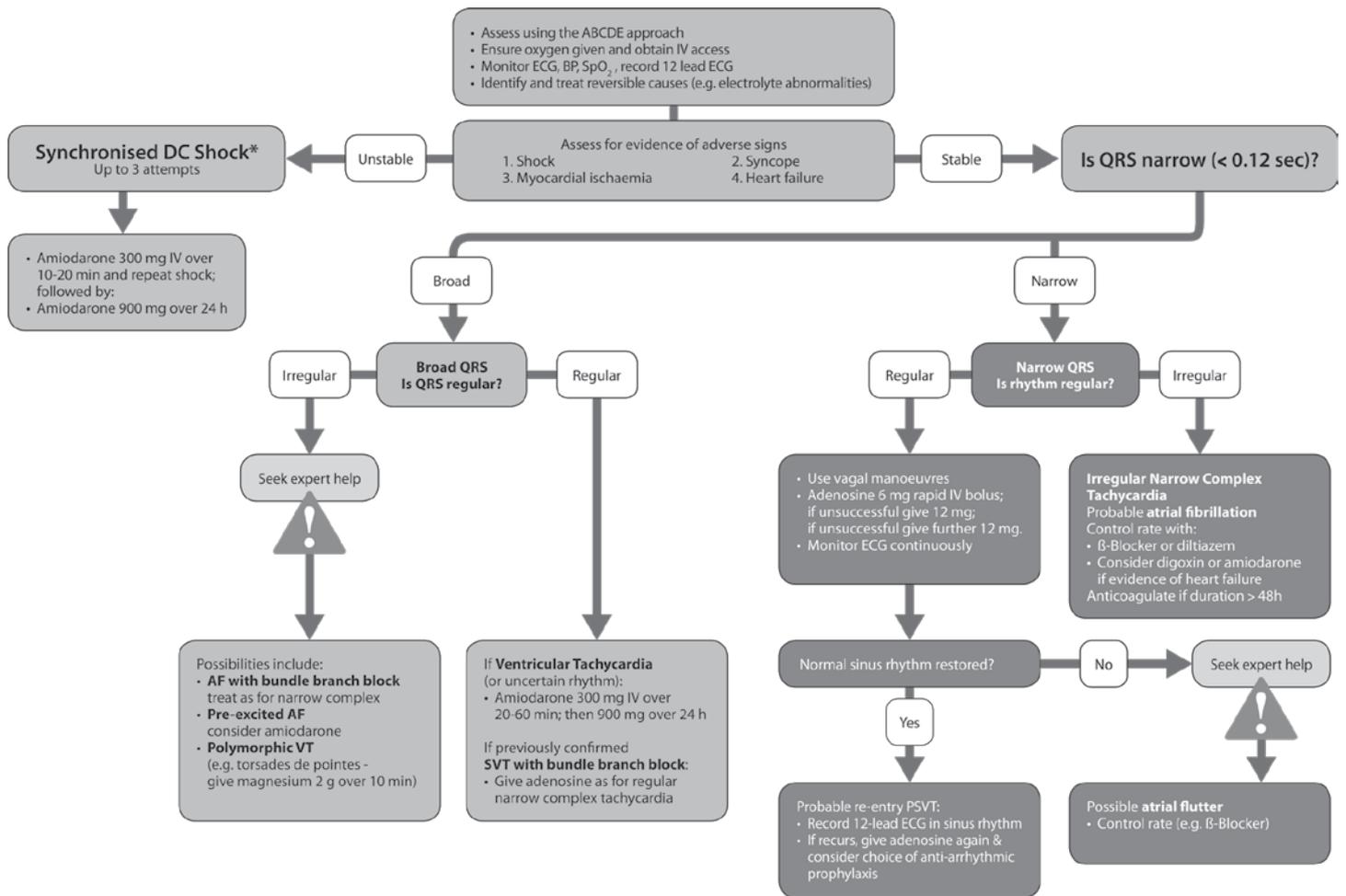


Figure 3. Tachycardia algorithm. Reproduced by kind permission of the European Resuscitation Council.

cardiac arrest to form the post cardiac arrest syndrome. The severity of this syndrome varies, depending on the cause, duration and management of the cardiac arrest. As with previous resuscitation guidelines a key aspect of improving outcome in cardiac arrest is optimising post resuscitation care.

- Hypoxaemia, hyperoxaemia and hypercarbia are associated with worse neurological outcomes and should be avoided. The inspired oxygen concentration should be titrated to maintain an SaO_2 of 94-98%.
- All post cardiac arrest patients suspected of having coronary artery disease should undergo early percutaneous coronary intervention (PCI), not just those with ECG evidence of ST elevation myocardial infarction (STEMI).
- The target range for blood glucose in post arrest patients has been relaxed after recent evidence that intensive glucose control in general ICU patients was associated with a higher 90 day mortality, and an increased risk of hypoglycaemia.⁴ Blood glucose in post cardiac arrest patient should now be maintained at less than 10mmol.l^{-1} (180mg.dl^{-1}) and hypoglycaemia should be avoided.
- The recommended use of therapeutic hypothermia has been extended to all comatose survivors of cardiac arrest, not just those

whose arrest rhythm was VF or pulseless VT. Induction of cooling should start as soon as possible after return of spontaneous circulation (ROSC), and the patient's core temperature should be maintained at $32\text{-}34^\circ\text{C}$ for 12-24 hours. While the rate of cooling should be as rapid as possible, subsequent re-warming should be achieved slowly, by no more than $0.25\text{-}0.5^\circ\text{C}$ per hour, to minimise physiological instability.

PAEDIATRIC BASIC LIFE SUPPORT

The paediatric BLS algorithm is largely unchanged. However there is now a reduced emphasis on locating a central pulse for the diagnosis of cardiac arrest. Instead responders are advised to look for signs of life, and begin chest compressions if they are abnormal. Trained responders may include palpation of a pulse, but the assessment must take no longer than ten seconds.

Those trained in paediatric life support should perform CPR with a 15:2 compression:ventilation ratio. However lay responders are encouraged to use the adult ratio of 30:2 for ease of training. Compressions should be at least one third of the antero-posterior depth of the child's chest, with subsequent complete release of pressure to allow the chest wall to rebound fully. Compressions should be performed at a rate of at least 100 per minute but not greater than 120 per minute.

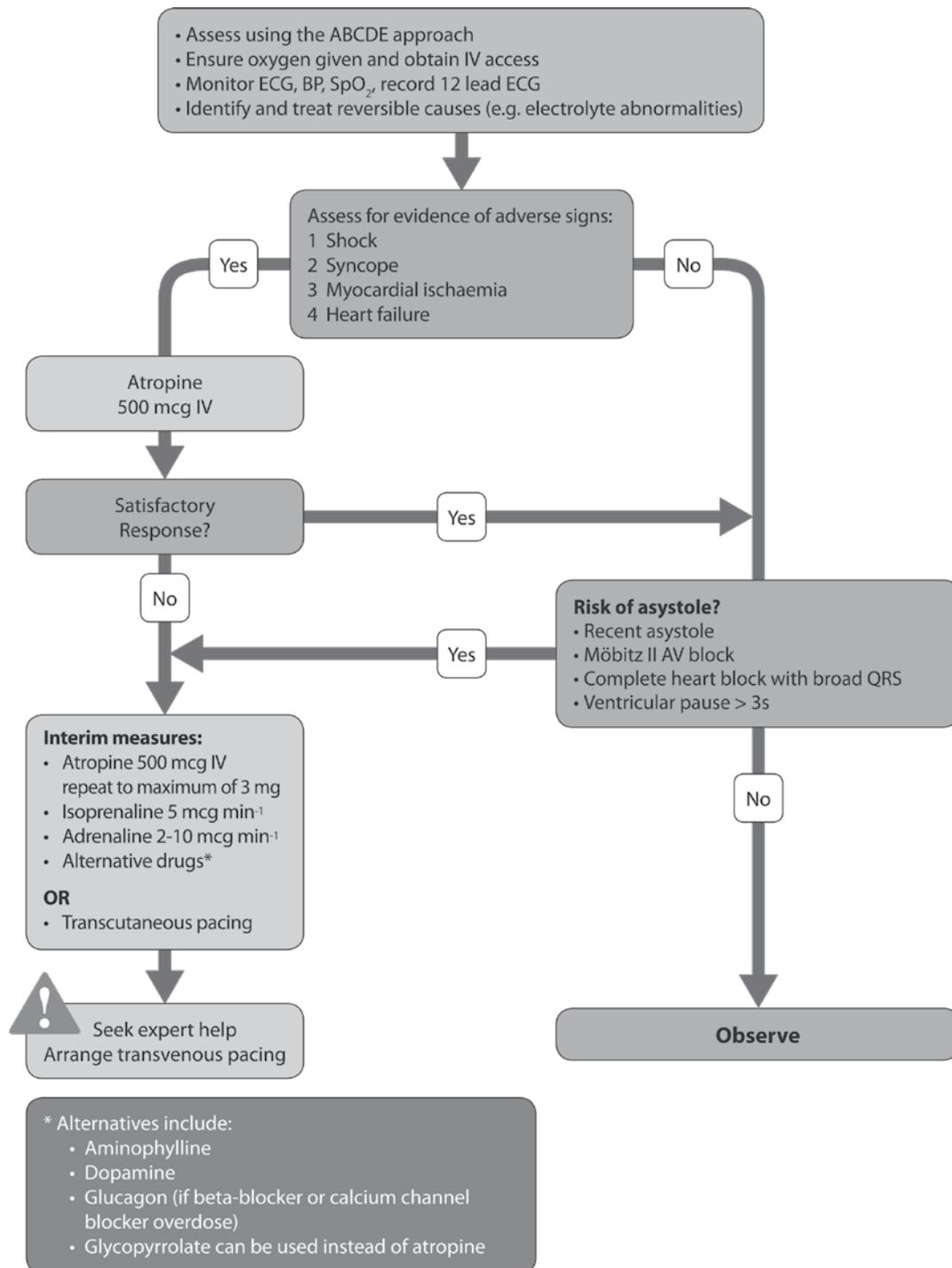


Figure 4. Bradycardia algorithm. Reproduced by kind permission of the European Resuscitation Council.

PAEDIATRIC ADVANCED LIFE SUPPORT

As with adult ALS a key aim is to minimise the interruption of chest compressions.

Defibrillation

- Chest compressions should continue while applying and charging defibrillator pads or paddles and paused only briefly to administer the shock. To maintain consistency with adult guidelines a single,

non-escalating, shock strategy is advised. Biphasic defibrillators are preferred to monophasic, but the same energy setting of 4Jkg^{-1} should be used for both.

- Automated external defibrillators (AEDs) can be used in children over 1 year of age. Ideally AED output should be reduced to 50-75J with purpose made attenuator pads, but adult energy levels may be used if these are unavailable.

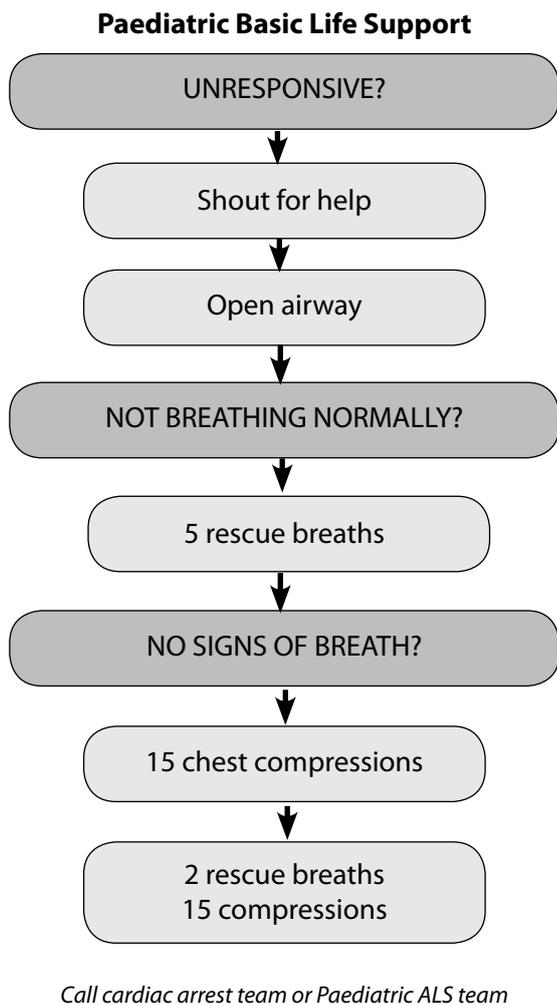


Figure 5. Paediatric Basic Life Support algorithm. Reproduced by kind permission of the European Resuscitation Council.

Airway

- Cuffed endotracheal tubes may be safely used in infants and young children, increasing the chance of first time placement of an appropriate sized tube, and improving ventilation of poorly compliant lungs. Cuff pressure should not exceed 25cm.H₂O.
- Capnography should be used to confirm ETT placement and monitor the effectiveness of CPR.

Drugs

- As with adult ALS, atropine should not be used in paediatric cardiac arrest.
- The dose of epinephrine remains unchanged at 10mcg.kg⁻¹ every 3-5 minutes.
- Amiodarone 5mg.kg⁻¹ should be given in VF/pulselessVT after the third and fifth shocks.

Post resuscitation care

The principles of management of post cardiac arrest syndrome in children are similar to those of adults:

- The inspired oxygen concentration should be titrated post ROSC to prevent hyperoxia.
- Hyperthermia has an established association with poor neurological outcome and should be avoided.
- Therapeutic hypothermia for comatose children post cardiac arrest remains unvalidated. However successful trials in adults and neonates support its extension to use in children. The current advice is that children may benefit from a similar cooling regime to that of adults. If a child with ROSC is already hypothermic they should not be actively rewarmed unless their core temperature is below 32°C.
- No specific blood glucose range is advocated but blood glucose should be monitored, and sustained hyperglycaemia or hypoglycaemia avoided.

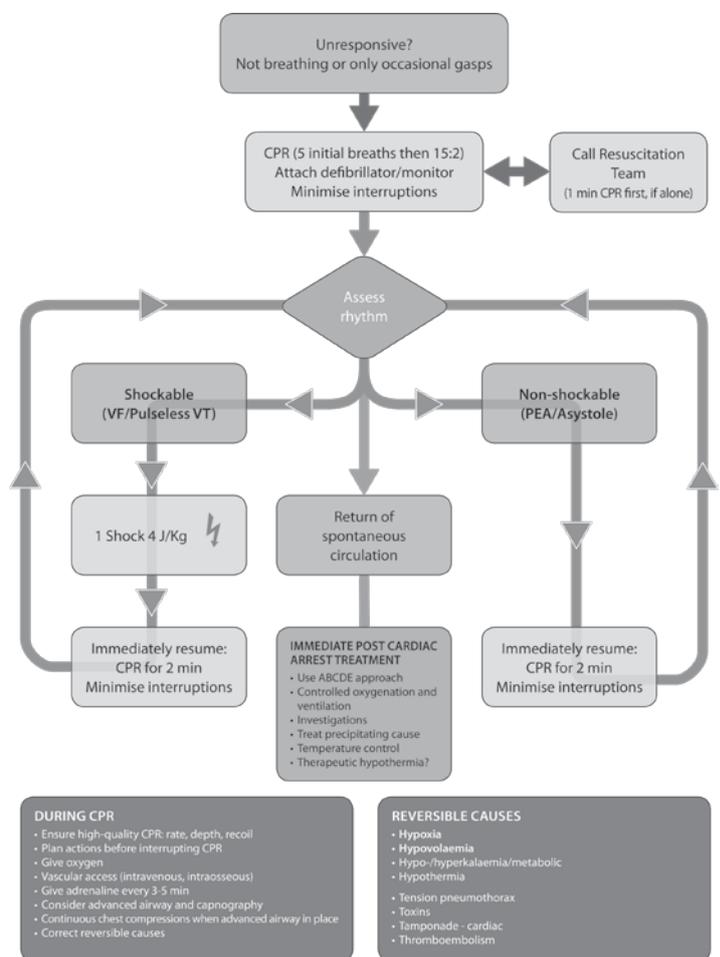


Figure 6. Paediatric Advanced Life Support algorithm. Reproduced by kind permission of the European Resuscitation Council.

RESUSCITATION OF BABIES AT BIRTH

In uncompromised newborns, cord clamping should be delayed by at least 1 minute from complete delivery. While delayed cord clamping may also benefit compromised babies, current advice is that commencing resuscitation remains the priority.

AT ALL STAGES ASK: DO YOU NEED HELP?

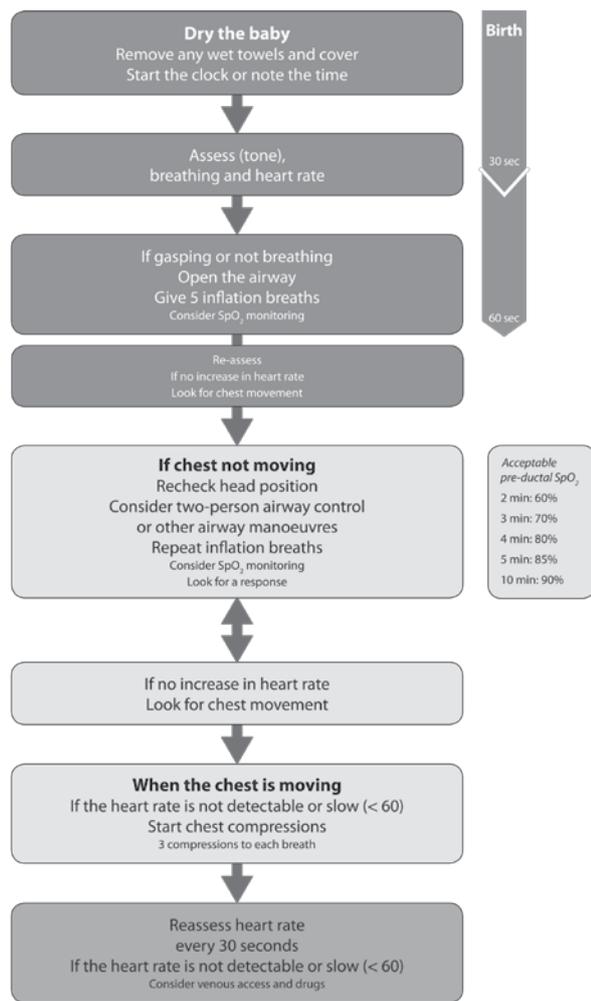


Figure 7. Newborn Life Support algorithm. Reproduced by kind permission of the European Resuscitation Council.

Air should be used for the resuscitation of term infants at birth. Oxygen supplementation can be added after initial ventilation as guided by pulse oximetry. Blended oxygen and air may be required for preterm infants born before 32 weeks gestation but both hyperoxia, and hypoxia, should be avoided.

Preterm babies of less than 28 weeks should not be dried after birth but instead immediately placed up to their necks in a plastic bag, or food wrap, and then stabilised under a radiant heater. If possible the delivery room temperature should be at least 26°C.

Rescue breaths, chest compressions and drug doses are unchanged from the 2005 guidelines.

Therapeutic hypothermia should be considered for term or near term neonates with moderate or severe hypoxic encephalopathy.

FURTHER READING

The full 2010 European Resuscitation Council guidelines can be found at: www.cprguidelines.eu/2010/

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Acute respiratory distress syndrome (ARDS)

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INTRODUCTION

First described in 1967, ARDS is a process of hypoxaemic respiratory failure associated with non-cardiogenic pulmonary oedema. It is the result of diffuse inflammatory damage to the alveoli and pulmonary capillaries from a range of local or systemic insults. ARDS is often associated with multiple organ dysfunction and carries a high mortality and financial cost.

DEFINITIONS

ARDS is diagnosed on clinical grounds. The 1994 criteria have been replaced (Table 1).

Acute lung injury (ALI), a less severe form of ARDS in which the $\text{PaO}_2/\text{FiO}_2$ ratio is $\leq 300\text{mmHg}$ (40kPa) is now termed mild ARDS.

EPIDEMIOLOGY

The true incidence of ARDS is unknown; estimates vary depending on the definitions used, with values ranging from 1.5 per 100 000 population per year to 75 per 100 000 population per year. Recent data from an Australian study, which used the 1994 consensus conference definition for ARDS, would suggest that one in ten non-cardiothoracic ICU patients will develop ARDS.¹

Although ARDS may affect children it is more common in those over the age of 65, which may reflect a higher incidence of predisposing conditions. Gender has no effect. In recent years mortality rates have decreased from about 60% to 30–40%, but mortality is higher in the elderly and in patients with factors such as chronic liver disease. Most of those who die do so from sepsis or multiple organ failure and not from respiratory failure. Survivors usually have little in the way of pulmonary sequelae, although the severest cases may have restrictive lung disease.

PATHOPHYSIOLOGY

It is not understood why some individuals develop ARDS while others with the same pattern of predisposing injury do not. In those that do there are said to be three overlapping phases: an inflammatory phase, a proliferative phase and a fibrotic phase caused by the subsequent reparative response.² Patients with ARDS do not have to progress through all three phases, as resolution can occur at any point. However, the severest form of ARDS will progress to the fibrotic phase. Common preceptants are listed in Table 2.

Inflammatory phase

This lasts for one week after the onset of respiratory

Summary

- Identify and treat the underlying cause
- Ventilate at low tidal volume
- Apply generous PEEP
- Maintain a low hydrostatic pressure in the lungs (avoid fluid overload)
- Consider the prone position in severe cases
- Consider steroids in persistent ARDS

Table 1. Proposed new definition of ARDS (European working group, awaiting formal publication).

	Mild ARDS	Moderate ARDS	Severe ARDS
Timing		Acute onset within 1 week of a known clinical insult or new/worsening respiratory symptoms	
Hypoxaemia	$\text{PaO}_2/\text{FiO}_2$ 201–300mmHg with PEEP/CPAP $\geq 5\text{cmH}_2\text{O}$	$\text{PaO}_2/\text{FiO}_2 \leq 200\text{mmHg}$ with PEEP $\geq 5\text{cmH}_2\text{O}$	$\text{PaO}_2/\text{FiO}_2 \leq 100\text{mmHg}$ with PEEP $\geq 10\text{cmH}_2\text{O}$
Origin of oedema		Respiratory failure not fully explained by cardiac failure or fluid overload	
Radiological abnormalities	Bilateral opacities	Bilateral opacities	Opacities involving at least 3 quadrants
Additional Physiological Derangement	N/A	N/A	Minute volume $>10\text{L}\cdot\text{min}^{-1}$ or compliance $<40\text{ml}\cdot\text{cmH}_2\text{O}^{-1}$

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failure. Neutrophils accumulate in the capillaries, interstitial tissue and airspaces, and cause cell damage through the production of free radicals, inflammatory mediators and proteases. However neutrophils are not the only cell type involved as ARDS does occur in neutropenic patients. Cytokines (most importantly TNF- α , IL-1, IL-6 and IL-8) are also released by endothelial and immune cells and promote similar microvascular damage. The result is leakage of fluid and plasma proteins into the alveoli and interstitial tissues ('non-cardiogenic pulmonary oedema'), while at the same time the plasma proteins denature alveolar surfactant causing alveolar collapse. This creates hypoxia as the fluid-filled alveoli shunt blood. Shunt is created when areas of lung receive a blood supply but are unable to oxygenate it (in this case by creating a diffusion barrier).

To complicate matters further, vasoconstriction and occlusion of pulmonary capillaries by neutrophils, platelets and fibrin also occurs leading to areas of lung that are ventilated but not perfused – deadspace.

The increase in total lung water also stiffens the lung (decrease in compliance) and this dramatically increases the work of breathing.

Proliferative phase

This phase is characterised by proliferation of type II pneumocytes and fibroblasts, with the formation of hyaline membranes. However, these pneumocytes do not make any surfactant and total production of surfactant decreases (this exacerbates the loss of surfactant caused by protein denaturing).

Fibrotic phase

Disordered collagen deposition occurs, leading to extensive lung scarring. This makes the lung stiffer and further increases the work of breathing. This can be severe enough to make it impossible to wean the patient from a ventilator, but normally it is a matter of restoring the patients muscle strength to the point where they are able to cope with the increased effort required.

PRESENTATION

The timing of the onset of clinical features varies from a few hours to several days after the precipitating insult.

History

Shortness of breath is universal, but other symptoms are related to the predisposing condition.

Examination

Findings are similar to those of pulmonary oedema due to other causes:

Respiratory – laboured breathing, tachypnoea, diffuse crackles, cyanosis.

Cardiovascular – sweating, tachycardia.

CNS – agitation, leading to lethargy and decreased level of consciousness.

In addition there may be features of the underlying condition.

Investigations

Arterial blood gases

- PaO₂/FiO₂ ratio of \leq 300mmHg (40kPa).
- Hypocarbica may be seen, although hypercarbia develops later, as respiratory failure progresses.

Radiology

Chest Xray shows diffuse bilateral fluffy shadows (although initially they may be less widespread or unilateral) and may show other pulmonary signs if there is a direct pulmonary predisposing condition.

MANAGEMENT – SUPPORTIVE MEASURES

There are no established treatments for ARDS, but treating the underlying condition (for example eradicating infection with antibiotics or surgery) and providing support for each system are paramount.

Respiratory support

Frequent chest Xrays will help to detect pneumothorax, fluid overload and pneumonia, which may all complicate ARDS. Pneumothorax in particular should be sought if there is a sudden increase in ventilation pressures or deterioration in blood gases. CT scanning may help to show occult pneumothorax.

Frequent physiotherapy is also important, to prevent plugging of airways by sputum. If plugging is suspected (for example by lobar

Table 2. Precipitants for ARDS can be classified as direct or indirect.

Direct	Indirect
Pneumonia	Multiple trauma
Lung contusion	Massive transfusion
Aspiration of gastric contents	Sepsis
Fat embolism	Pancreatitis
Toxic inhalation	Cardiopulmonary bypass
Near drowning	Burns
Reperfusion injury	Bone marrow transplant
Drugs and toxins	

collapse and deterioration in blood gases) bronchoscopy and lavage can help.

Cardiovascular support

The aim is to maintain adequate oxygen delivery to the tissues. In ARDS cardiac output can be decreased due to sepsis or due to medical treatments (high ventilation pressures, PEEP, or inverted inspiratory:expiratory ratios), thus monitoring of cardiac output and filling pressures are important. This can be achieved using a pulmonary artery catheter, oesophageal Doppler, LidCO or PiCCO devices, but clinical signs are also important, especially when these are unavailable. Fluid management is always difficult in these cases - excessive fluids will worsen lung function and inadequate fluids will exacerbate renal failure. Cardiac output monitoring allows assessment of fluid responsiveness - volume challenges of 250ml can be given to achieve the highest achievable stroke volume and if cardiac output is still inadequate then inotropes are indicated.

Appropriate targets are a cardiac index $3.5-5\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, Hb concentration $7-9\text{g}\cdot\text{dl}^{-1}$ (do not over-transfuse) and $\text{SaO}_2 \geq 90\%$ (see below).

Renal support

Renal failure is common, due to the underlying condition, low cardiac output, sepsis, and so on. Renal replacement therapy (for example with haemofiltration) may also improve gas exchange, by removing excess fluid.

Nutrition

Enteral nutrition should be established quickly, using nasogastric feed with prokinetics (such as metoclopramide) or nasojejunal feeding. Total parenteral nutrition (TPN) can be considered if all attempts at enteral feeding fail.

Managing sepsis

Sepsis may have precipitated the lung injury, or may develop during the course of ARDS. However, the systemic inflammatory response syndrome is often associated with ARDS in the absence of infection, thus detecting sepsis may be difficult.

Change in sputum colour and new shadows on the chest Xray may point to pulmonary infection. Other sources of sepsis should be reviewed frequently (line sites, urine, wounds).

If infection is suspected, appropriate samples should be sent for microscopy and culture. This may include bronchoscopy and lavage or removing and culturing invasive line tips, for example. Lavage is particularly useful in this setting. 20ml of normal saline is injected into the airway either through a bronchoscope or via a sterile suction catheter (placed blindly through the endotracheal tube until resistance is felt) and suctioned back into a culture pot. The likelihood of a significant positive result is higher with this technique and less tracheal contamination is encountered. Antimicrobial therapy should be guided by the results of these investigations, though 'blind' treatment may be reasonable if sepsis causes severe cardiovascular instability or impairment of gas exchange.

MANAGEMENT – VENTILATION STRATEGY

Continuous positive airways pressure (CPAP) may be of benefit in mild cases, however most patients will require early intubation and mechanical ventilation. Indications include hypoxaemic or hypercarbic respiratory failure, acidosis, exhaustion and reduced conscious level. Profound sedation is usually required for ventilation as struggling or coughing can cause loss of recruited lung and worse oxygenation. Paralysis may be necessary if sedation alone does not settle the patient.

The aim of ventilation is to improve oxygenation without causing further damage to the lungs. Difficulties arise as some alveoli are normal and open whilst other alveoli are stiff and collapsed. It is therefore necessary to try to open the collapsed alveoli without damaging the normal areas. The main causes of ventilator-induced lung damage are high FiO_2 (increased free radical damage) and over-distension of alveoli. Ventilation reduces the work of breathing and reduces oxygen demand and this should help correct acidosis and improve cardiovascular stability.

With the exception of low tidal volumes (see below) there is little evidence of survival benefit for any particular ventilation strategy; however volume-controlled ventilation is usually used initially, with the following targets:

- FiO_2 0.5-0.6 to minimise oxygen toxicity.
- $\text{PaO}_2 \geq 8\text{kPa}$ ($\text{SaO}_2 \geq 90\%$) - do not attempt to achieve higher values.
- $\text{PaCO}_2 < 10\text{kPa}$ as long as $\text{pH} > 7.2$. Do not attempt to achieve lower values if this requires excessively high tidal volumes ('permissive hypercapnia').
- Tidal volumes $6-8\text{ml}\cdot\text{kg}^{-1}$ body weight (to minimise alveolar distension and volutrauma), as suggested by the ARDS Network study.³
- Plateau pressures of $30\text{cmH}_2\text{O}$ to minimise alveolar distension and volutrauma.
- Positive end-expiratory pressure (PEEP) titrated to achieve best oxygen delivery – commonly $10-15\text{cmH}_2\text{O}$. This increases functional residual capacity, recruits alveoli and puts the lung on the steeper part of the compliance curve. Higher levels of PEEP should be avoided, as they decrease venous return and thus cardiac output – PEEP should be set to maximise oxygen delivery rather than oxygenation alone.
- Recruitment manoeuvres. This is the use of a high level of CPAP ($30-40\text{cmH}_2\text{O}$) for 30 seconds in an apnoeic patient via a ventilator. The aim is to recruit collapsed alveoli, and its occasional use may lead to marked improvements in oxygenation.

Pressure-controlled inverse ratio ventilation (PC-IRV)

When ventilation using the above targets fails to improve oxygenation, PC-IRV may be attempted. The key features are:

- The inspiratory time (I) is prolonged till it is equal to or greater than expiratory time (E), for example using an I:E ratio of 1:1,

2:1 or 3:1. This allows time for poorly compliant lung units to be ventilated and should improve oxygenation.

- The pressure-controlled nature of the breath allows a plateau pressure to be set, to prevent over-distension of compliant (less diseased) alveoli.
- Plateau pressures should not exceed 35 cmH₂O, and should be set to achieve tidal volumes of 6-8ml.kg⁻¹ body weight

This technique has important side effects:

- Mean intra-thoracic pressures will be raised, thus decreasing venous return and cardiac output.
- The shortened expiratory time may not leave enough time for gas to escape from the lung, leading to high levels of 'auto-PEEP' (also called 'intrinsic PEEP'). As well as further decreasing venous return, high auto-PEEP can impair ventilation, as the resting lung pressure becomes too high to allow expansion during inspiration. It is important therefore to periodically measure total PEEP (set PEEP plus auto-PEEP) and decrease set PEEP accordingly.

Auto-PEEP is measured by placing the ventilator into expiratory pause and measuring the highest airway pressure created. Airway pressure should be the same as PEEP but if gas trapping occurs airway pressure will rise as the alveoli empty - auto PEEP.

- The shortened expiratory time may also lead to hypercarbia – high respiratory frequency may be needed to avoid excessive respiratory acidosis.
- PC-IRV is also extremely uncomfortable for the patient, thus heavy sedation +/- paralysis are usually needed.

Ventilation in the prone position

The physiological rationale of prone ventilation is that it optimizes lung recruitment and ventilation perfusion matching while preventing alveolar over inflation and allowing better postural drainage. Dramatic improvements in oxygenation are often seen in patients who are turned into the prone position for several hours, and this improvement may be sustained when they are returned to the supine position⁴. The technique should be used for periods of 12 to 24 hours..

However, there are practical difficulties in turning the critically ill patient and in nursing the patient in the prone position. A recent meta analysis has shown an improved outcome in those patients with PaO₂/FiO₂ ratio of ≤ 100mmHg. Prone ventilation is free and can be readily implemented in any intensive care unit.

MANAGEMENT – ADDITIONAL MEASURES

A number of advanced techniques are available, but there is little evidence of increased survival with any of them.

Nebulised prostacyclin

This produces pulmonary vasodilation, dilating those vessels in well ventilated parts of the lung, thus improving ventilation/perfusion matching. Because it is removed from the circulation rapidly it does not cause systemic hypotension. Prostacyclin should be continuously

nebulised at a rate of 5-20ng.kg⁻¹.min⁻¹. There is little evidence to support its use.

Inhaled nitric oxide

Like prostacyclin this is a selective pulmonary vasodilator, and is used in doses of 1-40 parts per million. Neither agent has been shown to influence survival.

Corticosteroids

There is some evidence from a small study of a reduction in mortality associated with the use of methylprednisolone to suppress ongoing inflammation during the fibroproliferative phase of ARDS. The initial regimen consists of methylprednisolone 2mg.kg⁻¹ daily. After 3-5 days a response must be apparent. In 1-2 weeks the dose can be tapered to methylprednisolone 0.5-1.0mg daily. In the absence of a response, steroids can be discontinued.⁵ A more recent meta analysis by Peter et al found a possible reduced mortality when steroids were started after the onset of ARDS, but preventative steroids increased the risk of ARDS.⁶

Surfactant therapy

This aims to replace surfactant lost from the lung and thus improve compliance and alveolar stability, and decrease lung water. However early results have been disappointing.

High frequency oscillation ventilation

This can be used to raise mean airway pressure without dangerous increases in peak airway pressure, but is expensive and only available in specialist centres

Extracorporeal membrane oxygenation (ECMO)

ECMO consists of a pump oxygenator that performs gas exchange, allowing the lungs to be 'rested'. This is only available in specialist centres.

SUMMARY

ARDS is diagnosed clinically on the basis of the acute development of hypoxaemic respiratory failure, chest Xray changes and non-cardiogenic pulmonary oedema, on the background of a pulmonary or non-pulmonary precipitating condition. ARDS may affect one in ten intensive care unit patients, and it carries a mortality of 30-40%.

Pathologically ARDS is characterised by an inflammatory phase involving neutrophils and cytokines, followed by a reparative process that may end in fibrosis. Patients exhibit the signs and symptoms of pulmonary oedema, though features of the underlying condition may influence the picture.

Management consists of treating the underlying condition, providing support for failing systems and early invasive ventilation. Limiting the FiO₂ may help to prevent further lung damage, while limiting tidal volumes to 6-8ml.kg⁻¹ has been shown to reduce mortality. In cases of refractory hypoxaemia PC-IRV or ventilation in the prone position may improve blood gases. In addition there are many advanced techniques but many are only available in specialist centres, and none convincingly reduce mortality.

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Hospital-acquired pneumonia

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Summary

Hospital-acquired (nosocomial) pneumonia (HAP) is the second most common hospital-acquired infection, with an incidence of 5-15 per 1000 hospital admissions. The incidence is higher in Intensive Care Units, where it accounts for approximately 30% of all hospital-acquired infections and is accompanied by significant morbidity and mortality. It is particularly associated with mechanical ventilation, where it prolongs the duration of mechanical ventilation required and the length of ICU stay. Mortality in patients with HAP ranges from 20-50%. This is increased to approximately 75% in cases caused by multi-drug resistant organisms.

DEFINITIONS AND CAUSATIVE ORGANISMS

Pneumonia is an inflammatory condition of the lungs secondary to bacterial, viral or fungal infection. Pathogens are most commonly acquired in the community, prior to admission to hospital.

Hospital-acquired pneumonia (HAP) is defined as pneumonia occurring more than 48 hours after hospital admission.

Ventilator-associated pneumonia (VAP) is a specific sub-group of HAP, occurring in patients more than 48 hours after endotracheal intubation and initiation of mechanical ventilation.

HAP can be further classified as early or late onset, which can be useful in predicting the likely causative organisms and choosing appropriate antibiotics. Early onset HAP occurs within 5 days of admission to hospital and is more likely to be caused by community-acquired pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Such pathogens are usually susceptible to antibiotic therapy. Late onset HAP develops more than five days after admission and is more likely to be caused by opportunistic and drug-resistant organisms such as *Pseudomonas aeruginosa* and *meticillin-resistant Staphylococcus aureus* (MRSA). There has been a recent increase in the number of early onset HAPs caused by the more drug-resistant organisms

such as MRSA. Such patients have usually had a recent hospital admission (within the previous 90 days) or are resident in nursing homes. It is also more common in patients who attend hospital frequently, for example, for haemodialysis.

The most common causative organisms are outlined in Table 1. Polymicrobial infections occur in up to 60% of cases. Anaerobic infections are rare. Fungal infections can occur, most often in severely immunocompromised patients.

PATHOGENESIS AND RISK FACTORS

For pneumonia to develop, there must be colonisation of the lower respiratory tract with the offending pathogen. Development of pneumonia following colonisation then depends on the balance between host defences and the virulence and volume of pathogen present in the lungs.

In VAP, colonisation usually occurs by micro-aspiration from the oropharynx or the gastrointestinal tract, often due to leakage around a cuffed endotracheal tube. Colonisation of the tube itself and condensation in the ventilator circuit can also contribute. Macro-aspiration from the gastrointestinal tract will result in the direct inoculation of a large volume of pathogen into the lower airway. Haematogenous spread from a distant site of infection can also occur, but is rare in cases of HAP.

Table 1. Causative organisms in HAP/VAP.

Pathogen	Examples
Staphylococcus aureus	Meticillin-sensitive (MSSA) or meticillin-resistant (MRSA)
Enterobacteriaceae	Klebsiella, Escherichia coli, Proteus, Enterobacter, Serratia
Streptococcus spp.	Streptococcus pneumoniae
Haemophilus spp.	Haemophilus influenzae
Pseudomonas aeruginosa	
Acinetobacter spp.	
Neisseria spp.	
Others	Stenotropomonas, Moraxella, Enterococcus, Corynebacterium, anaerobes, fungi

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Bearing this in mind, the most significant risk factor for the development of HAP in ICU is therefore tracheal intubation and mechanical ventilation. Other risk factors include:

- **Patient factors**

Advanced age, immunosuppression, severe acute illness, co-existing chronic illness - particularly chronic lung disease, malnutrition.

- **Factors that enhance colonisation of the oropharynx and stomach**

Recent antibiotic therapy, gastric acid suppression, bolus enteral feeding, prolonged or recent hospital admission, poor oral hygiene.

- **Conditions predisposing to aspiration or reflux**

Tracheal intubation (especially frequent re-intubations), insertion of nasogastric tube, supine positioning, coma, paralysis.

- **Prolonged periods of mechanical ventilation**

Particularly with the development of ARDS.

DIAGNOSIS

The diagnosis of HAP can be difficult, as the clinical features can be non-specific and the patient may already be unwell from other causes, resulting in a mixed clinical picture. Infiltrates on the chest Xray can also occur due to a number of other disease processes, such as ARDS, cardiogenic pulmonary oedema and atelectasis or collapse of lung segments or lobes.

There are no universally accepted clinical criteria for the diagnosis of HAP. The American Thoracic Society suggests that the diagnosis should be considered in any patient with new or progressive radiological infiltrates and clinical features to suggest infection:¹

- Fever (core temperature $>38^{\circ}\text{C}$),
- Leukocytosis ($>10000\text{mm}^{-3}$) or leukopenia ($<4000\text{mm}^{-3}$),
- Purulent tracheal secretions,
- Increased oxygen requirements, reflecting new or worsening hypoxaemia.

There is little evidence to support the use of more advanced radiological imaging although, when available, computed tomography can be useful in certain cases to exclude other pathology.

While clinical, laboratory and radiological examinations may raise the suspicion of HAP, determining the microbiological cause is more difficult and relies on obtaining a positive culture from the lower respiratory tract. Samples can be obtained from expectorated sputum in non-intubated patients, endotracheal aspirates (ETA), broncho-alveolar lavage using a fiberoptic scope (BAL), and protected specimen brush (PSB) sampling. Sputum and ETAs are the easiest samples to obtain and are highly sensitive with a high negative predictive value. A negative sample will essentially exclude HAP from the differential diagnosis. However, colonising organisms from the lower or upper respiratory tract often contaminate the sample, making it difficult to distinguish these from the causative pathogen. Samples obtained by BAL or brushings are more specific, however this is more invasive and requires bronchoscopic guidance.

False negative results can also occur, due to taking the sample too early in the disease process (when bacterial load is low), sampling an unaffected segment of lung, or sampling after starting antibiotic therapy.

Taking these factors into account, recent UK guidelines recommend that the least invasive, least expensive and most readily available technique in the clinical setting is satisfactory.² Samples taken before antibiotics are given are more likely to yield a positive result, however, collection of samples should not delay commencing appropriate antibiotic therapy in critically ill patients.

PREVENTATIVE MEASURES

The majority of hospital-acquired infections are preventable by reducing the risk factors associated with their development and paying attention to basic infection control procedures. There is now good evidence supporting basic hand hygiene measures as a means of preventing disease transmission.^{2,3} However, there is a lack of robust evidence supporting many of the other recommended practices.

Recommendations come from the American Thoracic Society (US)¹ and the National Institute of Clinical Excellence (UK)³. One of the most important strategies involves delivery of preventative measures as part of a care bundle with appropriate education and training of all healthcare workers in its delivery. This has been shown to be a cost effective way of improving compliance with preventive measures.

Components of such a care bundle should include:

Prevention of transmission of microorganisms

- Good hand hygiene measures and wear gloves for contact with patient or contaminated secretions,
- No routine changing of ventilator circuits/heat and moisture exchangers unless specifically indicated (malfunction or visible contamination).

Prevention of aspiration related to endotracheal intubation

- Early weaning and daily sedation breaks to reduce the duration of endotracheal intubation and mechanical ventilation as much as possible,
- Avoidance of repeated re-intubations,
- Control of endotracheal cuff pressures between 20-30cmH₂O,
- Use of endotracheal tubes with sub-glottic drainage ports,
- Use of non-invasive ventilation if clinically appropriate.

Prevention of aspiration associated with enteral feeding

- Semi-recumbent positioning (30-45° head up) if possible,
- Confirm correct placement of nasogastric tube prior to use.

Prevention of oropharyngeal colonisation

- Oral hygiene strategy for patients at risk of HAP, including the use of an oral anti-septic agent e.g. chlorhexidine gel.

Selective decontamination of the digestive tract (SDD) involves the use of local and systemic antibiotics to prevent colonisation

of the gastrointestinal (GI) tract with gram-negative bacteria and yeasts, whilst maintaining normal levels of anaerobic flora. Specific regimes vary but most involve the oral administration of a non-absorbable aminoglycoside/anti-fungal, combined with an intravenous cephalosporin. A recent Cochrane review found that SDD was associated with a reduction in both the incidence of HAP and overall mortality.⁴ However, it remains controversial and is not used routinely in the UK, due to concerns over the emergence of drug-resistant bacteria and an increase in the rate of *Clostridium difficile* infections (pseudomembranous colitis).³

TREATMENT – CHOICE AND DURATION OF ANTIBIOTIC THERAPY

The general approach to the treatment of HAP involves prompt initiation of a broad-spectrum empirical antibiotic regime. Minimising any delay between recognition of HAP and initiation of treatment will improve prognosis and reduce length of stay and associated costs. After 48-72 hours, this is followed by de-escalation to a narrower spectrum of cover, guided by culture results.

Empirical antibiotics

The initial choice of empirical antibiotics depends on three factors:

- Timing of onset from admission to hospital (early or late),
- Risk factors for multi-drug resistant organisms,
- Knowledge of local pathogens and patterns of resistance.

In patients with early onset HAP, without risk factors for resistant organisms, antibiotic therapy should cover community-acquired pathogens and non-resistant gram-negative Enterobacteriaceae. For

late-onset HAP or for any patient with risk factors for multi-drug resistant (MDR) pathogens, empirical therapy should be broadened to cover MRSA and other resistant organisms.

Knowledge of local pathogens and patterns of resistance is essential as the most common reason for treatment failure is inadequate initial coverage, leading to further broadening of antibiotic coverage. Not only is this associated with poorer patient outcomes; it also increases the risk of new resistance patterns developing. De-escalation to a narrower spectrum, and preferably single, agent based on culture results, is also important in reducing the development of resistant pathogens.

Antibiotics should be administered intravenously and only stepped down to oral administration in patients with a good clinical response and a functioning GI tract. Aerosolised antibiotics have not been shown to be of any benefit in HAP.^{1,2}

Examples of specific regimes are detailed in Table 2.

DURATION OF ANTIBIOTIC THERAPY

The optimal duration of antibiotic therapy required in HAP is unknown. A large, multi-centre randomised control trial reported similar outcomes in patients with non-MDR organisms treated for 8 days and 15 days.⁵ Patients with MDR pathogens in the 8-day group were more likely to develop a recurrent infection than those in the 15-day group.

In general, 7-10 days is considered a suitable duration for patients with sensitive organisms. Those with resistant organisms may require 14-21 days of therapy. Clinical parameters such as improvement in

Table 2. Suggested empirical antibiotic regimes - MDR = multi-drug resistant.

Onset	Empirical antibiotic therapy	Example
Early onset	2nd/3rd generation cephalosporin or β-lactam/β-lactamase inhibitor or fluoroquinolone	cefuroxime/ceftriaxone amoxicillin + clavulanic acid ciprofloxacin/levofloxacin
Late onset or Risk factors for MDR pathogen	anti-pseudomonal cephalosporin or anti-pseudomonal carbapenam or broad spectrum β-lactam/β-lactamase inhibitor and either aminoglycoside or fluoroquinolone If MRSA suspected glycopeptide or oxazolidinone	ceftazidime meropenem piperacillin + tazobactam (Tazocin) gentamicin ciprofloxacin/levofloxacin vancomycin linezolid
	<i>Linezolid may have better tissue penetration than vancomycin in VAP</i>	

Table 3. Clinical Pulmonary Infection Score (CPIS).

Points	0	1	2
Tracheal secretions	Minimal	Abundant	Purulent
Chest Xray	No infiltrates	Diffuse infiltrates	Localised infiltrates
Temperature (°C)	36.5-38.4	38.5-38.9	≥39 or ≤36
Leukocytes (mm ⁻³)	4000-11000	<4000 or >11000	<4000 or >11000 plus band forms >500
PaO ₂ /FiO ₂ ratio (mmHg)	>240 or ARDS		<240 and no ARDS
Microbiology	Negative		Positive

oxygenation, white cell count and resolution of fever are more reliable in determining response to antibiotics and resolution of infection, than radiographic or microbiological parameters.

The Clinical Pulmonary Infection Score (CPIS) was originally designed as a tool to aid diagnosis of HAP but has been shown to have poor sensitivity and specificity in this role.⁶ However, a modified version can be used as a surrogate measure of response to antibiotic therapy (Table 3). A baseline score of ≥6 is indicative of HAP. Clinical improvement takes at least 48-72 hours. A falling score on day 3 indicates a response to treatment and can help identify patients who may be suitable to receive shorter courses of antibiotics. Of all the components of CPIS, an improvement in arterial oxygenation indicated by the PaO₂/FiO₂ ratio is the most valuable factor in predicting response to treatment.

CONCLUSION

Hospital-acquired pneumonia, in particular ventilator-associated pneumonia, is one of the most common complications associated with intensive care. It significantly contributes to morbidity and mortality, as well as increasing length of hospital stay and overall healthcare costs. Delivering a care bundle of simple preventive measures and ensuring timely initiation of appropriate antibiotics will help ensure better outcomes for patients with HAP.

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An introduction to mechanical ventilation

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INTRODUCTION

One of the main interventions offered in an Intensive Care Unit (ICU) is advanced respiratory support. An understanding of the indications and types of mechanical ventilation is therefore essential for anyone working in this environment.

INDICATIONS FOR MECHANICAL VENTILATION

The main indication for mechanical ventilation is respiratory failure. However, other clinical indications include:

- prolonged postoperative recovery,
- altered conscious level,
- inability to protect the airway, or
- exhaustion, when the patient is likely to develop respiratory failure.

The aim of mechanical/artificial ventilation is to improve gas exchange, to reduce the work of breathing and to avoid complications while maintaining optimal conditions for the patient to recover from their underlying illness. Whatever the indication for respiratory support, the underlying condition of the patient must be reversible; otherwise subsequent weaning may not be possible.

RESPIRATORY FAILURE

This is the primary indication for respiratory support. It occurs when pulmonary gas exchange is sufficiently impaired to cause hypoxaemia (PaO_2 less than 8kPa), with or without hypercarbia. The causes of respiratory failure are diverse and the problem may occur due to disease at the alveolar/endothelial interface (e.g. pulmonary oedema) or failure of the respiratory pump mechanism, resulting in inadequate minute ventilation (e.g. flail segment accompanying fractured ribs). It is difficult to define specific criteria for commencing mechanical ventilation and the decision is a clinical one, influenced by different factors for each patient.

Indications to consider include:

- Respiratory rate > 35 or < 5 breaths per minute,
- Exhaustion with a laboured pattern of breathing,
- Hypoxia - central cyanosis, $\text{SaO}_2 < 90\%$ on oxygen or $\text{PaO}_2 < 8\text{kPa}$,

- Hypercarbia - $\text{PaCO}_2 > 8\text{kPa}$,
- Decreasing conscious level (Glasgow Coma Score < 8),
- Significant chest trauma,
- Tidal volume $< 5\text{ml.kg}^{-1}$ or vital capacity $< 15\text{ml.kg}^{-1}$.

Causes of respiratory failure

Inadequate gas exchange

- Pneumonia, pulmonary oedema, acute respiratory distress syndrome (ARDS).

Inadequate breathing

- Chest wall problems e.g. fractured ribs, flail chest,
- Pleural problems e.g. pneumothorax, haemothorax,
- Respiratory muscle failure e.g. myasthenia gravis, poliomyelitis, tetanus,
- Central nervous system depression e.g. drugs, brain stem compression, head injury.

Obstructed breathing

- Upper airway obstruction e.g. epiglottitis, croup, oedema, tumour,
- Lower airway obstruction e.g. asthma and bronchospasm.

Other indications for ventilation

Patients in this category are ventilated to assist in the management of other, non-respiratory conditions and may include:

- Control of intracranial pressure in head injury,
- Airway protection following drug overdose,
- Following cardiac arrest,
- For recovery after prolonged major surgery or trauma,
- As support when other organs systems are failing – e.g. severe shock or acidosis requiring aggressive therapy.

Summary

Mechanical ventilation is the major invasive intervention offered in the ICU. In low income countries, where the facilities exist, it is appropriate that this therapy is only offered to patients suffering reversible critical illness. The basics of mechanical ventilation are described, with particular focus on overcoming common pitfalls.

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TYPES OF MECHANICAL VENTILATION

The most commonly used type of artificial ventilation is intermittent positive pressure ventilation (IPPV). The lungs are intermittently inflated by positive pressure, generated by a ventilator, and gas flow is delivered through an oral tracheal or tracheostomy tube.

Tracheal intubation is usually achieved by the oral route although nasal intubation may be better tolerated by the patient during prolonged ventilation. Although more secure, nasotracheal intubation is technically more challenging and has a higher incidence of bleeding and infective complications such as sinusitis. Tracheal intubation not only allows institution of IPPV, but also reduces dead space and facilitates airway suctioning. However, it is also possible to deliver positive pressure ventilation to cooperative patients in a non-invasive manner through a tight-fitting face or nasal mask (Non-invasive ventilation, NIV).¹

In general, there are two main modes of ventilation commonly in use in ICU - modes where the ventilator delivers a preset tidal volume, and those that deliver a preset inspiratory pressure, during each inspiration. Modern ventilators allow different modes of ventilation and the clinician must select the safest and most appropriate mode of ventilation for the patient.

Volume-controlled ventilation (or volume-cycled ventilation)

The ventilator delivers a preset tidal volume regardless of the pressure generated. The lung compliance (stiffness) of the lungs determines the airway pressure generated, so this pressure may be high if the lungs are stiff, with the resultant risk of barotrauma. Barotrauma describes

rupture of the alveoli resulting in pneumothorax and mediastinal emphysema, but also describes acute lung injury that can result from over-distension of alveoli (volutrauma).

Pressure-controlled ventilation (or pressure-preset ventilation)

The ventilator delivers a preset target pressure to the airway during inspiration. The resulting tidal volume delivered is therefore determined by the lung compliance and the airway resistance.

MODES OF VENTILATION

Overview

Modern ventilators have a variety of modes that can be selected depending on the patient's illness. For example (see Figure 1) a patient with severe respiratory disease (whether primary or secondary to other disease), who requires ventilation, will initially require full ventilation with mandatory breaths; they will be heavily sedated and may require paralysis. As another example, one of the primary goals of ventilation in a severely head-injured patient is to achieve a low-normal CO₂ level, which requires a controlled minute volume, delivered by fully controlled ventilation.

As the patient's respiratory disease improves, the patient will generate their own respiratory rate and require less positive pressure support during each breath. So, as their clinical state improves, the mode and settings of the ventilator are adjusted to reflect this. In time the low level of support they require will indicate that they are in a fit state for extubation and withdrawal of respiratory support. Figure 1 shows a simplified summary of this process in a theoretical patient.

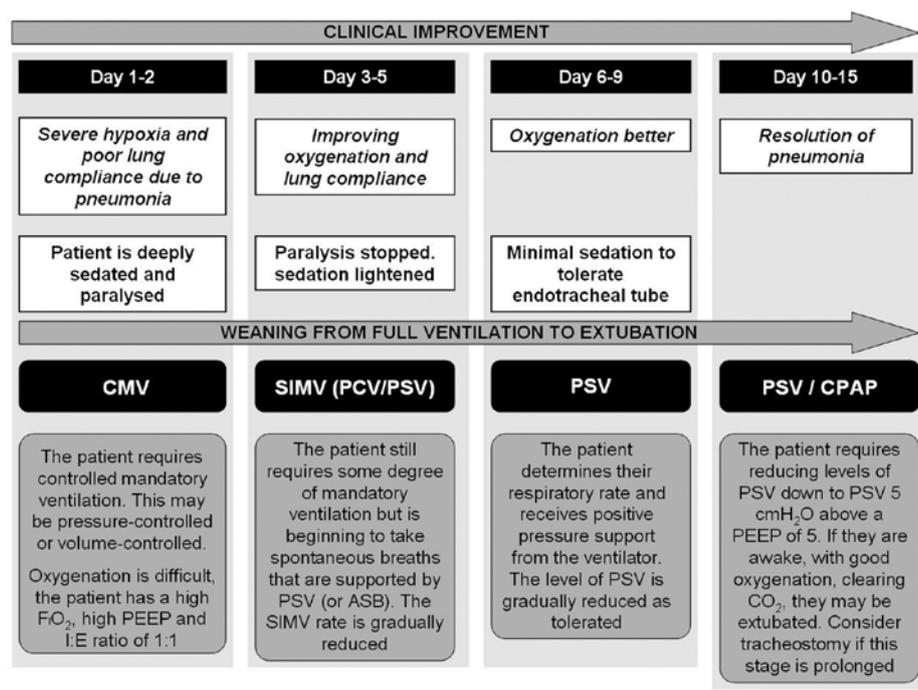


Figure 1. Summary of modification of ventilator mode and settings, mirroring improvement in a theoretical patient's clinical state and respiratory performance; CMV - controlled mandatory ventilation; PSV - pressure support ventilation; ASB - assisted spontaneous breathing; SIMV - synchronised intermittent mandatory ventilation.

In some resource-poor settings, the ventilator used in ICU may offer only a mandatory mode. This is suitable for full ventilation of heavily sedated and paralysed patients, but is poorly tolerated as patients improve, wake up and begin to breathe for themselves. Gradual weaning through SIMV and pressure support ventilation is not possible and so weaning must be achieved through daily 'sedation holds' to see how the patient copes when breathing without ventilatory support, receiving supplemental oxygen from a T-piece. Many of the more modern ICU ventilators, with advanced modes of ventilation, are unsuited to an environment where malfunction is more likely (due to heat, humidity and dust), piped or cylinder air and oxygen may not be available and spare parts and servicing are unavailable or not affordable. Machines designed to run from an electric power source and using oxygen from an oxygen concentrator are available; an example is the HT50[®] ventilator (Newport Medical Instruments, California), however long term use is limited by damage to more fragile parts of the breathing circuit, such as the expiratory valve.



Figure 2. The HT50 ventilator (Newport Medical Instruments, California).

Controlled mechanical ventilation (CMV)

Ventilation with CMV is determined entirely by the machine settings, including:

- the airway pressure/tidal volume,
- respiratory rate and
- inspiratory to expiratory (I:E) ratio.

This mode of ventilation does not allow any synchronisation with the patient's own breathing and is only tolerated when patients are deeply unconscious and paralysed. CMV is normally used in theatre when the patient is receiving a full general anaesthetic to optimise surgical conditions. As described above, in many ICUs in resource-poor settings this may be the only available mode of ventilation on a ventilator that is shared with theatre. In this situation it is often necessary to use deep sedation and muscular paralysis to avoid 'fighting the ventilator' and to allow effective gas exchange.

Assisted mechanical ventilation (AMV)

There are several different modes of ventilation designed to work with

the patients' own respiratory effort. The patient's inspiratory effort is detected as a drop in pressure and triggers the ventilator to 'boost' the inspiratory breath. These modes have two important advantages; first they are better tolerated by the patient and so reduce the requirement for heavy sedation, and second they allow patients to perform muscular work throughout the breath, thereby reducing the likelihood of developing respiratory muscular atrophy. The ventilator-assisted breaths can be supported either by a preset inspiratory pressure or by a preset tidal volume. There are several variations of assisted ventilation.

Intermittent mandatory ventilation (IMV)

This is a combination of spontaneous and mandatory ventilation. Between the mandatory controlled breaths, the patient can breathe spontaneously and unassisted. IMV ensures a minimum minute ventilation, but there will be variations in tidal volume between the mandatory breaths and the unassisted breaths.

Synchronised intermittent mandatory ventilation (SIMV)

With SIMV, the mandatory breaths are synchronised with the patient's own inspiratory effort which is more comfortable for the patient.

Pressure-support ventilation (PSV) or assisted spontaneous breathing (ASB)

A preset pressure-assisted breath is triggered by the patient's own inspiratory effort. This is one of the most comfortable forms of ventilation. The preset pressure level determines the level of respiratory support and can be reduced during weaning. There are no mandatory breaths delivered, and ventilation relies on the patient making some respiratory effort. There is, however, no back up ventilation should the patient become apnoeic, unless this mode is combined with SIMV. The name given to this mode of ventilation is determined by the manufacturer of each machine.

Positive end-expiratory pressure (PEEP)

PEEP should be used with all forms of IPPV. A positive pressure is maintained during expiration, preventing collapse of the distal airways, minimising damage to alveoli by repeated deflation and re-inflation, and also improving the compliance of the lung. PEEP improves arterial oxygenation and, in severe disease (e.g. ARDS), higher levels of PEEP cause sequentially improved oxygenation. However, PEEP causes a rise in intrathoracic pressure and can reduce venous return and so precipitate hypotension, particularly in hypovolaemic patients. With low levels of PEEP (5-10cmH₂O) these effects are usually correctable by intravenous volume loading. In its simplest form PEEP can be achieved using an adjustable valve on the expiratory limb of the breathing circuit. PEEP valves are available that attach to the Ambu-E valve of a simple circuit, used with an Oxford bellows.

Continuous positive airway pressure (CPAP)

CPAP is effectively the same as PEEP but in spontaneously breathing patients. Effective delivery of CPAP requires a source of oxygen in excess of the maximal inspiratory flow in inspiration (usually about 30L.min⁻¹). This is difficult to achieve where the sole source of oxygen is an oxygen concentrator. CPAP is useful for patients with poor oxygenation, but gives no ventilatory support, so does not generally improve CO₂ clearance.

INITIATING MECHANICAL VENTILATION

The act of sedating, paralysing and intubating a critically ill patient is challenging and can result in severe cardiac and/or respiratory compromise or even death. Choose the drugs that you are most familiar with, but aim to use a fraction of the dose that the patient would require when well. Ketamine is useful as an induction agent as it confers some degree of haemodynamic stability. Some intensivists favour a combination of fentanyl and midazolam. Induction of anaesthesia rapidly obtunds the production of endogenous catecholamines in patients who have a high work of breathing; this, for example in otherwise young fit asthmatics with an acute exacerbation, may precipitate profound haemodynamic compromise. For patients on the verge of cardiovascular collapse, it is sometimes safest to intubate using only local anaesthesia, applied topically to the airway and larynx.

When initiating artificial ventilation, the aim is to provide the patient with a physiological tidal volume and ventilatory rate that is adjusted to allow for the demands of their pathological condition. Recommendations for initial ventilator settings are generally derived from the ARDSnet study, that showed that a 'lung protective ventilation strategy' (in ARDS) reduced the contribution that mechanical ventilation made to lung trauma during critical illness.² Bear in mind that it is very difficult to adequately replicate the respiratory compensation of a patient with a severe metabolic acidosis, with mechanical ventilation. Acidosis is likely to worsen in the initial period after intubation and commencement of mechanical ventilation.

Suggested initial ventilator settings are:

- FiO₂ 1.0 initially but then reduce – aim for SaO₂ 93-98%,
- PEEP 5cmH₂O,
- Tidal volume 6-8ml.kg⁻¹,
- Inspiratory pressure 20cmH₂O (15cmH₂O above PEEP),
- Frequency 10-15 breaths per minute,
- Pressure support (ASB) 20cmH₂O (15cmH₂O above PEEP),
- I:E ratio 1:2,
- Flow trigger 2L.min⁻¹,
- Pressure trigger -1 to -3 cmH₂O.

These settings should be titrated against the patient's clinical state and level of comfort. Some conditions require particular consideration. Patients with severe bronchospasm are at risk of dynamic hyperinflation ('breath-stacking') - a prolonged expiratory phase means that the next inspired breath occurs before full expiration has taken place. The result is high intra-thoracic pressures, with worsening lung compliance and haemodynamic collapse. Initial ventilation should be by hand, using a bag-valve-mask, with auscultation to ensure expiration is complete

- the required ventilatory rate to allow this may be as slow as 3 to 4 breaths per minute. For all patients in whom effective ventilation is difficult due to obstructive disease or due to poor compliance, the CO₂ should be allowed to rise in order to avoid excessive high pressure ventilation. This *permissive hypercapnea* is tolerated until it causes a dangerous level of acidosis.

OPTIMIZING OXYGENATION

When settling a patient on the ventilator, it is sensible practice to initially set the FiO₂ at 1.0 (100%) and then wean rapidly to a FiO₂ adequate to maintain SaO₂ of > 93%. An FiO₂ of greater than 0.6 for long periods should be avoided if possible because of the risk of oxygen-induced lung damage.

PEEP

Strategies to improve oxygenation (other than to increase FiO₂) include increasing the mean airway pressure by either raising the PEEP to 10cmH₂O or, in pressure-preset ventilation modes, by increasing the peak inspiratory pressure. However, care should be taken to avoid very high inflation pressures (above 35cmH₂O) as this may cause barotrauma to the lungs. In severe hypoxia, it may be possible to improve oxygenation by increasing the PEEP further to 15cmH₂O (or above) and using small (6-8ml.kg⁻¹) tidal volumes more frequently. However, this may cause a reduction in blood pressure and may be poorly tolerated by the patient, requiring intravenous fluid loading and inotropic or vasopressor therapy. The PEEP strategy employed in the ARDSnet trial is widely used as a guide to application of appropriate levels of PEEP and is shown in Box 1.²

Altering the I:E ratio

Because oxygenation is largely determined by the mean airway pressure through the respiratory cycle, prolonging the inspiratory time may improve this. This is achieved by increasing the I:E ratio (to 1:1) or even inverting the ratio (e.g. to 1.5:1 or 2:1). Heavy sedation and paralysis are usually required for this. Ensure that sufficient time is allowed for expiration.

Lung recruitment strategies

Improvements in oxygenation can be achieved by exposing the lungs a higher pressure for a short period of time. An example of such a recruitment manoeuvre is to apply high CPAP at 40cmH₂O for 40 seconds.

Prone positioning

Placing the patient face down (prone) whilst well sedated may improve oxygenation by re-expanding collapsed alveoli and improving the distribution of blood perfusion in the lung relative to ventilation. In this position, patient monitoring and care is difficult, and this approach should be undertaken with caution. There is a high risk of dislodging tubes or cannulae whilst rolling, and the patient should

Box 1. Guide to acceptable levels of PEEP²

FiO ₂	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	20-24

not remain in the prone position for more than 18 hours in every 24-hour period. Patients should have all pressure areas protected (eyes, nose, neck, shoulders, thorax, pelvic area, knees) whilst allowing free diaphragmatic and abdominal movement to prevent high abdominal pressures.

Airway pressure release ventilation (APRV)

The ventilator alternates a high PEEP (e.g. 20cmH₂O) for long periods (e.g. 3-4 seconds), with low PEEP (e.g. 5cmH₂O) for short periods (e.g. 1 second). This maintains recruitment of lung tissue, and the patient can take further breaths during the high pressure period. However carbon dioxide removal can be difficult and achieving optimal sedation for the patient to breathe on top of the ventilator breaths can be problematic.

Other methods of ventilation which may improve oxygenation, are detailed at the end of the article.

OPTIMISING CARBON DIOXIDE ELIMINATION

Carbon dioxide elimination is improved by increasing minute ventilation, either by increasing the tidal volume or the respiratory rate. Aiming for a normal level of carbon dioxide may require high minute volumes and can be hard to achieve in sick patients. The PaCO₂ is usually allowed to rise, causing a respiratory acidosis. This is termed *permissive hypercapnia* and can be accepted as long as the blood pH does not fall below 7.20. This level of acidosis is usually well tolerated.

Sedation

Most patients require sedation in order to tolerate the endotracheal tube. Ideally, only light sedation should be given so that the patient can understand and cooperate with ventilation, while continuing to make some respiratory effort.

PROBLEMS DURING MECHANICAL VENTILATION

'Fighting the ventilator'

When a patient starts to breathe out of phase with the ventilator or becomes restless or distressed during IPPV, there is a fall in the delivered tidal volume, due to a rise in respiratory resistance. This may result in inadequate ventilation and hypoxia. Factors to consider include:

- *Patient factors* - breathing against the ventilator's inspiratory phase, breath holding and coughing.
- *Decreased pulmonary compliance* - pulmonary pathology, including oedema or infection and pneumothorax.
- *Increased airway resistance* - bronchospasm, aspiration, excess secretions
- *Equipment* - ventilator disconnection, leak, failure. ET tube blocked, kinked, dislodged.

Management of a patient 'fighting the ventilator'

Is the patient hypoxic? If yes - follow ABC:

- Is the endotracheal tube patent and correctly positioned? Reintubate if necessary.
- Give 100% O₂ by manual ventilation via self-inflating bag.

- Check chest expansion is adequate.
- Auscultate chest to assess bilateral air entry.
- Check heart rate and blood pressure.
- Check ventilator and apparatus for disconnection/leak/failure.

Diagnosing the problem

High airway pressure due to blocked ET tube

- The patient may be biting the tracheal tube - insert oral airway and sedate patient.
- Tube is blocked by secretions - suction with catheter and consider irrigation with 5ml saline. Change ET tube if necessary.
- ET tube over-inserted into right main bronchus - pull tube back.

High airway pressure due to intrapulmonary factors

- Is there evidence of bronchospasm? Ensure ET tube not over-inserted, stimulating the carina. Give bronchodilators.
- Is there evidence of pneumothorax, haemothorax, lung collapse or pleural effusion? Examine, request chest Xray and treat appropriately.
- Is there pulmonary oedema? Treat with diuretics, treat cardiac failure or arrhythmias.

Sedation/analgesic factors

- Is the patient hyperventilating due to hypoxia or hypercarbia (cyanosis, tachycardia, hypertensive and sweating). Increase FiO₂ and increase the mean airway pressure with PEEP. Increase minute ventilation (if hypercarbic).
- Coughing, discomfort or pain (raised heart rate and blood pressure, sweating and grimacing). Look for causes of discomfort, e.g. endotracheal tube irritation, full bladder, pain. Review analgesia and sedation. Change ventilation mode to one better tolerated e.g. SIMV, PSV. Neuromuscular blockade - only if all other options explored.
- Ideally sedation is delivered by infusion pumps - commonly propofol is used with an infusion of an opioid such as morphine. Where pumps are not available regimes of intramuscular benzodiazepine and intramuscular opioid are used, although this technique is associated with periods of over-sedation and periods of under-sedation.

PROVIDING OPTIMAL VENTILATION AND PREVENTING HARM

There is no single correct form of ventilation - each clinician has their favourite method, depending on the clinical circumstances. However, mechanical ventilation can cause harm, so where possible the following should be considered:

- Check the ET tube cuff pressure if possible, and aim to keep between 30-60cmH₂O. If there is a leak from the ETT, then the

cuff is either deflated or damaged and the ET tube should be replaced.

- Position the patient 30° head up, to reduce oesophago-gastric reflux and the risk of ventilator-associated pneumonia.
- Keep peak inspiratory pressure less than 35cmH₂O, regardless of the mode of ventilation.
- Aim to have a peak plateau pressure of less than 30cmH₂O.
- Tidal volumes should be 6-8ml.kg⁻¹ of *ideal* body weight.
- Avoid high respiratory rates if possible - these can worsen atelectrauma.
- Avoid hyperoxia as far as possible – aim SaO₂ 93-98%, or PaO₂ 8-10kPa.
- Use all of the monitoring that you have available in order to ensure that the patient remains haemodynamically stable whilst ventilated. Set the alarms to provide you with information on clinically relevant changes in the measured variables. In particular, it is recommended that, where available, all ventilated patients are monitored with capnography in order to detect problems with ventilation early.
- Aim to avoid the patient fighting the ventilator, especially in the early stages of their illness.
- Provide a sedation break every day, unless maintaining optimal ventilation is absolutely critical (e.g. when prone or using neuromuscular blockade).
- Maintain a negative fluid balance in ARDS using diuretics, unless there is critical renal function which cannot be supported. This will not be possible early in a septic illness where volume resuscitation is paramount.
- Use prophylaxis for GI ulcers – although these raise the gastric pH and make ventilator-associated pneumonia more likely, the mortality from GI bleeding is high. Nasogastric feed should be used to prevent gastric ulcers and to mitigate weight loss in critically ill patients.
- Use thromboprophylaxis for venous thrombosis. Pulmonary embolism is common and high risk in critically ill patients. A combination of compression stockings, mechanical calf pumps and pharmacological prophylaxis is best if possible.
- Maintain oral hygiene, preferably using chlorhexidine mouthwash. These reduce the oral flora and aim to reduce the incidence of ventilator-associated pneumonia
- Reduce ventilator settings, sedation and other organ support whenever possible during weaning.

WEANING FROM VENTILATION

There are a number of complications associated with mechanical ventilation, including barotrauma, pneumonia and decreased cardiac output. For these reasons, it is essential to discontinue ventilatory support as soon as the patient improves. Indeed in most resource-poor settings, prolonged ventilation is unsustainable and inappropriate.

Weaning is indicated when the underlying condition is resolving. Many patients are ventilated for a short period or time, for example those recovering from major surgery, whereas others are ventilated for many days (e.g. for ARDS). During long periods of prolonged ventilatory support, the respiratory muscles weaken and atrophy. As a consequence, the speed of weaning is often related to the duration and mode of ventilation. Assisted modes of ventilation and good nutritional support are important to prevent atrophy of the respiratory muscles.

Patients recovering from prolonged critical illness are at risk of developing critical illness polyneuropathy. In this condition, there is both respiratory and peripheral muscle weakness, with reduced tendon reflexes and sensory abnormalities. Treatment is supportive. There is evidence that long-term administration of some aminosteroid muscle relaxants (such as vecuronium) may cause persisting paralysis. For this reason, vecuronium should not be used for prolonged neuromuscular blockade.

Indications for weaning

The decision to start weaning is often subjective and based on clinical experience. However, there are some guidelines that may be helpful:

- Underlying illness is treated and improving.
- Respiratory function:
 - Respiratory rate < 35 breaths per minute,
 - FiO₂ < 0.5, SaO₂ > 90%, PEEP < 10cmH₂O,
 - Tidal volume > 5ml.kg⁻¹,
 - Vital capacity > 10ml.kg⁻¹,
 - Minute volume < 10L.min⁻¹.
- Absence of infection or fever.
- Cardiovascular stability, optimal fluid balance and electrolyte replacement.

Prior to weaning, there should be no residual neuromuscular blockade and sedation should be minimised so that the patient can be awake, cooperative and in a semirecumbent position. Weaning is likely to fail if the patient is confused, agitated or unable to cough.

Modes of weaning

There is debate over the best method for weaning and no one technique has been found to be superior to others. There are several different approaches.

Unsupported spontaneous breathing trials

The machine support is withdrawn and a T-Piece (or CPAP) circuit can be attached intermittently for increasing periods of time. The patient gradually takes over the work of breathing, with shortening rest periods back on the ventilator.

Intermittent mandatory ventilation (IMV) weaning

The ventilator delivers a preset minimum minute volume which is gradually decreased as the patient takes over more of the respiratory workload. The decreasing ventilator breaths are synchronised to the patient's own inspiratory efforts (SIMV).

Pressure support weaning

In this mode, the patient initiates all breaths and these are 'boosted' by

the ventilator. This weaning method involves gradually reducing the level of pressure support, thus making the patient responsible for an increasing amount of ventilation. Once the level of pressure support is low (5-10cmH₂O above PEEP), a trial of T-Piece or CPAP weaning should be commenced.

Failure to wean

During the weaning process, the patient should be observed for early indications of fatigue or failure to wean. These signs include distress, increasing respiratory rate, falling tidal volume and haemodynamic compromise, particularly tachycardia and hypertension. At this point it may be necessary to increase the level of respiratory support as, once exhausted, the respiratory muscles may take many hours to recover.

It is sensible to start the weaning process in the morning to allow close monitoring of the patient throughout the day. In prolonged weaning, it is common practice to increase ventilatory support overnight to allow adequate rest for the patient.

Tracheostomy in the intensive care unit

The commonest indication of tracheostomy in an ICU setting is to facilitate prolonged artificial ventilation and the subsequent weaning process. Tracheostomy allows a reduction in sedation and thus increased cooperation with weaning. It also allows effective tracheobronchial suction in patients who are unable to clear pulmonary secretions, either due to excessive secretion production or due to weakness following critical illness. Oral hygiene is improved and the shorter tracheostomy tube aids weaning.

OTHER METHODS OF VENTILATION

Some patients have such severe respiratory illness that the techniques above cannot provide sufficient oxygen to prevent organ failure. In this situation there are a number of other techniques that may be used, although an improvement in mortality for these techniques has not been shown.

High frequency oscillatory ventilation

This mode maintains high mean airway pressures (24-40cmH₂O) with very fast respiratory oscillations (3-15Hz). Therefore there is no 'tidal volume', as the volume of gas moving with each oscillation is very small. The method of gas flow in this mode is very complex and cannot be compared to normal mechanical ventilation. Problems include hypercapnia, thick tenacious secretions with mucous plugging, barotrauma, the requirement for heavy sedation and neuromuscular blockade and hypotension from increased intra-thoracic pressure necessitating fluid loading and inotropic support.

CONCLUSION

The ability to offer short term ventilatory support for patients with reversible respiratory failure is a major feature of intensive care management. This article has outlined the very basics of ventilatory management. Each clinician must become familiar with the machines available to them and develop strategies to institute and wean ventilation safely. It is vital that each unit has clearly defined criteria to decide which patients will benefit from ventilatory support. In resource poor settings prolonged ventilation does not represent appropriate use of medical resources and for each patient there must be a good prospect for successful and timely weaning of ventilation.

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Tracheostomy

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INTRODUCTION

Tracheotomy refers to the surgical opening of the trachea, while tracheostomy refers to the creation of a stoma at the skin surface, which leads to the trachea. Tracheostomies may be temporary or permanent. A temporary tracheostomy may be used as a permanent tracheostomy, however there will still be a communication between the pharynx and the lower airway via the larynx.

INDICATIONS FOR TRACHEOSTOMY

Upper airway obstruction

This is no longer the most common indication for tracheostomy, owing to the improvement in designs of intubating laryngoscopes and alternative management strategies. Upper airway obstruction may be caused by swelling resulting from burns, anaphylaxis, trauma or infection or as a direct result of facial trauma or fractures.

Prolonged ventilation

This is now the most common indication for tracheostomy, certainly in the intensive care setting. A tracheostomy is a more secure airway and decreases dead space, which facilitates weaning from ventilation. The timing of tracheostomy for this purpose is still controversial (see later).

To provide pulmonary toilet and/or to protect the airway.

Tracheostomies may sometimes be performed for conditions associated with excessive tracheo-bronchial secretions requiring regular secretion clearance by suction. Examples are bulbar palsy, infections or neurological conditions where cough and swallow are impaired.

Tracheostomy may also be indicated as part of another procedure, for example, head and neck surgery.

EFFECTS OF A TRACHEOSTOMY

- The larynx is bypassed and so the patient is unable to speak.
- There is decreased anatomical and respiratory dead space, decreasing the work of breathing.

- There is loss of humidification and filtration function by the nasal mucosa.
- There is an increased risk of respiratory tract infection.
- There is a redundant area above tracheal opening and below the larynx in which mucus can accumulate and fall back into the lungs.
- A foreign body reaction can occur, causing local inflammation.

TIMING OF TRACHEOSTOMY IN CASES OF PROLONGED VENTILATION

The timing of tracheostomy remains an issue of debate. In a study of tracheostomy in mechanically ventilated adult ICU patients, Terragni et al found no statistically significant difference in the rates of ventilator-associated pneumonia with early tracheostomy (after 6-8 days of laryngeal intubation) versus late tracheostomy (after 13-15 days of laryngeal intubation).¹

Meanwhile a large, retrospective cohort analysis including nearly 11,000 critically ill patients evaluated the impact of tracheostomy timing on mortality. The authors found a slight overall improvement in survival in patients who underwent tracheostomy within the first 10 days of intubation.²

The TracMan study was carried out in the United Kingdom to assess the impact of early (day 1-4 of ICU admission) versus late (day 10 or later) tracheostomy.³ The study included 909 patients from 87 UK hospitals who were expected to stay 7 days or more in the ICU, between March 2006 and December 2008. Patients were randomised to early (n=455) or late (n=454) tracheostomy. Patient characteristics were similar across both groups, with respiratory failure the most common cause of admission to the ICU.

There was no significant difference in mortality between the early and late tracheostomy groups at 30 days (139 versus 141 deaths) or at 2 years post randomisation, with a 74% follow up rate. There was also no significant difference in ICU or hospital length of stay and no significant difference in antibiotic use. However, mean days of sedation were predictably reduced - to 6.6 days in the early group, compared with 9.3 days in the late group.

Summary

This article describes the indications for this relatively common ICU procedure. It is of particular importance that ICU staff know how to manage airway emergencies in patients with tracheostomy. An example of a management algorithm is included.

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At the study's presentation, at the 29th International Symposium of Intensive Care and Emergency Medicine, the lead author stated the following: "If you had 100 patients requiring tracheostomy, doing it early results in 2.4 days less sedation overall, but you would perform 48 more, with 3 more procedural complications and no effect on mortality or ICU length of stay."

TECHNIQUES FOR INSERTION

Tracheostomy may be performed using a percutaneous or an open surgical technique.

Percutaneous tracheostomies are performed by anaesthesiologists or intensivists, usually under fiberoptic bronchoscopic guidance. Open surgical tracheostomies are performed by ENT surgeons and in some countries, trauma surgeons. Percutaneous tracheostomy was first described in the late 1950s and 1960s, but received widespread acceptance following introduction of commercial kits.

Two initial techniques were described – a serial dilatational technique described by Ciaglia et al in 1954 and a guidewire dilating forceps (GWDF) method described by Griggs and colleagues in 1990. In 2000, Byhahn et al modified the Ciaglia technique by introducing the 'Blue Rhino'.⁵ This hydrophilically coated, curved dilator allows progressive dilatation of the tracheal stoma in a single step, reducing the risk of posterior tracheal wall injury, intraoperative bleeding and the adverse effect on oxygenation during repeated airway obstruction by sequential dilators.



Figure 1. The Blue Rhino single stage dilator (Cook Medical).

Percutaneous tracheostomy insertion

Many commercial kits are available but they all employ a Seldinger guidewire technique for tracheostomy tube insertion. Techniques may vary slightly, depending upon operator preference and experience. A full description of this technique is beyond the scope of this article.

CAUTIONS AND RELATIVE CONTRAINDICATIONS FOR PERCUTANEOUS TRACHEOSTOMY⁶

The relative contraindications are subject to the experience and clinical judgement of the operator and are not set in stone.

Box 1. Contraindications to percutaneous tracheostomy

Emergency airway access (cricothyroidotomy preferred)

Difficult anatomy

- Morbid obesity with short neck
- Limited neck movement
- Cervical spine injury – suspected or otherwise
- Aberrant blood vessels
- Thyroid or tracheal pathology

Moderate coagulopathy

- Prothrombin time or activated partial thromboplastin time greater than 1.5 times the reference range
- Platelet count less than 50 000 per mL

Significant gas exchange problems

e.g. PEEP > 10cmH₂O or FIO₂ greater than 0.6

Evidence of infection in the soft tissues of the neck at the insertion site

Age less than 12 years

CARE OF THE TRACHEOSTOMY

Changing tracheostomy tubes

While changing a tracheostomy tube can be hazardous, failing to change one when required also carries risks. Guidance from the Intensive Care Society points out that recommendation regarding the timing of tube changes is inconsistent and not evidence based.⁶

It is recommended that tracheostomies without inner tubes be changed every 7-14 days, with the frequency decreasing as the stoma becomes better formed and pulmonary secretions decrease. EEC guidance, from 1993, states that tracheostomies with inner tubes may be left in place for up to thirty days.

The first change should not occur within 72 hours of the tracheostomy being sited and ideally not for 7 days after a percutaneous insertion. This is to allow for the formation of a more reliable 'track' for the new tube to pass through. Emergency airway equipment, including a smaller tracheostomy tube and emergency drugs, should be immediately available during the change.

The tracheostomy tube may be changed over a soft suction or airway exchange catheter or soft tipped Ryle's tube. The use of a rigid gum-elastic bougie for this purpose may increase the risk of creating a false passage (i.e. the new tracheostomy comes to lie next to, rather than within, the trachea). If a soft tipped Ryle's tube or similar is used, it may be reassuring to see fogging within that tube with respiration. This will help to confirm that the exchange tube is in the airway and not in a false passage prior to passing the new tracheostomy tube. Alternatively, the track may be gently dilated with a gloved little finger.

There should be a low threshold for suspicion of erroneous placement if it is difficult to ventilate the patient. If difficulty is encountered in replacing the tracheostomy tube, the clinical need for a tube must be re-assessed. If in doubt, re-intubation with an oral endotracheal tube may be required.

Humidification

Cold and unfiltered air is an irritant when inhaled and can lead to increased production and viscosity of secretions. This can be uncomfortable for the patient as well as causing tracheal mucosal keratinisation. The increasingly viscous secretions will be difficult to clear, causing sputum retention, atelectasis, impaired gas exchange and even life threatening blockage of the tracheostomy tube. It is therefore essential that inhaled oxygen is appropriately humidified using conventional techniques such as heat and moisture exchange (HME) filters or heated water baths.

Nutrition

It is conventional to feed intubated, ventilated patients enterally unless there is a good reason not to. This is usually via a nasogastric or nasojejunal tube, but it may be possible for patients with tracheostomies to be fed orally. However, swallowing is still adversely affected by the presence of a tracheostomy tube, which has a tendency to limit normal movement of the larynx. In addition, the inflated cuff causes a sense of pressure in the upper oesophagus and the difficulty that occurs with swallowing may result in an increased risk of aspiration of food into the lungs.

Patients may be fed orally, with the cuff inflated or partially deflated, but staff must be alert to signs of aspiration, such as coughing, increased secretions and impaired gas exchange. It is prudent to commence with sips of water and some form of swallowing assessment.

FEATURES OF TRACHEOSTOMY TUBES

The important features of a tracheostomy tube are as listed below:

Diameter

The tracheostomy tube has an inner and an outer diameter. The size of the tracheostomy tube refers to the internal diameter (ID) and ranges from 5.0mm to 9.0mm in adult practice. The size quoted is for the outer tube for single lumen devices, and the inner tube for double lumen devices, but only if the internal cannula is required for connection to a breathing circuit (Figure 2).



Figure 2. A standard, single cannula, size 7.0 tracheostomy tube.

Cuff

The cuff reduces aspiration and leakage of air during anaesthesia and positive pressure ventilation. The tube can be changed to an uncuffed tube when mechanical ventilation is not required or when there is deemed to be minimal risk of aspiration. Whilst most patients can be weaned by simply deflating the cuff, it may still restrict airflow around the tube and changing to an uncuffed or smaller tube may help.

Inner tube

The inner tube has the advantage of being easily and quickly removed to relieve life threatening obstruction due to blood clots or secretions. This is balanced by the slight reduction in internal diameter, which can result in increased work of breathing and lengthened weaning. It is recommended that dual cannula tubes should be used whenever possible because of this safety advantage (Figure 3).

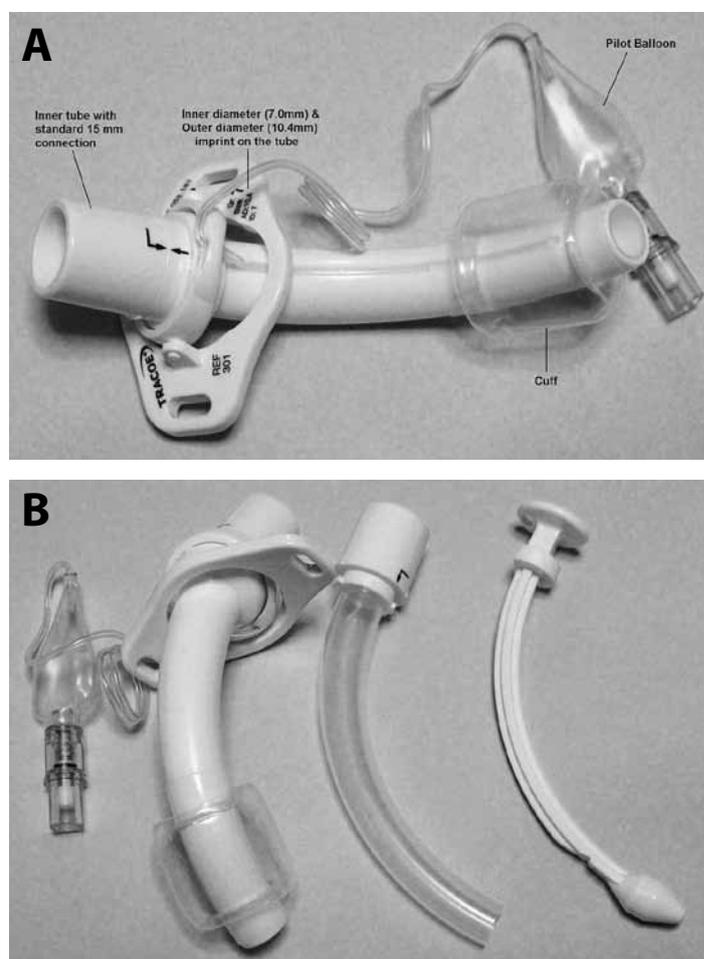


Figure 3. Standard, dual cannula tracheostomy tube, A - assembled; B - disassembled, with outer cannula (left), inner cannula (centre) and obturator (right). (Copyright: Dr Rakesh Bhandary).

Fenestration

Fenestrations maybe be single or multiple and are positioned at the site of maximum curvature of the tracheostomy tube. These aid speech by allowing airflow through the fenestration into the larynx. The fenestration needs to be well placed for each patient's anatomy, in order to work well. Simply deflating the cuff is an alternative

approach in patients who do not require positive pressure respiratory support (Figure 4).

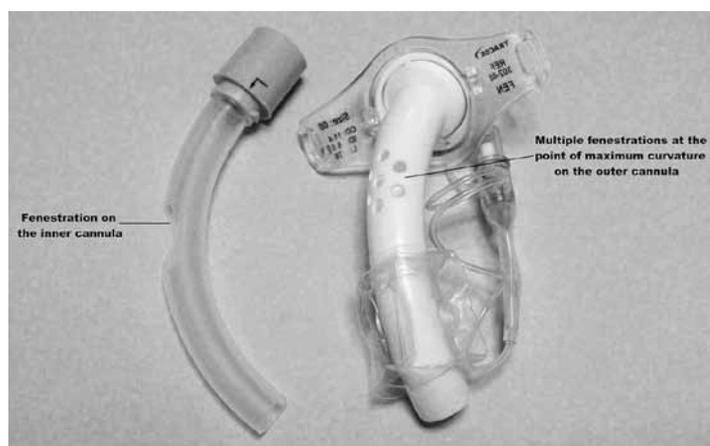


Figure 4. A fenestrated dual cannula tracheostomy tube (Copyright: Dr Rakesh Bhandary).

Flexibility

Flexible or reinforced tracheostomy tubes resemble reinforced endotracheal tubes. They are used in patients where a rigid tube may lie at an angle and cause abrasion or tube obstruction as its lumen abuts the posterior tracheal wall.

Adjustable flange

The length of the tube from the tracheal lumen to the position of the stoma on the exterior can be adjusted in this variation of the tracheostomy tube. This is useful in obese patients or those with local tissue swelling, where the soft tissue depth is increased (Figure 5).

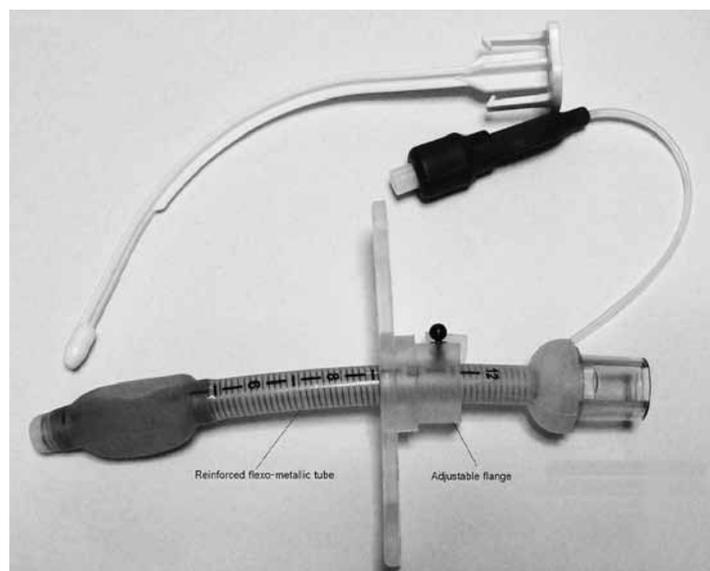


Figure 5. An adjustable flange, flexible tracheostomy tube (Copyright: Dr Rakesh Bhandary).

Subglottic suction

Some newer tracheostomy tubes include a subglottic suction port, the aim of which is to try and reduce the incidence of ventilator-associated pneumonia.

Speaking valve

Speaking valves (like the Passy Muir valve) are one-way valves that are designed to be used with fenestrated tracheostomy tubes or unfenestrated tubes (with the cuff deflated). They allow inspiration but not expiration. Hence the expired air is forced through the larynx allowing the patient to phonate (Figure 6).



Figure 6. A Passy Muir speaking valve. This is inserted into the external orifice of the tracheostomy tube (Copyright: Dr Rakesh Bhandary).

COMPLICATIONS OF TRACHEOSTOMY

Complication rates range between 4% and 31% for percutaneous tracheostomy and 6% to 66% for surgical tracheostomy.⁷ Kost in 2005 reported on the use of percutaneous tracheostomy in 500 consecutive intubated adults in the intensive care unit.¹⁰ When this procedure was performed in conjunction with bronchoscopy, she stated the complication rate as acceptably low (9.2%). No serious complications (pneumothorax, pneumomediastinum, death) occurred. The 2 most common complications were oxygen desaturation in 14 patients (defined as a drop [even transient] to less than 90%) and bleeding in 12 patients (when intervention was required to control the bleeding).

This is one of many studies that demonstrate a favourable complication rate for the percutaneous method compared to the surgical method.

The complications of tracheostomy can be grouped as immediate, intermediate and long-term and are listed overleaf

Immediate or early complications

Bleeding is the most common and the most commonly fatal complication of tracheostomy. The incidence is higher in an emergency procedure. Intraoperative bleeding is commonly due to cut edges of the vascular thyroid gland, anterior jugular vessels or inferior thyroid vessels; bleeding in the immediate postoperative period may be exacerbated by emergence from anaesthesia and hypertension. Vasoconstrictors infiltrated during the procedure may also be wearing off.

Table 1. The different types of commonly used tracheostomy tubes.

Make	Material	Inner tube	Cuffed / uncuffed	Fenestration	Speaking valve	Flexibility
Portex	Polyurethane	No	Both	No	Yes	Rigid
Shiley	PVC	Yes	Both	Both	Yes	Rigid
Tracoe	Polyurethane	Yes	Both	Both	Yes	Rigid
Bivona	Silicone	No	Cuffed	No	No	Flexible
Negus	Silver	Yes	Uncuffed	Both	Yes	Rigid

Although this may necessitate a return to the operating room, bleeding may be controlled with pressure, local packing – perhaps with dressings or Kaltostat soaked in dilute adrenaline, sutures or hypertension control.

Major bleeding can cause cardiovascular compromise, but may also cause respiratory difficulties, particularly if clots form and obstruct any part of the airway. In this situation, control of the airway should be achieved by conventional intubation, making sure that the cuff of the endotracheal tube is below the stoma. This may require an uncut tube. Surgical exploration is then necessary.

Other early recognised complications include pneumothorax, which may result from direct injury to pleura, pneumomediastinum and injury to local structures like recurrent laryngeal nerve, cartilages and oesophagus.

Malposition of the tracheostomy is always possible but should, in theory, be minimised by the use of fiberoptic bronchoscopy for percutaneous insertions.

Intermediate complications

Delayed haemorrhage may be due to displaced blood clots or ligatures, infective erosion into a blood vessel or rarely from a tracheoinnominate

fistula, which may result from a long tube or low tracheostomy. As with an endotracheal tube, the tracheostomy tube may also cause tracheal mucosal necrosis at the level of the cuff. The tube may also erode into the surrounding structures leading to tracheoesophageal fistula, pneumothorax or pneumomediastinum. Surgical emphysema may also be seen due to tight closure of tissue around the tube, tight packing material around the tube, or the false passage of the tube into pretracheal tissue.

Delayed complications

Tracheal stenosis may occur at the level of the stoma due to collapse of the cartilaginous ring or at the level of the tube cuff, due to mucosal necrosis and fibrosis. Modern high volume low-pressure cuffs have reduced the incidence of tracheal stenosis.

A tracheal granuloma may develop or healing may be delayed, leading to a persistent tracheocutaneous fistula or sinus. Sometimes, patients fail occlusion trials or even decannulation for no apparent reason. Possibilities to consider include an obstructing granuloma previously held out of the way with the tube, bilateral vocal cord paralysis, fractured cartilage, and anxiety. Evaluation should include fiberoptic laryngoscopy and bronchoscopy through the stoma.

Table 2. Complications of tracheostomy.

Immediate	Intermediate	Long-term
Aspiration	Delayed haemorrhage	Tracheal stenosis
Haemorrhage	Tube displacement	Decannulation problem
Air embolism	Surgical emphysema	Tracheocutaneous fistula
Failure of procedure	Pneumomediastinum	Disfiguring scar
Structural damage to tracheal rings	Pneumothorax	
	Infection	
	Tracheal necrosis	
	Tracheoarterial fistula	
	Tracheoesophageal fistula	
	Dysphagia	

EMERGENCY MANAGEMENT OF A DISPLACED OR BLOCKED TRACHEOSTOMY TUBE

This complication can be fatal and it is important that those caring for patients with a tracheostomy are alert to its clinical presentation and are familiar with a plan for its management.

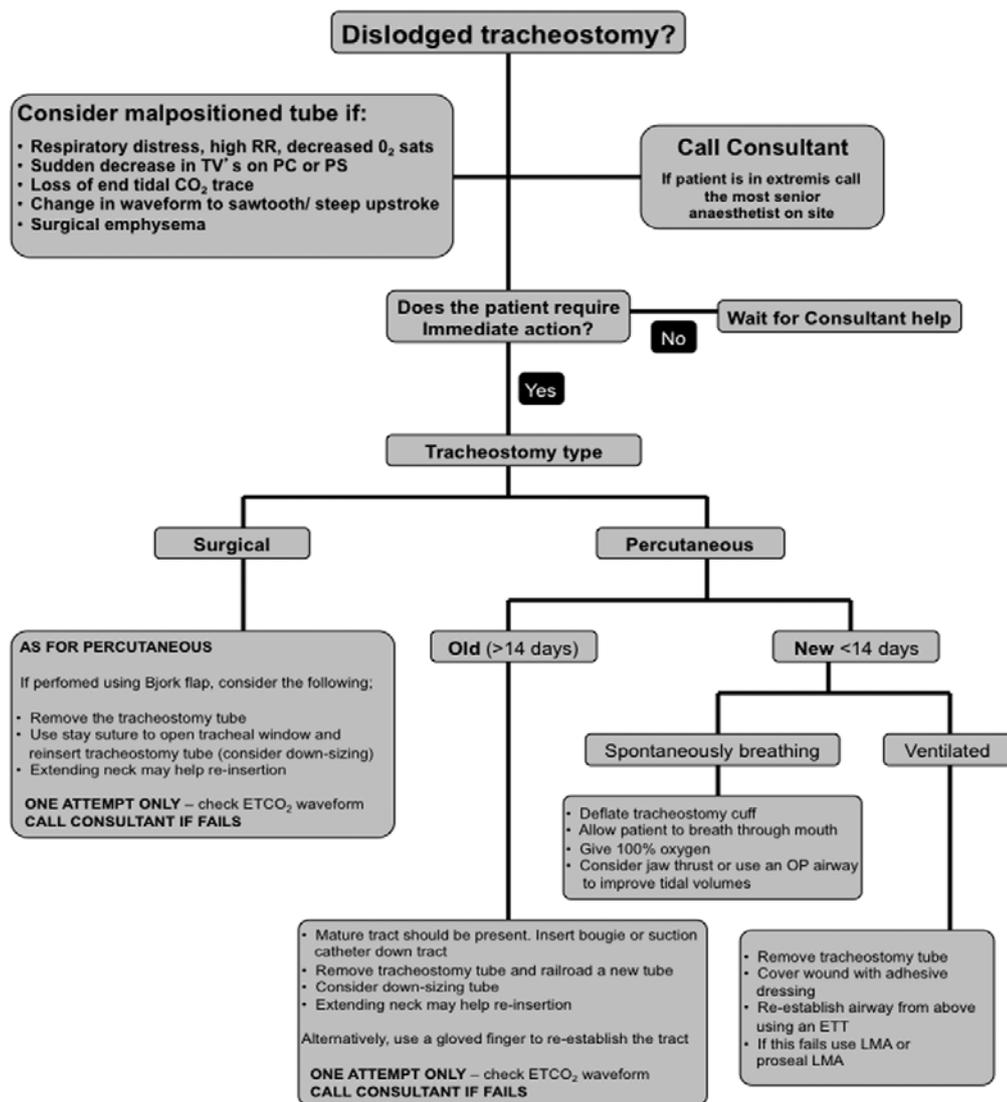
The Royal College of Anaesthetists and Difficult Airway Society recently published the results of the National Audit Project 4 – Major Complications of Airway Management in the United Kingdom.⁹ In its Executive Summary, the authors made the following comment on

the management of displaced tracheostomies:

‘Displaced tracheostomy, and to a lesser extent displaced tracheal tubes, were the greatest cause of major morbidity and mortality in ICU. Obese patients were at particular risk of such events and adverse outcome from them. All patients on ICU should have an emergency re-intubation plan.’

An example of an emergency management plan is illustrated in Appendix 2 of the audit’s report whilst another example is provided in Figure 7.

Critical Care Algorithm for Dislodged Tracheostomy Tube



Re-inserting a tracheostomy tube into a false passage and ventilating through it will lead to surgical emphysema and may make laryngoscopy impossible. **Avoid multiple attempts.** Consider establishing an airway from above **early rather than late.**

The **Bjork flap** is a U-Shaped flap sutured to the lower skin edge producing a well defined tract. Upward and lateral traction on stay sutures placed through the tracheal wall on either side of the tracheostomy will facilitate replacement of the tracheostomy

Figure 7. An algorithm for managing a displaced tracheostomy tube. Reproduced with kind permission of Dr Peter Ford, Dept of Anaesthesia, Royal Devon & Exeter NHS Foundation Trust, UK.

Both of these algorithms share some common themes. Understanding that this can become a rapidly fatal complication, emphasis is placed on recognising the clinical picture of a patient with a displaced or blocked tracheostomy tube and calling for senior help early. Advice is given on how and when to attempt to replace the tracheostomy tube but, if in any doubt, the tube should be removed and attempts should be made to maintain and secure the airway from above using a facemask, supraglottic airway devices and ultimately, oral endotracheal intubation.

WEANING AND DECANNULATION

The tracheostomy tube should be removed as soon as is feasible. Decannulation allows the patient to resume breathing through the upper airway and reduces dependence (psychological and otherwise) on the lower resistance of the tracheostomy tube.

There are many ways of assessing the adequacy of breathing around the tracheostomy tube. Patients can be trialled with increasing periods of cuff deflation. This allows patients to become re-accustomed to swallowing more normally and to having to clear their own secretions.

Alternatively, an occlusion cap may be used which completely blocks the tracheostomy tube. This must be used with a fenestrated tube or an unfenestrated tube with the cuff deflated, and this greatly increases the work of breathing, due to the increased airway resistance. It is harder for patients to breathe in this situation than without the tracheostomy in place and this must be taken into account when interpreting the success or failure of such a trial.

Decannulation can be carried out when:

- The patient is not dependent on ventilatory support and has an adequate respiratory reserve (dead space will be increased without the tracheostomy tube).
- The patient is able to cough and swallow effectively and manage their own secretions, whilst being able to protect their own airway.
- Patient can tolerate cuff deflation or capping of the tracheostomy tube.

Decannulation itself should be performed in the morning, with a rested patient and daylight hours in which to review their progress. The tube is removed and the stoma is covered with a semi-permeable dressing. The patient is encouraged to gently press over this defect with whilst speaking or coughing.

They should subsequently be monitored for signs of respiratory distress. Equipment and expertise to re-secure the airway, either via the stoma or via oral intubation, should be available.

PERMANENT STOMA, TRACHEOESOPHAGEAL PUNCTURE AND PROSTHETIC SPEECH VALVES

Even though complex laryngectomies are carried out in hospitals providing ENT services, some patients may present themselves to hospitals that do not offer this service. As a result, these patients may present to staff that are less familiar with permanent stomas.

The basic options for speech rehabilitation after total laryngectomy include artificial larynx, oesophageal speech and tracheoesophageal speech. Tracheoesophageal speech provides the advantage over the

other two options, that air supply for speech is pulmonary, phonation sounds natural, and voice restoration occurs within 2 weeks of surgery.

During total laryngectomy, a surgical fistula is created between the oesophagus and the trachea – primary tracheoesophageal puncture (TEP). Alternatively TEP may be performed few weeks or even months after total laryngectomy – secondary TEP. The TEP is kept patent in the immediate postoperative period using a Foley's self retaining catheter or feeding tube, which has the added benefit of enabling enteral feeding. Two to three weeks post-operatively, an appropriately sized Bloom-Singer valve is inserted into the tracheoesophageal fistula.

A Bloom-Singer valve is a hollow, 16- or 20-French, silicone tube that has a one-way flap valve positioned within its proximal tip. The valve serves two purposes; first, it allows the patient to phonate by allowing pulmonary air to pass through the valve, into the pharynx and out of the mouth and second, it prevents saliva and oral secretions from being aspirated into the tracheo-bronchial tree from the pharynx. To phonate, the patient inhales air through the permanent stoma, occludes the permanent stoma with the thumb and then exhales. The occluded stoma diverts air through the Bloom-Singer prosthesis and up the oesophagus to the mouth. Vibration of opposed mucosal surfaces along the oesophagus and pharynx produces a variably husky or hoarse quality voice that is articulated by the tongue, lips, and teeth into intelligible speech.

The following complications may be seen with a Bloom-Singer valve:

- Candida infection in and around the prosthesis
- Leakage through the valve due to a defective one-way valve
- Periprosthetic leakage
- Occlusion of the prosthesis
- Inadvertent displacement and aspiration.

What to do if a patient presents with displaced Bloom-Singer valve

Two main problems are encountered if a patient presents with a displaced Bloom-Singer valve prosthesis. First, oral secretions may be aspirated into the tracheo-bronchial tree and second, the TEP may be seal spontaneously, warranting another surgical procedure. If these patients present to a hospital that does not provide ENT services, a self-retaining Foley's catheter, equivalent in size to the B-S valve, can be introduced through the TEP into the oesophagus under local anaesthetic spray. The balloon is inflated with 3 ml of air, gently retracted and taped to the side of the neck, while awaiting inter-hospital transfer. If the valve has been aspirated, it can be removed using a fibre-optic bronchoscope.

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Acute kidney injury – diagnosis, management and prevention

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INTRODUCTION

The term *kidney failure* implies that the damage the kidney has been done, and this has now largely been replaced the term acute kidney injury (AKI), describing a pathology for which timely intervention can prevent or minimize organ damage. The formalisation of a definition for AKI is a significant step forward in our understanding of prevention and management of this extremely common problem, which affects approximately 1 in 5 patients admitted to hospital and 35% of those admitted to the intensive care unit.^{1,2} In a multicentre observational study (the BEST study) 6% of those admitted to critical care units required renal replacement therapy.³

AKI is part of a multisystem disorder, whether it is the primary insult or secondary to other organ dysfunction. It may be that some doctors feel that as long as we can offer dialysis to these patients, then although they may die *with* renal failure, they will not die *because of* renal failure. This assumption is incorrect, particularly since the vast majority of developing world ICUs do not have access to renal replacement therapy. A rise in creatinine as small as 26 $\mu\text{mol.L}^{-1}$ (0.3 mg.dl^{-1}) is associated with a mortality that is four times higher than those patients who did not show an elevation of creatinine.⁴ A rise in creatinine by 180 $\mu\text{mol.L}^{-1}$ increased the risk of death by sixteen times. When corrected for comorbidity, age and disease severity, renal failure is associated with double the mortality in the critically ill.⁵

AKI has long term implications; at 3-year follow up 41.7% of patients haemofiltered for AKI had chronic kidney disease, with 15% still requiring dialysis.⁶ It is therefore imperative that we concentrate our efforts on diagnosing and treating AKI efficiently, in order to improve patients' short and long term prognosis. This article explains the pathophysiology of the different forms of AKI, going on to explain how to detect, categorise and treat the patient presenting with an acute kidney injury.

DEFINITION

Historically, studies have used a threshold serum creatinine level, or the need for renal replacement therapy (RRT), to diagnose acute renal failure. This

approach has led to difficulty in understanding the epidemiology of AKI and comparing various therapeutic options. The diagnosis of AKI has now been standardised, enabling clinicians to identify patients with an AKI, as well as those at risk of the development of renal failure. The Acute Dialysis Quality Initiative, a collaboration between nephrologists and critical care physicians, developed the RIFLE criteria (Figure 1).⁵ The acute phase of AKI has been further refined by the Acute Kidney Injury Network.⁷ Both use two criteria, creatinine and urine output, to diagnose AKI. A patient has AKI if they fulfill either criterion.

PATHOPHYSIOLOGY

Acute kidney injury should be seen as the final common pathway of a variety of insults, in much the same way that left ventricular cardiac dysfunction can be due to a variety of causes, including ischaemic heart disease, myocarditis, cardiotoxic medication or valvular disorders.

The driving force for filtration at the glomerulus is the pressure gradient between the glomerulus and the Bowman space - the glomerular filtration pressure. Glomerular pressure is primarily dependent on renal blood flow (RBF) and is controlled by the relative resistances of afferent (flowing into the glomerulus) and efferent (flowing away from the glomerulus) arterioles. Regardless of the cause of AKI, reductions in RBF represent a common pathological pathway for decreasing glomerular filtration rate (GFR). The aetiology of AKI can be usefully classified into three main mechanisms; prerenal, intrarenal (or intrinsic) and postrenal. Although a disease process can cause an AKI through any one of these pathological mechanisms, many diseases cause a combination of factors. For example in malaria, AKI can be triggered by associated sepsis, gastrointestinal bleeding (prerenal), ischaemic acute tubular necrosis, interstitial nephritis and glomerulonephritis (intrarenal), and mechanical obstruction by affected erythrocytes causing haemoglobinuria (postrenal).

Prerenal AKI

This is defined as AKI that is caused by a haemodynamic disturbance, resulting in a reduced pressure gradient

Summary

This article describes the causes, diagnosis and management of acute kidney injury (AKI). Many centres in the developing world do not have access to renal replacement therapy and the emphasis is on prompt recognition, treatment and prevention of worsening AKI.

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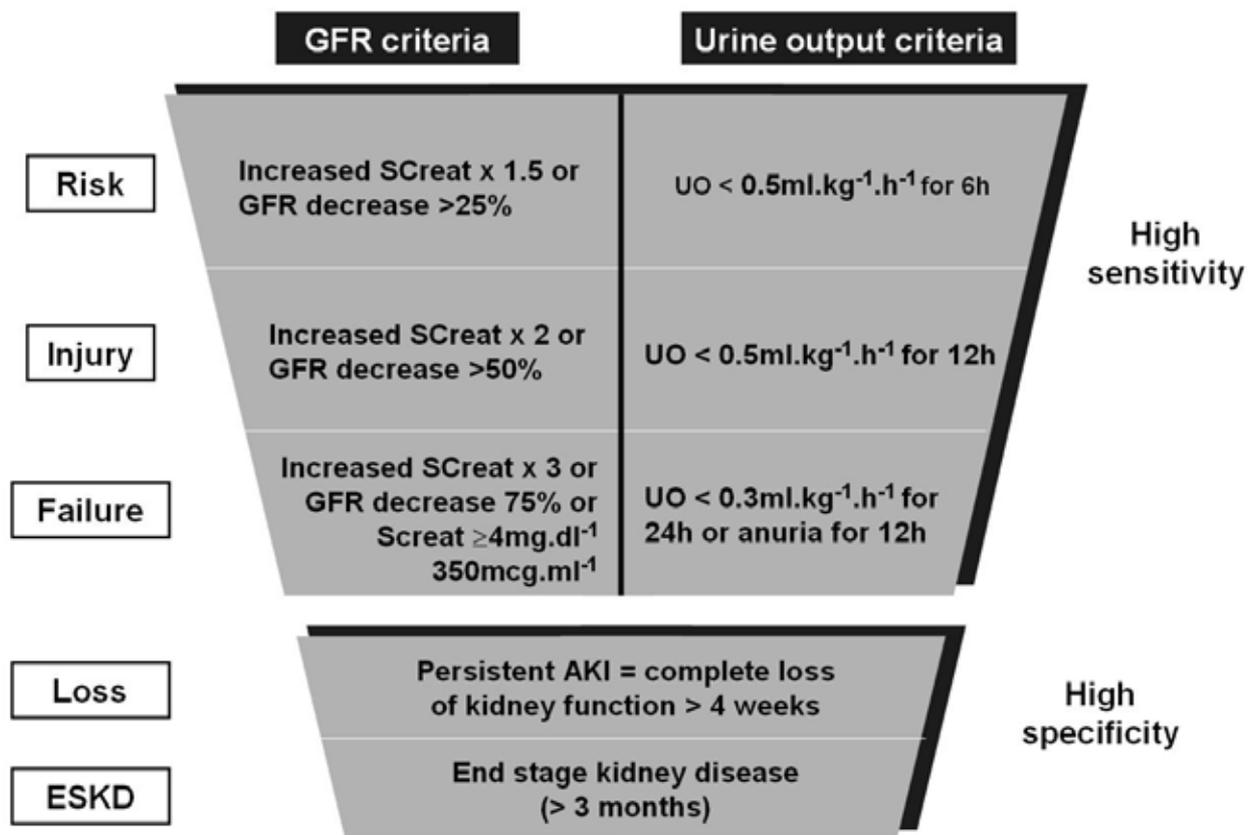


Figure 1. The RIFLE criteria (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease). Note that the 'F' component is present even if the increase in serum creatinine (SCreat) is less than three-fold, as long as the new SCreat is greater than 4.0mg.dl⁻¹ (350mcmol.L⁻¹) in the setting of an acute increase of at least 0.5mg.dl⁻¹ (44mcmol.L⁻¹). The designation RIFLE-FC should then be used to denote 'acute-on-chronic' disease. Similarly, when the RIFLE-F classification is achieved by urine output (UO) criteria, a designation of RIFLE-FO should be used to denote oliguria. The shape of the figure denotes the fact that more patients will be included in the mild category (high sensitivity), including some without actually having renal failure (less specificity). In contrast, at the bottom of the figure the criteria are strict and therefore specific, but some patients will be missed (low sensitivity).

between the glomerulus and Bowman's capsule. As there is no actual damage to the renal parenchyma, if the cause is corrected there is usually rapid recovery of function. However, it can lead to intrarenal AKI if it is not promptly corrected. Volume loss due to gastrointestinal, renal, or cutaneous (e.g. burns) disease, and internal or external haemorrhage can result in this syndrome.

Prerenal AKI can also result from decreased renal perfusion in patients with heart failure or shock (e.g. sepsis, anaphylaxis). The damage may occur on a macrovascular level, but is more commonly a microvascular problem at the level of the afferent and efferent arterioles or the capillary beds. Sepsis is responsible for 50% of AKI, causing a reduction in the mean arterial blood pressure and renal blood flow, as well as reduced vasomotor tone of the efferent arteriole, preventing the maintenance of intraglomerular pressure and resulting in a fall in perfusion pressure.

Intrarenal (intrinsic) AKI

Sources of damage to the kidney itself are termed intrinsic and can be due to damage to the glomeruli, renal tubules or the interstitium. Common causes of each are glomerulonephritis (GN), acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) respectively.

Glomerulonephritis

GN is a renal disease (usually of both kidneys), characterised by inflammation of the glomeruli, or the small blood vessels in the kidneys. They are categorised into several different pathological patterns, which are broadly grouped into non-proliferative or proliferative types. Diagnosing the pattern of GN is important because the treatment and outcome differs in different types. Primary causes are intrinsic to the kidney; secondary causes are associated with certain infections (bacterial, viral or parasitic pathogens), drugs, systemic disorders (systemic lupus erythematosus, vasculitis), or diabetes.

Acute tubular necrosis

ATN may be classified as either toxic or ischemic. Toxic ATN occurs when the tubular cells are exposed to a toxic substance (also termed nephrotoxic ATN). Toxic ATN can be also caused by free pigments, such as haemoglobin or myoglobin, by medications, including antibiotics such as aminoglycosides and by cytotoxic drugs such as cisplatin. Toxic ATN is characterised by proximal tubular epithelium necrosis, due to the toxic substance. Necrotic cells fall into the tubule lumen, obliterating it, and exacerbating the problem.

Table 1. Causes of prerenal AKI.

Fluid loss	Decreased cardiac output	Systemic vasodilation	Afferent arteriolar vasoconstriction	Renal arterial disease
Renal losses <i>diuretics, polyuria</i>	Heart failure	Sepsis	Hypercalcemia	Renal arterial stenosis <i>atherosclerotic, fibromuscular dysplasia</i>
GI losses <i>vomiting, diarrhoea</i>	Pulmonary embolus	Anaphylaxis	Drugs <i>NSAIDs, amphotericin B, ephedrine, metaraminol, radiocontrast agents</i>	Embolic disease <i>thrombus septic cholesterol</i>
Cutaneous losses <i>burns, Stevens-Johnson syndrome</i>	Acute myocardial infarction	Anaesthetic agents	Hepatorenal syndrome	
Haemorrhage	Severe cardiac valvular disease	Drug overdose		
	Abdominal compartment syndrome			

Ischaemic ATN occurs when the tubular cells suffer from inadequate oxygen delivery, often resulting from prerenal causes. Tubular cells are highly sensitive and susceptible to hypoxia, due to their very high metabolic rate. ATN specifically causes skip lesions throughout the tubules, where certain portions of tubules remain unaffected. Often the tubule basement membrane remains intact, so regeneration of the tubular epithelium and reversal of AKI is possible.

Acute interstitial nephritis

AIN is a form of nephritis affecting the interstitial tissue that surrounds the tubules. The majority of cases of AIN are caused by drugs, such as penicillins, quinolones, sulphonamides and nonsteroidal anti-inflammatory drugs (NSAIDs). The time between exposure to the drug and the development of acute tubulointerstitial nephritis can be anywhere from five days to five months. The kidney is remarkably resistant to structural damage in bacterial infections and, in the absence of obstruction, damage from bacterial infection in the kidney parenchyma is unlikely to occur.

Postrenal AKI

Postrenal AKI occurs when there is bilateral (or unilateral in the case of a single kidney) obstruction of urine flow. Intratubular pressure increases and in turn decreases the glomerular filtration pressure. Obstruction of urine flow is a relatively uncommon cause of AKI and is more common in the community than in the intensive care unit (ICU). Postrenal AKI can be divided into renal and extrarenal causes. Extrarenal causes include prostatic disease, pelvic malignancy, and retroperitoneal disorders. Intrarenal causes include crystal deposition, as occurs in ethylene glycol ingestion, or uric acid nephropathy in tumor lysis syndrome. Cast formation and tubular obstruction also occur in light-chain diseases such as multiple myeloma. If the site of obstruction is unilateral, then there may be no rise in serum creatinine level due to contralateral renal function. However there may be a significant fall in GFR, with the risk of progression if the obstruction is not relieved.

Whatever the cause of the AKI, it results in the failure of the kidneys

Table 2. Examples of pathological processes causing intrinsic (intrarenal) AKI.

Glomerular	Toxic ATN	Ischaemic ATN	Interstitial
Anti-glomerular basement membrane (GBM) disease <i>Goodpasture's</i>	Haem pigment <i>rhabdomyolysis, intravascular haemolysis</i>	Renal artery obstruction <i>thrombosis, emboli, dissection, vasculitis</i>	Drugs <i>penicillins, cephalosporins, NSAIDs, proton-pump inhibitors, allopurinol, rifampicin, sulfonamides</i>
Anti-neutrophil cytoplasmic antibody-associated glomerulonephritis (ANCA-associated GN) <i>Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis</i>	Crystals <i>tumor lysis syndrome, seizures, ethylene glycol poisoning, acyclovir, methotrexate</i>	Renal vein obstruction <i>thrombosis</i>	Infection <i>pyelonephritis, viral nephritides</i>
Immune complex GN <i>Lupus, postinfectious, cryoglobulinaemia, primary membranoproliferative glomerulonephritis</i>	Drugs <i>aminoglycosides, lithium, amphotericin B, cisplatin, radiocontrast agents</i>	Microangiopathy <i>disseminated intravascular coagulation, pre-eclampsia, sickle-cell crisis, malaria, haemolytic uraemic syndrome</i>	Systemic disease <i>Sjögren syndrome, sarcoid, lupus, lymphoma, leukaemia, tubulonephritis, uveitis</i>
		Malignant hypertension	
		Scleroderma renal crisis	
		Transplant rejection	
		Atheroembolic disease	

to perform their three main functions:

1. Impairment of nitrogenous waste product (urea) excretion,
2. Loss of water and electrolyte regulation,
3. Loss of acid-base regulation.

CLINICAL PRESENTATION

History

Patients with AKI often do not have any specific symptoms and it is only detected through abnormal biochemistry results or a reduced urine output. However, an accurate and detailed history is essential to determine the cause of AKI and its investigation and treatment. It is important to distinguish between acute and chronic renal disease. Patients with chronic kidney disease often have symptoms such as fatigue, weight loss, nausea and pruritis. Asking about the patient's urine output can be helpful, as oliguria (a urine output of less than $0.5\text{ml.kg}^{-1}\text{h}^{-1}$) generally favors AKI. Abrupt anuria (total lack of urine output) suggests acute urinary obstruction, acute and severe glomerulonephritis, or embolic renal artery occlusion. A gradually diminishing urine output may indicate a urethral stricture or bladder

outlet obstruction due to prostate enlargement. In patients with chronic renal insufficiency, the decrease in functioning nephrons means that even a trivial nephrotoxic insult may cause AKI.

When working in the tropics, it is important to consider and screen for diseases that are specific to these areas, including malaria, typhoid, leptospirosis and viral haemorrhagic fevers. Exposure to plant toxins causing AKI is also more common in tropical countries, as patients are more likely to have sought the help of traditional healers prior to their admission to hospital.

In areas with a high prevalence of HIV/AIDS and tuberculosis, screen for these diseases by asking about symptoms such as recurrent infections (i.e. possible immunosuppression), weight loss and night sweats. Ask about the patient's family history to identify disorders such as sickle cell disease and glucose-6-phosphate dehydrogenase deficiency, in which an acute crisis can cause AKI.

EXAMINATION

General examination

Certain rashes are suggestive of systemic vasculitis (livido reticularis, palpable purpura, digital ischaemia). Allergic interstitial nephritis

Table 3. History in different types of AKI.

Prerenal AKI

- Hypovolaemia causes thirst, decreased urine output, dizziness and orthostatic hypotension (i.e. hypotension on rising from lying to sitting or standing).
- Ask about fluid loss from vomiting, diarrhoea, sweating, polyuria, or haemorrhage.
- Consider sepsis as a contributing factor.
- Orthopnoea and paroxysmal nocturnal dyspnoea suggest significant cardiac failure leading to depressed renal perfusion.

Intrinsic (intrarenal) renal AKI

- A nephritic syndrome (haematuria, oedema and hypertension) indicates a glomerular aetiology of AKI.
- Ask about prior throat or skin infections (post-streptococcal GN).
- Suspect ischaemic ATN in any patient presenting after a period of hypotension secondary to cardiac arrest, haemorrhage, sepsis, drug overdose, or anaesthesia / surgery.
- Enquire about exposure to nephrotoxins, including a detailed list of all current medications and any recent radiological examinations (for exposure to radiological contrast agents).
- Toxic pigment-induced ATN should be suspected in patients with possible rhabdomyolysis (muscular pain, prolonged collapse, seizures, intoxication, excessive exercise or limb ischaemia) or haemolysis.
- Acute interstitial nephritis should be suspected with fevers, rash, arthralgia, and exposure to certain medications, including NSAIDs and antibiotics.

Postrenal AKI

- Usually occurs in older men with prostatic obstruction and symptoms of urgency, frequency, and hesitancy.
 - Flank pain and haematuria may suggest renal calculi or papillary necrosis.
 - Use of acyclovir, methotrexate, triamterene, indinavir, or sulfonamides implies the possibility of tubular obstruction by crystals of these medications.
 - Retroperitoneal fibrosis is often associated with various immune-related conditions, malignancy and certain drugs (methysergide, hydralazine and beta blockers).
-

is associated with a maculopapular rash. Consider endocarditis and septic emboli in patients with a history or signs of intravenous drug abuse (track marks).

Eye examination may reveal keratitis, iritis, uveitis (autoimmune vasculitis), jaundice (liver disease) or signs of diabetes mellitus and hypertension. Hearing loss may be evident in aminoglycoside toxicity.

Cardiovascular examination

Assess the patient's volume status by examining skin turgor, mucous membranes and capillary refill time, as well as the pulse rate and lying and standing blood pressures, to assess for a postural drop. The jugular venous pressure (JVP) may be helpful and the lung bases and dependent areas should be assessed for the presence of oedema. Remember that oedema does not mean 'fluid overload', more that the fluid is in the wrong place and the patient may still be hypovolaemic in terms of their vascular space. In hospitalised patients, accurate daily records of fluid input and output and of the patient's weight should be recorded.

Other clinical findings that may point towards a diagnosis include:

- Irregular cardiac rhythms (e.g. atrial fibrillation) predispose to thromboembolic renal disease,
- Heart murmurs can be suggestive of underlying cardiac failure or endocarditis,
- A raised JVP, lung base crepitations and the presence of a third heard sound (gallop rhythm) suggests cardiac failure,
- Severe hypertension with renal failure suggests renovascular disease, glomerulonephritis, vasculitis, or atheroembolic disease.

Respiratory examination

- Kussmaul's (acidaemic) respiration suggests significant metabolic acidosis,
- Fine crackles and/or haemoptysis may indicate a pulmonary-renal syndrome such as Goodpasture's or Wegener's granulomatosis.

Abdominal examination

- Pulsatile abdominal masses and renal bruits suggest the presence of atheroembolic disease,
- Costovertebral (renal) angle tenderness is seen with renal stones, papillary necrosis, renal artery thrombosis and renal vein thrombosis,
- Abdominal, pelvic, rectal masses, prostatic hypertrophy can suggest a postrenal (obstructive) cause,
- A distended bladder is indicative of a postrenal AKI,
- A distended, tense abdomen suggests raised intra-abdominal pressure and possibly abdominal compartment syndrome (post laparotomy, trauma, abdominal aortic aneurysm repair).

Neurological and extremities

- Confusion is caused by many factors, including uraemia, vasculitic and embolic disease,

- Focal neurological findings may indicate embolic disease,
- Asterixis (a flapping tremor) is suggestive of uraemia or hepato-renal failure,
- Limb oedema can suggest underlying cardiac failure or hypoalbuminaemia secondary to albumin loss from an intrarenal pathology,
- Absent peripheral pulses suggest atheroembolic disease,
- Limb ischaemia can be indicative of rhabdomyolysis causing a toxic ATN.

INVESTIGATING THE CAUSE OF AKI

Several laboratory tests are useful for assessing the aetiology of AKI, and the results may determine the appropriate treatment. These tests include a full blood count (FBC), serum biochemistry, urine analysis with microscopy and urine electrolytes.

Plasma biochemistry

Urea and creatinine	Raised levels confirm the presence of an AKI
Potassium	May be dangerously high in the presence of a severe AKI, prompting rapid treatment
pH	To assess the presence of a metabolic acidosis due to dysfunction of renal acid-base balance
Lactate dehydrogenase	Acute elevation occurs in renal infarction
Creatine kinase	Acute elevation occurs in rhabdomyolysis
Plasma electrophoresis	As part of a multiple myeloma screen

Haematology

- Eosinophilia may suggest a suggests vasculitis,
- Raised erythrocyte sedimentation rate suggests vasculitis,
- Fragmented red cells and/or thrombocytopenia suggests intravascular haemolysis due to accelerated hypertension or haemolytic uraemic syndrome.

Blood film

This may demonstrate schistocytes (haemolytic uraemic syndrome) or increased rouleaux formation (multiple myeloma), or a heavy burden of malarial parasites.

Immunology

Where available, measurement of complement components, autoantibodies and cryoglobulins aid in the diagnosis.

Urine biochemistry

- 24-hour creatinine clearance is useful in measuring the severity of renal failure.

Table 4. Interpretation of urine analysis and microscopy.

Urinalysis

<i>Haematuria</i>	Haematuria on a dipstick, with the absence of red cells on microscopy, suggests myoglobinaemia (rhabdomyolysis)
<i>Proteinuria</i>	Strongly suggestive of glomerular disease
<i>Glycosuria</i>	With a normal blood sugar indicates tubular disease

Microscopy

<i>White cells</i>	Suggests an active bacterial urinary infection and possible pyelonephritis
<i>Eosinophilia</i>	Strongly suggestive of allergic tubulo-interstitial nephritis
<i>Granular casts</i>	Formed from abnormal cells within tubular lumen. Indicates ATN
<i>Red cell casts</i>	Highly suggestive of GN

- Urinary osmolarity can be used as a measure of the concentrating ability of the kidney, which is lost in intrarenal AKI.
- Urine electrophoresis is necessary for the detection of light chains when multiple myeloma is suspected.

Microbiology

<i>Urine culture</i>	To diagnose pyelonephritis
<i>Antibodies to streptococcal antigens</i>	If post-streptococcal GN is possible
<i>Antibodies to HIV</i>	
<i>Early morning urine and sputum culture</i>	Acid-fast bacilli to detect tuberculosis
<i>Thick and thin blood films</i>	Malaria
<i>Widal test for typhoid, blood and urine test for Leptospirosis</i>	

Electrocardiography (ECG)

The characteristic changes of hyperkalaemia are usually seen with a potassium level above 6.5mmol.L^{-1} - tall tented T waves, flat P waves and increased PR interval. QRS widening, a sinusoidal pattern and VF are seen with extreme hyperkalaemia.

Renal tract ultrasound

Renal ultrasonography is useful for evaluating existing renal disease and to identify or exclude obstruction of the urinary collecting system. The degree of hydronephrosis does not necessarily correlate with the degree of obstruction. Mild hydronephrosis may be observed with complete obstruction if found early. Small kidneys suggest chronic renal failure.

Doppler scans rarely differentiate between prerenal and intrarenal AKI, but can be useful if thromboembolic or renovascular disease is suspected.

Other investigations

Radionuclide imaging (e.g. with technetium^{99m}) can be used to assess renal blood flow and tubular function but, because of a marked delay in tubular excretion of radionuclide in prerenal disease and intrarenal disease, the value of these scans is limited. Aortorenal angiography (using computed tomography and magnetic resonance imaging

studies) can be helpful in establishing the diagnosis of renal vascular diseases, including renal artery stenosis, renal atheroembolic disease, and atherosclerosis with aortorenal occlusion. The radiocontrast used with CT is nephrotoxic and can exacerbate an AKI.

Renal biopsy

A renal biopsy can be useful in establishing the diagnosis of intrarenal causes of acute kidney injury (AKI) and can be justified if it will change management (e.g. initiation of immunosuppressive medications). Renal biopsy may also be indicated when renal function does not return for a prolonged period and a prognosis is required to develop long term management.

QUANTIFYING THE SEVERITY OF AKI

Oliguria is a marker of an AKI and is defined as a urine output of less than $0.5\text{ml.kg}^{-1}.\text{h}^{-1}$. Creatinine is a breakdown product of creatine phosphate in muscle and is usually produced at a constant rate by the body. Serum levels correlate directly with the glomerular filtration rate (GFR) of the kidneys and can be used to quantify and monitor renal function. However, the level of serum creatinine is also affected by the muscle mass of the individual patient and therefore by their age, sex and ethnicity. The normal upper limit of serum creatinine in different patient groups is best estimated with reference to your local laboratory.

Glomerular filtration rate (GFR)

The serum creatinine level can also be used to estimate the glomerular filtration rate of the kidneys, using a formula (see box below). According to the National Kidney Foundation, normal results range from $90\text{-}120\text{ml.min}^{-1}$ per 1.73m^2 body surface area.

Box 1. Estimated GFR (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula

For creatinine in mcmol.L^{-1} :
$$\text{eGFR} = 32788 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]$$

For creatinine in mg.dl^{-1} :
$$\text{eGFR} = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times [1.212 \text{ if black}] \times [0.742 \text{ if female}]$$

Creatinine levels in mcmol.L^{-1} can be converted to mg.dl^{-1} by dividing them by 88.4.

The RIFLE model⁵

As shown in Figure 1, the RIFLE criteria quantify the severity of the AKI. 'Loss' and 'end-stage renal disease' (ESRD) are separated to acknowledge the important adaptations that occur in ESRD, that are not seen in a persistent acute kidney injury. Persistent AKI (loss) is defined as need for renal replacement therapy (RRT) for more than 4 weeks, whereas ESRD is defined by need for dialysis for longer than 3 months.

The classification system includes separate criteria for creatinine and urine output (UO). A patient can fulfil the criteria through changes in serum creatinine (SCreat) or changes in UO, or both. The criteria that lead to the worst possible classification for that patient should be used. As serum creatinine levels and eGFR are affected by additional factors not considered in their calculation or the normal values, it is most useful if a baseline level is known. However, if it is not known, using normal levels as an estimated baseline function is acceptable.

MANAGEMENT OF THE PATIENT WITH AKI

The sooner AKI is recognised and treated, whatever its severity, the higher the chances of recovery of renal function. As well as following the basic measures detailed below, it is often appropriate to seek specialist advice, especially if the measures below do not cause improvement within the first twenty-four hours.

Correction of the underlying cause

Measures to correct underlying causes of acute kidney injury should begin at the earliest indication of renal dysfunction. A large proportion of the renal mass is damaged before any biochemical evidence of renal dysfunction; the relationship between the GFR and the serum creatinine level is not linear, especially early in disease. A rise in serum creatinine may not be evident until 50% of the GFR is lost.

- In a prerenal AKI - improve renal perfusion e.g. treat sepsis, treat haemorrhage and rehydrate,
- In a intrarenal AKI - treat the cause e.g. remove nephrotoxic drugs, give steroids in GN,
- In a postrenal AKI - remove the cause of obstruction e.g. catheterise the bladder.

Optimization of conditions for recovery

Maintenance of volume homeostasis remains the primary goal of treatment. In patients with prerenal AKI, aggressive fluid resuscitation is often required to improve renal perfusion. It is appropriate to start with 0.9% saline or Ringer's lactate, aiming to restore circulating volume but avoid volume overload, as this may worsen renal function. Once the patient is fluid resuscitated it is important that further fluid input matches their output.

Clinically reassess the patient's response to fluid resuscitation frequently. If large fluid volumes or vasopressors are required, or if the patient has cardiac dysfunction, some form of cardiac output monitoring is useful (see page 51).

There is no evidence that diuresis using furosemide is beneficial and the majority of patients with AKI will be unresponsive to diuretics. It is reasonable to attempt diuresis with furosemide where you are sure

that they are hypervolaemic, particularly where RRT is not available. High doses may need to be administered and doses over 80-100mg should be given as an infusion due to the risk of ototoxicity. In some patients, where RRT is unavailable, symptomatic hypervolaemia, causing pulmonary oedema can be treated by venesection of blood (to a volume that improves symptoms).

There is no evidence for using low dose dopamine for renal protection. Lactic acidosis should be treated by optimising the circulation, not with sodium bicarbonate.

Maintain biochemical homeostasis

Dietary modification is an important consideration in the treatment of acute kidney injury. Salt and fluid restriction becomes crucial in the management of oliguric renal failure, because the kidneys do not excrete toxins and fluids adequately. Potassium and phosphate are excreted poorly in AKI; where available, blood levels should be measured at least daily, with prompt treatment of levels that are symptomatic or very elevated. Critically ill patients should receive at least 1g.kg⁻¹ of protein in their diet per day, but should avoid over-feeding (hyperalimentation), which can increase blood urea nitrogen levels, exacerbate metabolic acidosis and cause water loss resulting in hypernatremia.

Protection from further damage

Whatever the initial cause of the AKI, the kidneys remain vulnerable to the toxic effects of various chemicals. All nephrotoxic agents (e.g. radiocontrast agents, antibiotics with nephrotoxic potential, heavy metal preparations, cancer chemotherapeutic agents and NSAIDs) should either be avoided or used with extreme caution. A common dilemma is whether to give contrast for a CT abdomen in a patient with an AKI, who needs to be investigated for abdominal sepsis - the need to reach a diagnosis and therefore initiate appropriate treatment usually supersedes the risks of radiocontrast to the kidneys, but it is reasonable to perform a non-contrast scan first, as this may show an obvious diagnosis and negate the need for contrast.

The doses of all medications cleared by renal excretion (most commonly antibiotics in the ICU setting) should be adjusted appropriately. (See 'The Renal Drug Handbook' in Further Reading).

Management of life-threatening complications

Severe metabolic acidosis

Correcting severe acidosis (pH < 7.2) with intravenous bicarbonate administration can be an important 'holding measure', either whilst initiating emergency RRT or waiting for treatment, such as fluid resuscitation, antibiotics and vasopressors, to take effect. There are no specific therapeutic agents for AKI and dopamine, nesiritide, fenoldopam and mannitol may cause harm.

Hyperkalaemia

Serum potassium levels of greater than 6.5mmol.L⁻¹ require urgent treatment. Protection from its effects on cardiac conduction can be achieved with intravenous calcium administration (10ml 10% calcium gluconate or chloride IV over 10 minutes), repeated whenever the ECG changes worsen.

Reduction of potassium levels can be achieved through the careful administration of intravenous insulin, which drives potassium into the cells from the serum. Add 15 units of fast-acting insulin, such as Actrapid, to 50mls 50% glucose and administer over 30 minutes. Nebulised salbutamol (5mg) also drives the passage of potassium into cells. These are again holding measures, while the underlying cause is treated or dialysis is started. Potassium will leak back into the serum and these treatments may need to be repeated. Calcium resonium (15g every eight hours orally or via an NGT) can be used to help to remove potassium via the gastrointestinal tract.

Uraemic pericarditis, cardiac tamponade and pulmonary oedema

These serious complications are best treated by dialysis, although symptomatic management with oxygen, peripheral vasodilators, pericardiocentesis (drainage of pericardial fluid) and occasionally venesection can be helpful whilst waiting for dialysis to be started.

Managing Resolving AKI

During tubular dysfunction the patient is oliguric or anuric. Glomerular filtration tends to return before regeneration of the tubules, particularly their ability to concentrate the urine by retention of water. This, together with a high osmotic load from renal toxin accumulation, can drive profound polyuria or poorly concentrated urine. Urine volumes may be as high as 10 litres per day. Few patients can comfortably maintain an intake of more than 4 litres per day orally, so intravenous fluids are frequently required. Standard practice is to replace the previous hour's urine output with the next hour's IV input. Serum electrolytes should be measured at least daily. Ringer's lactate or 0.9% saline with potassium supplementation are the usual crystalloids of choice.

Prevention of further AKI and the development of chronic kidney disease

Patients who have suffered an AKI are at increased risk of further episodes and of developing chronic kidney disease (CKD). They should ideally be reviewed yearly by a healthcare provider, with a thorough history and clinical examination, serum biochemistry (urea, creatinine and electrolytes) and urinalysis to monitor kidney and urinary tract health. Patients should be advised to drink enough fluids to maintain regular passage of urine, to avoid dehydration and to avoid taking substances or medications that are nephrotoxic (e.g. NSAIDs). They should be advised that if they experience a reduced urine output, difficulties urinating or haematuria, this should prompt a visit to their physician.

CONCLUSION

This article provides an overview of the major causes of acute kidney injury and the underlying pathophysiology. It describes how to detect and treat AKI in a timely and effective manner. A clear understanding of these concepts is essential when working with critically ill patients, as a good practical knowledge of the assessment and management of the patient with an AKI is vital in improving both the short and long term prognosis of patients.

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Renal replacement therapy in critical care

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INTRODUCTION

Acute renal failure, also known as acute kidney injury (AKI), is defined as an abrupt (within 48 hours) reduction in kidney function. The AKI network defines the reduction in kidney function as the presence of any one of the following:¹

- An absolute increase in serum creatinine of $\geq 0.3\text{mg.dl}^{-1}$ ($\geq 26.4\text{mmol.L}^{-1}$),
- A percentage increase in serum creatinine of $\geq 50\%$ (1.5-fold from baseline),
- A reduction in urine output ($< 0.5\text{ml.kg}^{-1}$ per hour for more than six hours).

It is estimated that a third of patients in the critical care setting have an AKI² and approximately 5% will require renal replacement therapy (RRT).³ The hospital mortality in patients with an AKI requiring RRT is as high as 60%.⁴

The initial management of AKI involves treating the underlying cause, stopping nephrotoxic drugs and ensuring that the patient is euvolaemic, with an adequate mean arterial blood pressure. However, no specific treatments have been shown to reverse the course of AKI, so RRT forms the basis of further management.

INDICATIONS FOR RRT

Indications for RRT are:

Acute kidney injury (AKI) with:

- Fluid overload (unresponsive to diuretics)
- Hyperkalemia ($K^+ > 6.5$)
- Severe metabolic acidosis ($\text{pH} < 7.1$)
- Rapidly climbing urea/creatinine (or urea $> 30\text{mmol.L}^{-1}$)
- Symptomatic uraemia: encephalopathy, pericarditis, bleeding, nausea, pruritus
- Oliguria/anuria.

There are no universally accepted levels of urea, creatinine, potassium, or pH at which to start therapy. The figures quoted above are given as a rough guide. Initiation of RRT should be prompted more by the rate of change of renal parameters, and by the patient's overall condition, than by arbitrary levels.

There is some suggestion that starting RRT early (defined as a urea $< 27\text{mmol.l}^{-1}$ in the PICARD study) may offer a survival benefit, however guidance on exact timing of RRT is still lacking.⁵

Summary

Acute kidney injury is common in the critically ill and RRT has a role in its management. It is also indicated in some cases of poisoning and in management of patients with severe sepsis. RRT is not universally available, however the next article describes how peritoneal dialysis may be a more cost-effective and safer technique in resource poor settings.

Table 1. Examples of drugs/toxins removed or not removed by RRT.

Removed	Not removed
Lithium	Digoxin
Methanol	Tricyclics
Ethylene glycol	Phenytoin
Salicylates	Gliclazide
Barbiturates	Beta-blockers (except atenolol)
Metformin	Benzodiazepines
Aminoglycosides, metronidazole, carbapenems, cephalosporins and most penicillins	Macrolide and quinilone antibiotics Warfarin

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Overdose with a dialysable drug or toxin

Some drugs are removed by RRT but some are not. As a general rule, drugs are cleared by RRT if they are water soluble and not highly protein bound (Table 1).

Severe sepsis

Recent studies have investigated the role of haemofiltration in removal of inflammatory mediators in patients with severe sepsis and septic shock. A number of small studies (with 25 subjects or less) have suggested that high volume haemofiltration ($40\text{--}85\text{ml.kg}^{-1}.\text{h}^{-1}$) may reduce vasopressor requirements and possibly improve survival in patients with septic shock, irrespective of whether they have AKI.^{6,7,8,9} However, strong recommendations cannot be made about the role of RRT in this area until larger, well designed trials have been completed.

TYPES OF RRT IN USE IN INTENSIVE CARE

RRT encompasses peritoneal dialysis and renal transplantation but for the purpose of this article we will focus on the forms of RRT most extensively used in the intensive care setting. These are:

Intermittent haemodialysis (IHD)

Continuous renal replacement therapies (CRRT)

- Continuous venovenous haemofiltration (CVVH)
- Continuous venovenous haemodialysis (CVVHD)
- Continuous venovenous haemodiafiltration (CVVHDF)
- Slow continuous ultrafiltration (SCUF)
- Continuous arteriovenous haemofiltration (CAVHD).

Hybrid therapies e.g. Sustained low-efficiency dialysis (SLED)

The functional differences between the techniques listed above can be classified in terms of:

- The mechanism of solute removal (filtration versus dialysis)
- The duration of the treatment (continuous versus intermittent).

DEFINITIONS

Convection

Solute transport across a membrane together with a solvent (usually water) in response to a pressure gradient across the membrane.

Dalton

A unit of mass used to express atomic and molecular masses. It is the approximate mass of a hydrogen atom, a proton, or a neutron.

Diffusion

Solute transport from a compartment with high concentration to a compartment with low concentration.

Fick's Law of diffusion

States that the rate of diffusion across a membrane is proportional to the concentration gradient across that membrane

Hydrostatic pressure

The pressure exerted by a fluid at equilibrium at a given point within the fluid, due to the weight of the fluid above. In the context of haemofiltration, this pressure is created by the rollerball pump system of the extracorporeal circuit.

Semipermeable membrane

A barrier, either cellulose or synthetic, that allows water, electrolytes and other molecules to pass through, while cellular components and larger molecules are held on one side.

Ultrafiltrate

Plasma water and solutes that pass through the semipermeable membrane.

Ultrafiltration

Transport of water across a membrane by a pressure gradient.

MECHANISM OF SOLUTE REMOVAL

Filtration (convection) versus dialysis (diffusion)

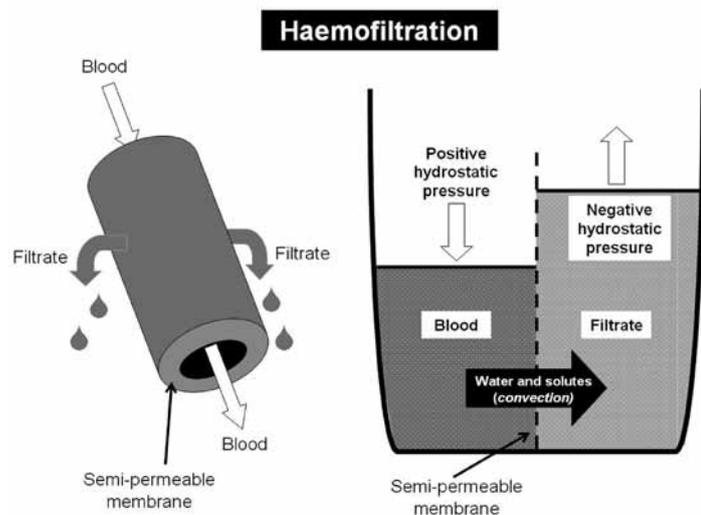
Haemofiltration involves blood being pumped through an extracorporeal system that contains a semi-permeable membrane. The hydrostatic pressure that is created on the blood-side of the filter drives plasma water across the filter. This process is referred to as ultrafiltration. Molecules that are small enough to pass through the membrane (<50,000 Daltons) are dragged across the membrane with the water by the process of convection. The filtered fluid (ultrafiltrate) is discarded and a replacement fluid is added in an adjustable fashion, according to the desired fluid balance.

Haemodialysis involves blood being pumped through an extracorporeal system that contains a dialyser. Blood flows through the dialyser in one compartment, separated from crystalloid solution (dialysate) in a second compartment, by a semipermeable membrane. Solutes move across the membrane, down their concentration gradient (i.e. from high concentration to low) from one compartment of the dialyser to the other (Fick's law of diffusion). For example, bicarbonate moves from dialysate to blood whereas urea and potassium move from blood to dialysate. In order to maintain these essential concentration gradients and enhance the efficiency of the system the dialysate flows in the opposite direction to the flow of blood (*countercurrent*). When removal of water is required, the hydrostatic pressure on the blood side of the membrane is increased in order to force water molecules into the dialysate compartment.

Haemodiafiltration is a combination of filtration and dialysis. There is no evidence to suggest that CVVDF has a survival benefit when compared to CVVH, but it may be a useful way of increasing clearance of small solutes.

Slow continuous ultrafiltration is used when the only requirement is water removal. Effectively, it is CVVH with a low filtration rate. It can remove up to 6 litres of fluid a day but solute removal is minimal.

A



B

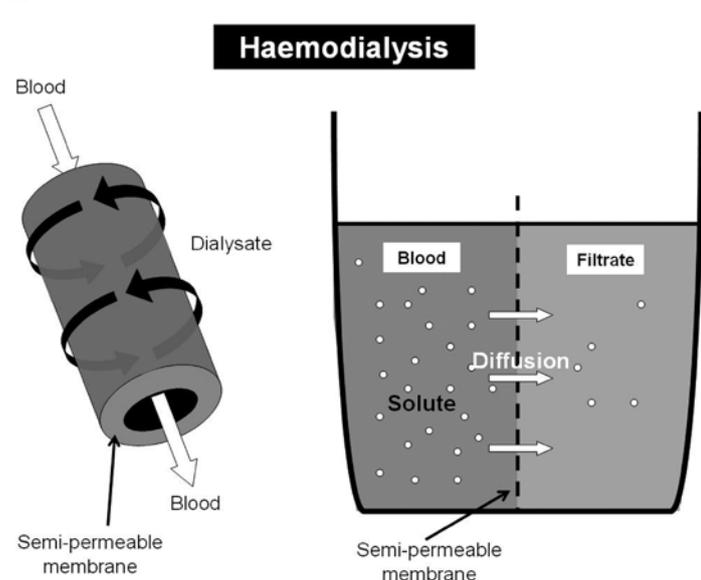


Figure 1. Schematic diagram comparing the different modes of solute removal in A - haemofiltration; B - haemodialysis (redrawn from emcrit.org).

Table 2. How the choice of RRT can be determined by the aim of treatment.

What do you want to remove?	Size of molecule (Daltons)	Example	Preferred type of RRT
Small molecules/electrolytes	< 500	Urea, creatinine, K ⁺ , H ⁺ , lithium	Dialysis or filtration
Middle molecules	500 – 5 000	Large drugs e.g. vancomycin	Filtration better than dialysis
Low molecular weight proteins	5 000 – 50 000	Cytokines, complement	Filtration
Water	18		Filtration better than dialysis

DURATION OF TREATMENT

Intermittent (IHD) versus continuous (CRRT)

Intermittent haemodialysis involves dialysing with higher flow rates than CRRT for defined periods of time. A typical regime is 3-5 hours of dialysis 3 times a week. The high flow rates and rapid fall in plasma osmolality mean that it is only suitable for patients who are cardiovascularly stable. It forms the basis of long term RRT for chronic renal failure and is not commonly used in the critical care setting.

CRRT involves filtering and/or dialysing on a continuous basis. It allows better fluid management and creates less haemodynamic disturbance, but it is more expensive than IHD and requires continuous rather than intermittent anticoagulation. There is some evidence to suggest that CRRT is superior to IHD in patients with sepsis, cardiovascular instability or with a head injury. However, a large RCT comparing IHD with CRRT, in patients with an AKI and multiple-organ dysfunction syndrome, showed no difference in survival at 60 days.¹⁰

Sustained low efficiency dialysis (SLED) is an example of a hybrid therapy which aims to combine the logistic and cost advantages of IHD with the relative cardiovascular stability of CRRT. Treatments are intermittent but usually daily and with longer session durations than conventional IHD. Solute and fluid removal are slower than IHD, but faster than CRRT. Some are confident that hybrid therapies are the future of RRT in ICU, but there is little evidence to support this. At present, it is not a technique used in the UK.

WHICH FORM OF RRT SHOULD WE USE?

No single RRT technique has been shown to offer a survival benefit over the others in the critical care setting, so the decision about which technique to use depends on:

- 1. What we want to remove from the plasma (Table 2)**
- 2. The patient's cardiovascular status**
 - CRRT causes less rapid fluid shifts and is the preferred option if there is any degree of cardiovascular instability.
- 3. The availability of resources**
 - CRRT is more labour intensive and more expensive than IHD
 - Availability of equipment may dictate the form of RRT.

4. The clinician's experience

- It is wise to use a form of RRT that is familiar to all the staff involved.

5. Other specific clinical considerations

- Convective modes of RRT may be beneficial if the patient has septic shock.
- CRRT can aid feeding regimes by improving fluid management.
- CRRT may be associated with better cerebral perfusion in patients with an acute brain injury or fulminant hepatic failure.¹¹

OPTIMAL FLOW RATES / DOSE OF RRT

The desired variables for RRT must be prescribed. The flow rate refers to the ultrafiltrate produced by the filtration process, as well as any effluent dialysate flow. The flow rate is a marker of solute clearance so it can simplistically be thought of as the dose of RRT.

Two recent randomised controlled trials have concluded that there is no benefit in increasing the flow rate from 20 to 35ml.kg⁻¹.h⁻¹:

The Randomised Evaluation of Normal versus Augmented Level of renal replacement therapy in ICU (RENAL) study randomised 1400 critically ill patients with AKI to intensive (35ml.kg⁻¹.h⁻¹) or non-intensive (20ml.kg⁻¹.h⁻¹) CRRT and no difference in mortality was seen in the two groups at 90 days.¹²

The Acute Renal Failure Trial Network (ATN) study compared intensive or less intensive dosing strategies for patients undergoing CRRT (35ml.kg⁻¹.h⁻¹ versus 20ml.kg⁻¹.h⁻¹), IHD (daily versus alternate days) and SLED. The recovery of renal function and the mortality at 60 days were the same in both arms of the trial, but there were more hypotensive episodes in the intensive group.¹³

High volume haemofiltration may be of benefit in patients with septic shock, so there is currently a trend to increase flow rates in patients with septic shock and AKI. This is being investigated in the IVOIRE (Impact of High-volume Venovenous Continuous Hemofiltration in

the Early Management of Septic Shock Patients With Acute Renal Failure) study.

PRACTICAL ISSUES

Vascular access

Venovenous RRT requires a double lumen vascular catheter placed in a central vein. The tip should be sited in the inferior vena cava for femoral lines or superior vena cava (1-2cm from right atrium) for internal jugular and subclavian lines. The catheters are usually made of polyurethane or silicone and need to be stiff enough to prevent collapse under high negative pressures, but soft enough to prevent kinking. The lumens can be arranged in various fashions but, as long as each lumen is at least 11 French gauge, there is no evidence that one design is superior to the others.

Good flow through the intravenous catheter is crucial to prevent stasis of blood in the circuit and clotting of the filter. There are a number of things to take into account when choosing the site of the vascular access (Table 3).

Extracorporeal circuits

Most CRRT techniques utilise a pump driven, venovenous circuit, as this provides a high constant flow rate. Arteriovenous techniques are described and were used historically, but are associated with catheter associated complications and are less reliable.

Anticoagulation

All modes of RRT that utilise an extracorporeal circuit will activate coagulation pathways and the premature 'clotting off' of a filter is a common problem. Even a small amount of clot formation will reduce filter performance, but if a filter clots off completely the blood contained in the circuit is lost and there an interruption in treatment while a new circuit is prepared.

Clot formation in the filter will trigger the transmembrane pressure alarm, whereas clot in the venous catheter will trigger the access pressure alarm. Kinking of the catheter or a collapsing vein can also

Table 3. Considerations when choosing where to site the central venous catheter.

Line Site	Advantage	Disadvantage
<i>Internal jugular vein</i>	<ul style="list-style-type: none"> • Straightest route (esp right side) and, overall, the preferred site 	<ul style="list-style-type: none"> • Swings in intrathoracic pressure reduce flow • Often occupied by other lines
<i>Subclavian vein</i>	<ul style="list-style-type: none"> • Cleanest site • Most comfortable for patient 	<ul style="list-style-type: none"> • Exposed to intrathoracic pressure changes (as above) • Subclavian vein stenosis* • Pneumothorax
<i>Femoral vein</i>	<ul style="list-style-type: none"> • Fairly straight route and often provides good flows when tip in IVC 	<ul style="list-style-type: none"> • Highest risk of infection (especially in obese patients)

* There is a significant chance of subclavian vein stenosis after large bore venous catheter insertion. This is problematic if an arteriovenous fistula is subsequently required for long term dialysis. However mortality of patients on CRRT is high and those who survive are not usually dialysis dependant.

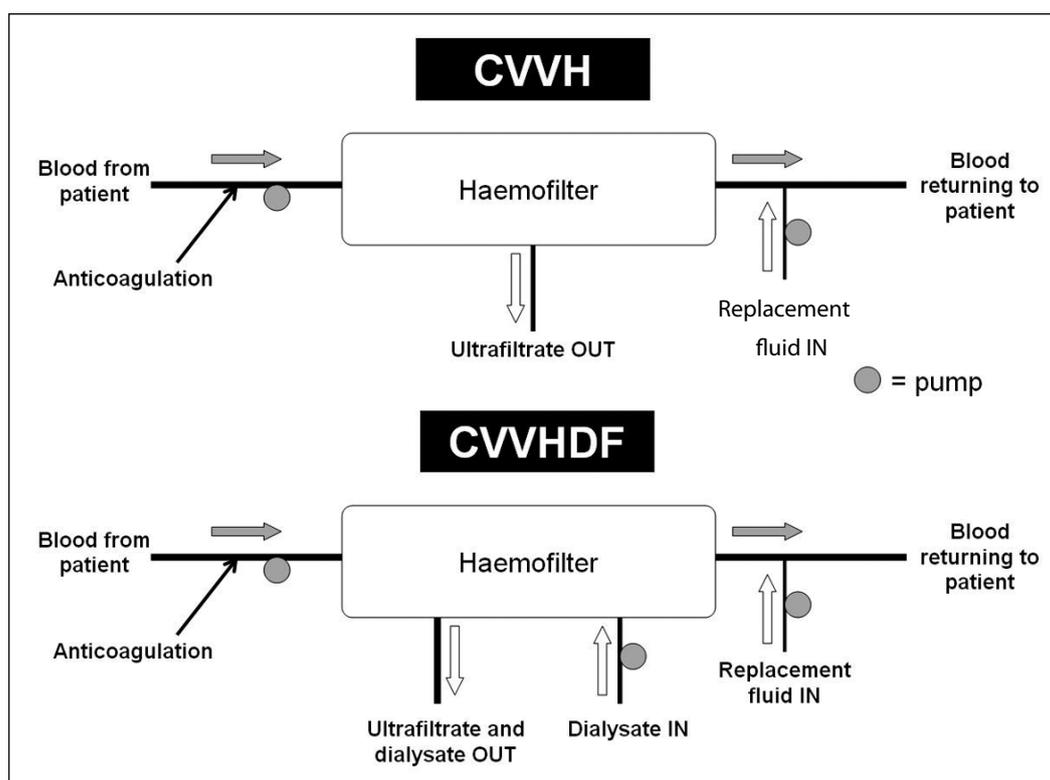


Figure 2. Schematic representation of CVVH and CVVHDF circuits.

be responsible for triggering the access pressure alarm.

Non-pharmacological measures to reduce clot formation include ensuring the patient has an adequate central venous pressure, optimising vascular access and adding a proportion of the replacement fluid to the patient's blood before it passes through the haemofilter (this is *predilution*).

Guidelines published in 2009 by Intensive Care Society (UK) suggest that anticoagulation is NOT required when:¹⁴

- There is already a degree of coagulopathy
 - INR > 2-2.5
 - APTT > 60 seconds
 - platelet count < $60 \times 10^3 \text{.mm}^{-3}$
- There is a high risk of bleeding.

Anticoagulation should be considered in all other situations and the aim is to anticoagulate the filter and not the patient. In practice, this can be more difficult than it sounds. The forms of anticoagulation available are:

Unfractionated or low molecular weight heparins

Unfractionated heparin (UFH) [5-30kDa] is the most commonly used anticoagulant in the UK and a typical regime involves a 40-70IU.kg⁻¹ bolus followed by a pre-filter infusion at 5-10IU.kg.⁻¹h⁻¹. It is the most cost effective anticoagulant and is fully reversible with protamine. The APTT should be monitored to avoid excessive anticoagulation but

there is no evidence that elevating the APTT prolongs filter life.

Low molecular weight heparins (LMWH) [4.5-6kDa] are only used for RRT in 4% of intensive care units in the UK.¹⁵ They are dependant on renal elimination, so in this setting their dosing needs to be guided by anti-factor Xa levels (aiming for 0.25-0.35IU.ml⁻¹). The half life of LMWHs is longer than for UFH (2 - 6hours versus 1.5 - 3hours) and their effect can only be partially reversed with protamine. There is not a huge amount of data on the use of LMWH in CRRT and there is no evidence to suggest that they are superior to UFH.¹⁶

Prostaglandins

Prostaglandins (prostacyclin or prostaglandin E₂) inhibit platelet function and can either be used on their own or in combination with

heparin, with which they have a synergistic effect. Prostaglandins have a short half life (several minutes) so are administered as an infusion (2.5-10ng.kg⁻¹.min⁻¹). The anticoagulant effect stops within 2 hours of discontinuing the infusion, making them a useful alternative to heparin in patients at high risk of bleeding. The main side effect is vasodilation, which may include a reduction in hypoxic pulmonary vasoconstriction leading to hypoxaemia. The other disadvantage is that they are expensive and so are only used as second line therapy.

Regional citrate anticoagulation

Regional citrate anticoagulation is an effective therapy, especially when there is an increased risk of bleeding. It is often used as an alternative to heparin in the USA, but it is rarely used in the UK. Sodium citrate is infused into the circuit pre-filter which chelates calcium and inhibits clot formation. The calcium citrate complex is freely filtered so a calcium infusion is required post-filter.

Others

There is no evidence to suggest newer heparin alternatives such as danaparoid, hirudin, fondaparinux or argatroban are better than UFH/LMWHs.

Filters

The properties of a filter that have an impact on its function are:

Biocompatibility

The degree to which the membrane will activate the patient's inflammatory and coagulation pathways. The greater the biocompatibility of a membrane, the less activation it will cause.

Flux

The permeability of the filter. High flux membranes are hydrophobic and may have more or larger pores allowing more water and solute to move across the membrane.

Adsorption

The ability of larger solutes to adhere to the surface of the membrane. A highly adsorptive membrane offers the potential benefit of adsorbing mid sized molecules, including inflammatory mediators, but only until it is saturated with them (usually after the first few hours).

Thickness

Thinner membranes allow greater movement of solute by diffusion and also favour convective movement.

Surface area

The surface area of the membrane determines the available area for diffusion and ultrafiltration.

Filters are either cellulose-based or synthetic. Synthetic filters, such as polysulphone and polyamide, are more biocompatible and are higher-flux membranes so seem more suitable for CRRT, however, there is no conclusive evidence that they improve outcome. In practice, most filters used for CRRT are synthetic, high-flux membranes with a surface area of 0.6–1.2m² and a pore size allowing the passage of molecules up to 50,000 Daltons.

Replacement fluid

Replacement fluids vary slightly in their composition, but all are balanced salt solutions with either a lactate or bicarbonate buffer.

Lactate based solutions are stable and hence the cheaper and more practical option, however their buffering capacity depends on the conversion of lactate into bicarbonate. Under normal physiological conditions the body converts lactate into bicarbonate on an equimolar basis. This is not always the case in critically ill patients, particularly if they have impaired liver function or already have a lactic acidosis. In these situations, RRT using a lactate based replacement fluid can worsen the patient's acidosis, so a bicarbonate based replacement solution should be used. If this is not possible, and serum lactate levels are not excessive, then an alternative option is to continue with the lactate based replacement solution and commence an intravenous infusion of bicarbonate.

Bicarbonate based replacement solutions have a more reliable buffering capacity, but need to be prepared just prior to use. At present, there is no evidence to suggest that the choice of replacement fluid has an impact on survival or renal recovery.

Replacement fluid can be added pre- or post-filter in varying ratios. The benefit of adding some of the replacement fluid pre-filter is that it lowers the haematocrit of the blood, which reduces the likelihood of the filter clotting. The downside is that pre-dilution reduces solute clearance and a compensatory increase in flow rates should be considered. (15% for ultrafiltration rates of 2L.h⁻¹ and up to 40% for rates of 4.5L.h⁻¹).

Pharmacokinetics while on RRT

Some say that while a patient is receiving RRT drugs should be dosed as if the GFR is 10–50ml.min⁻¹, but unfortunately it is probably not

this simple since there are numerous variables. The most reliable guide to dosing is by measuring drug levels but this is not usually a feasible option, so referring to the drug manufacturer's recommendations is a reasonable place to start.

The factors that affect the pharmacokinetics while on RRT are:

Protein binding

Drugs that are highly protein bound (e.g. warfarin, diazepam, propranolol and phenytoin) are only cleared by RRT in small amounts. However, as the patient's protein levels fall, the free fraction of the drug increases along with its clearance.

Size of drug molecule and mode of RRT

Small molecules (<500 Daltons) are cleared by all (convective versus diffusive) types of RRT, but as molecule size increases diffusion becomes less effective.

Timing of RRT

Drugs given between sessions of IHD or SLED (intermittent versus continuous) will not be cleared until the subsequent session.

Dose of RRT

Reduced flow rates and/or shorter dialysis sessions will reduce clearance of drugs.

Membrane permeability

The high-flux haemofilter membranes used in CRRT are permeable to most non-protein-bound drugs.

The patient's residual GFR

This also needs to be taken into consideration.

Prescription of RRT

A typical prescription for a 75kg patient requiring CRRT for an AKI would be as follows:

Anticoagulation:

- Unfractionated heparin: 5000IU bolus followed by a pre-filter infusion at 500IU.h⁻¹,
- Aim to anticoagulate filter but ensure APTTR <2.

Fluid balance over 24 hours:

- Aim for an even balance if the patient is euvolaemic,
- Aim for the appropriate negative balance if the patient is fluid overloaded (<1500ml.24h⁻¹).

Type of replacement fluid/Dialysate:

- Use solutions without potassium if serum potassium is high, but switch to potassium containing solutions as serum potassium normalises.
- Use a bicarbonate based buffer rather than a lactate based buffer if there are concerns about lactate metabolism or if serum lactate > 8mmol.L⁻¹ [Note - An intravenous bicarbonate infusion may be required if a lactate based buffer is used]

Table 4. CRRT flow rates for a 75kg patient with an AKI.

Hourly flow rate	Hourly exchange rate for a 75kg patient (L.h ⁻¹)	CVVH	CVVHDF	
		Ultrafiltration rate (L.h ⁻¹)	Ultrafiltration rate (L.h ⁻¹)	Dialysate flow rate (L.h ⁻¹)
Standard flow rate (20ml.kg ⁻¹ .h ⁻¹)	1.5	1.5	0.75	0.75
High flow rate* (35ml.kg ⁻¹ .h ⁻¹)	2.6	2.6	1.3	1.3

*Consider high flow rates in patients with septic shock and AKI

Exchange rate/treatment dose:

- 1500ml.h⁻¹ (75kg x 20ml.kg⁻¹.h⁻¹)

The treatment dose is usually prescribed as an hourly ‘exchange rate’ which is the desired hourly flow rate adjusted for the patient’s weight. In the case of CVVH, the exchange rate simply represents the ultrafiltration rate, whereas in CVVHDF it represents a combination of the ultrafiltration rate and the dialysate flow rate. In CVVHDF, the ratio of ultrafiltration to dialysate flow is often set at 1:1, but it can be altered to put the emphasis on either the dialysis or filtration component (Table 4).

COMPLICATIONS

Complications common to IHD, CRRT, and hybrid therapies include:

- Complications related to the vascular access catheter (including line-related sepsis)
- Haemodynamic instability
- Air emboli
- Platelet consumption
- Blood loss
- Electrolyte imbalances
- Hypothermia
- Effects of anticoagulation (bleeding or specific side effects of the anticoagulant used e.g. heparin induced thrombocytopenia).

PROGNOSIS OF PATIENTS WITH AKI ON RRT

Bagshaw et al looked at the outcomes in 240 patients with AKI requiring RRT and showed that, although the mortality rate was high (around 60%), the majority of survivors (78%) were free from RRT at one year. Of those requiring chronic RRT, 63% had pre-existing chronic renal impairment with a median pre-admission creatinine of 232µmol.L⁻¹.⁴

SUMMARY

AKI is common and 5% of the critical care population receive RRT. There are various forms of RRT, but they all remove unwanted solutes using the processes of diffusion (dialysis) and/or convection (filtration). RRT can be administered continuously or intermittently.

No single form of RRT has been shown to offer a survival benefit over the others, but there are often other reasons why a particular technique may be preferable in a given situation. There is some evidence that

high volume haemofiltration may improve survival in patients with septic shock but there have been no large randomised controlled trials in this area.

The lifespan of the circuit is dependant on good quality vascular access and appropriate anticoagulation. Pharmacokinetics must be considered on an individual basis, but there are some general rules, such as drugs which are protein bound are not easily removed.

60% of people receiving RRT for AKI will die during that admission but 80% of the survivors will be free from RRT one year later.

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Peritoneal dialysis in acute kidney injury

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INTRODUCTION

Renal failure requiring renal replacement therapy (RRT) is common and occurs in approximately 6% of hospital admissions, but that number is closer to 35% in intensive care units (ICU). Very little is published about the use of peritoneal dialysis (PD) in acute kidney injury (AKI) due largely to the predominance of publications from high-resource countries, where the high cost of continuous veno-venous therapies is not prohibitive. However, many practitioners from poorly resourced settings have used peritoneal dialysis for a number of years and are well aware of its value. There are a number of reasons why PD may be as good as, and more appropriate than, other forms of RRT for treating patients with acute kidney injury in the ICU (Table 1). In developing countries the cost of PD is often significantly lower than that of haemofiltration, thus allowing more efficient use of precious resources.

BASIC PRINCIPLES OF PERITONEAL DIALYSIS

The peritoneal space is filled with approximately 100ml fluid in normal states and is lined by both visceral and parietal peritoneum. This peritoneal membrane is made up of three components – the mesothelium, interstitium and capillaries.

The mesothelium acts as a protective barrier, but also

increases the surface area of the membrane through villous processes (finger-like projections from the mesothelium). This means the average peritoneal membrane surface area is approximately 20m². It has no role in regulating flow of solute. The interstitium is the matrix which holds the membrane together. The capillaries are the site of selective movement of solutes and water - i.e. the capillary walls **ARE** the semipermeable membrane.

Solute removal

Dialysis occurs through both diffusion and convection. Diffusion is the selective movement of a solute down a concentration gradient through a semipermeable membrane. As an example consider a tea bag from which tea moves into the surrounding water. Convection is the movement of solute with water through a semipermeable membrane, also called solute drag – squeeze a tea bag and more tea comes out with the water. Unlike diffusion this is not a selective process and there is no control over which solutes are removed (as in haemofiltration). Diffusion is responsible for movement of small solutes (K⁺, urea, creatinine etc), convection is the predominant mechanism for movement of proteins and large molecules.

Table 1. Relative benefits of peritoneal dialysis and haemofiltration.

Peritoneal dialysis	Haemofiltration
Cheaper	More ability to control ultrafiltration rate
Biocompatible membrane	Suitable for patients post laparotomy
Cardiovascular stability	
No need for vascular access	
No anticoagulation	
No specialized equipment or nursing required	
More rapid recovery of renal function than haemodialysis	
Easy transition to long term PD	

Summary

The author describes their first-hand experience with this technique in a resource poor setting. Although published trials of its efficacy and safety are few, the significantly lower cost of PD make it the ideal option in a low resource setting.

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How do we achieve these two methods of solute removal?

The PD solution is instilled into the abdominal cavity, causing potassium, urea and creatinine to move from the serum, where levels are high, to the peritoneal fluid where levels are low. Water also moves into the PD fluid by osmosis (see later) and this drags larger molecules with it. Therefore, in order to increase the amount of solute removed, we need to continually replace the fluid that has equilibrated with serum, with new solution to reset the concentration gradient.

A very important factor in achieving clearance of solutes is the time the fluid is in contact with the peritoneal membrane. Therefore time spent draining the dialysis fluid in and out is not effective dialysis time and therefore this needs to be kept to a minimum (see 'Dialysis prescription').

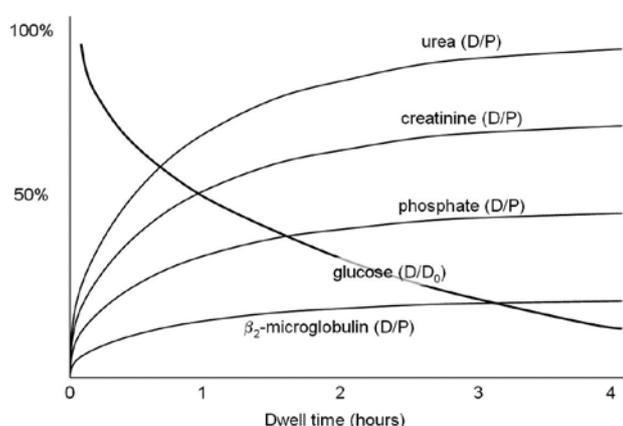


Figure 1. Time taken by various solutes to equilibrate with the serum; D/P = dialysate/plasma ratio; D/D_0 = the ratio of dialysate glucose concentration compared to concentration at time zero.

Fluid removal

Fluid is removed by osmosis. This requires a crystalloid osmotic pressure gradient and this is achieved through the addition of glucose to the PD fluid. Other agents such as amino-acids and icodextrin are also used but not in PD for acute kidney injury.

The higher the concentration of glucose, the more water will be transported into the peritoneal space by osmosis. Unfortunately glucose also diffuses down its concentration gradient in the opposite direction (into the patient) and so, over time, the osmotic gradient falls. If left long enough the glucose level will be so low that there will be a net absorption of fluid by the patient.

Increased fluid removal requires a dialysate with a higher glucose concentration, or reduction in the cycle time, in order to ensure no reabsorption has occurred.

PERITONEAL ACCESS

Originally acute peritoneal dialysis was achieved through various designs of rigid and flexible catheters. The desired features of an acute PD access device are that there is maximal hydraulic flow and minimal interaction with the peritoneal space. It should be simple to insert and reduce the chances of leaks and peritonitis.

There are two commonly used devices used today. The rigid 'stick'

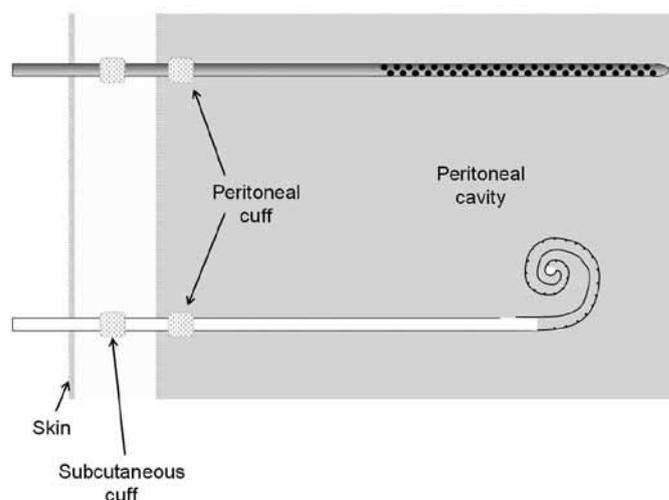


Figure 2. Tenckhoff catheters.

catheter is a plastic catheter, mounted on a stylet that is introduced through a subumbilical incision and directed into the pelvis before the stylet is removed. These catheters are prone to complications and, as they have a narrow lumen, flow of dialysate is sluggish. They also frequently get blocked with fibrin and require flushing. This has the potential to facilitate introduction of bacteria and cause peritonitis. The rigidity of the tube also means that leakage and hemorrhage, due to vessel erosion, are relatively common.

An advantage of these catheters is that they are very easy to insert and the technique can be performed by unskilled staff. They are also cheaper than the more flexible Tenckhoff catheters (see below) but are much less efficient. It is the author's belief that these catheters should only be used if there is no option to use a flexible catheter.

The flexible Tenckhoff catheter is a silastic catheter with two Dacron cuffs and either a straight or coiled end (see Figure 3). It can be inserted by a percutaneous approach at the bedside if there are no contraindications, such as:

- Midline surgical scar
- Previous abdominal TB
- Vertical incision for Caesarean section
- Complicated appendicitis/cholecystectomy.

If contraindications are present, insertion should be done by a surgeon to ensure there is no bowel adherent to the anterior abdominal wall. The percutaneous approach is through a sub-umbilical incision using a guidewire and 'peelaway' sheath, through which the catheter is introduced. The catheter is then tunneled under the skin to facilitate patient care and prevent leaks (Figure 3).

DIALYSIS PRESCRIPTION

There has been concern over the ability of PD to provide adequate clearances in patients with AKI, especially when compared to haemodialysis. This may be true in those cases where a rigid catheter is used and the amount of PD fluid instilled is small. However clinicians in Brazil and India have shown that it is possible to get clearances of urea in excess of those seen with intermittent haemodialysis.^{1,2} Gabriel

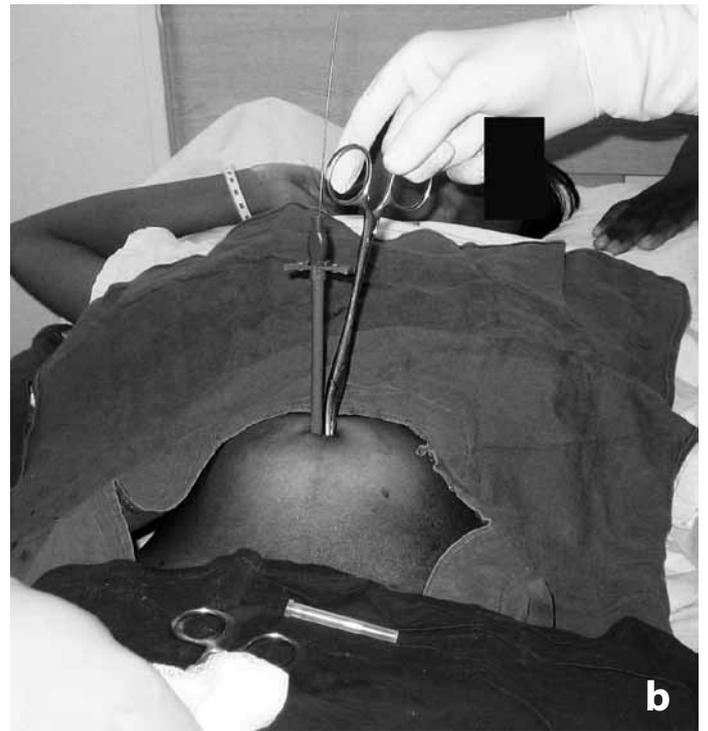


Figure 3. Percutaneous insertion of a Tenckhoff catheter; (a) guidewire inserted through needle or cannula into peritoneal cavity; (b) 'peelaway' sheath inserted with dilator over guidewire; (c) dilator removed and catheter inserted through sheath that is then peeled away; (d) catheter is tunneled under skin.

and Balbi in Brazil randomized critically ill patients with AKI to daily haemodialysis or PD. The mortality was no different and patients recovered renal function 3 days earlier when using PD.¹ It is also possible that clearances of cytokines from the blood may be greater due to the large pores, but this has not yet been confirmed.

The dialysis prescription needs to take into account two factors:

1. Is the patient fluid overloaded?
2. Do they need rapid correction of hyperkalaemia or acidosis?

The dialysis fluid comes in three strengths – 1.36% (1.5%), 2.27% (2.5%), and 3.86% (4.25%) glucose (with the equivalent dextrose

figures in brackets). The higher the concentration of glucose the more fluid is removed into the dialysate. Therefore in a patient with pulmonary oedema due to fluid overload, 3.86% fluid should be used. If the patient is dehydrated, then 1.36% fluid is indicated. It is not only the strength of the fluid, but also how rapidly the cycles are performed, that determines the rate of fluid removal. With increased frequency of fluid exchanges, more fluid is removed. This cycle time should not be less than one hour as the time spent draining in and out becomes greater than the time spent dialysing.

For patients with hyperkalaemia or acidosis, again it is the frequency of fluid exchanges that determines correction of the abnormality. In life

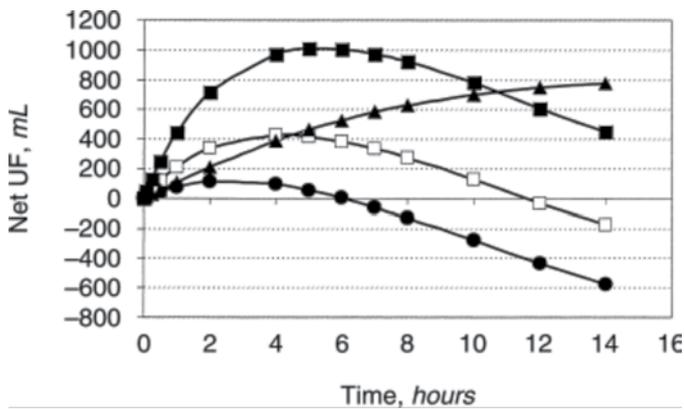


Figure 4. Ultrafiltration profiles of 1.35% (closed circles), 2.27% (open circles) and 3.86% (closed squares) glucose (from reference 3)

threatening disease hourly exchanges can be done until the potassium and pH levels are within a safe range. If hyperkalaemia or acidosis is not severe then two-hourly exchanges are preferable. Usual practice is to continue two-hourly exchanges until the potassium and pH are in the normal range (usually 24 hours) then change to 4 hourly exchanges. This facilitates the clearance of larger molecules and cytokines. It also reduces the cost of dialysis. Remember dialysis will NOT correct a lactic acidosis; this requires management of the precipitating cause.

The volume of fluid is dependant on the size of the patient. The following are recommended:

Table 2. Recommended volume exchanges.

Weight (kg)	Exchange volume (ml)
<50	1000
51-80	1500
>80	2000

Table 3. Suggested dialysis prescription.

	Fluid overload	No fluid overload
K+ > 6.5	Hourly 3.86%	Hourly 1.36%
pH < 7.1	Hourly 3.86%	Hourly 1.36%
K+ < 6.5 and pH > 7.1	Hourly 3.86%	2 Hourly 1.36%
Day 2 onwards	4 hourly 3.86%	4 hourly 1.36%

COMPLICATIONS

Haemoperitoneum is common after the catheter has been inserted, but should clear after a few exchanges. Peritonitis occurs mainly due to touch contamination of the end of the catheter. Bacteria are then

flushed into the peritoneal space. The pH of the PD fluid impairs macrophage function and makes infection more likely. It is therefore imperative that nursing staff understand the importance of cleaning their hands well and not allowing the tip of the catheter to touch anything unsterile. Peritonitis is diagnosed by cloudy PD effluent and a white cell count on the PD fluid of greater than 100ml^{-1} . In acute PD it can often be detected early by doing daily urine dipstix on the fluid. If dipstix shows 2+ leukocytes then 10ml effluent fluid should be sent to the laboratory in blood culture bottles, in order to isolate the causative organism.

If over 100 white blood cell per ml are seen then start empiric antibiotics using vancomycin or a 1st generation cephalosporin (to cover gram positive organisms) and either ceftazidime or an aminoglycoside to cover gram negative organisms including pseudomonas. They should be added to each bag using a sterile technique to inject them. If the range of antibiotics available is limited, then gentamicin is probably the best choice to cover *Staphylococci* (usually coagulase negative) and Gram negative organisms. Some sites find that amikacin provides better cover.

If the bags have not become clear by day 3, or if the patient develops sepsis with no other evident source, or if the culture reveals a fungal infection, the catheter should be removed.

Fibrin is commonly found in the fluid of patients on acute PD and

Table 4. Antibiotic dosing for peritonitis.

Vancomycin	Load 1g.L^{-1} then 25mg.L^{-1}
Cefazolin	Load 500mg.L^{-1} then 125mg.L^{-1}
Ceftazidime	Load 500mg.L^{-1} then 125mg.L^{-1}
Amoxicillin	125mg.L^{-1} in all bags
Oxacillin	125mg.L^{-1} in all bags
Chloramphenicol	500mg - 1g 6hrly IV
Gentamicin	Load 8mg.L^{-1} then 4mg.L^{-1}

often contributes to blocking of catheters and poor drainage. This can be prevented by adding 500 units of heparin to each litre of PD fluid.

If the catheter blocks try flushing with 20ml 0.9% saline, using a sterile pack and gloves. If that does not work then passing a central venous catheter guidewire down the catheter may work. It may also be that the catheter is wrapped in omentum in which case it will need to be removed, but a new catheter can be inserted through the same incision.

Hypokalaemia can occur with rapid exchanges used to treat pulmonary oedema. If the potassium falls, add 4mmol KCl to each litre of fluid. This will not result in hyperkalaemia as the potassium will only equilibrate and extra potassium will not be absorbed. Hyponatraemia may occur with rapid cycling. If the patient is not fluid overloaded, 5% glucose can be infused intravenously to maintain normal sodium levels.

CONCLUSION

Peritoneal dialysis offers significant advantages over haemodialysis and haemofiltration in its simplicity, cost effectiveness, lack of need for expensive machinery and more rapid recovery of renal function. There is evidence of similar outcomes when compared to haemodialysis and filtration, although larger trials are needed.

It should be considered in all centres where haemofiltration cannot be offered or costs are prohibitive.

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Neurological causes of muscle weakness in the Intensive Care Unit

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Summary

Muscle weakness can be the cause of admission to ICU, or may develop during the ICU stay. The common causes are described with detailed description of critical illness polyneuropathy and myopathy.

INTRODUCTION

Patients with muscle weakness may require ICU admission due to ventilatory failure or for airway protection against pulmonary aspiration. Some neurological conditions causing muscle weakness also cause autonomic nervous system failure, requiring invasive monitoring and haemodynamic support. Significant weakness may also develop secondary to ICU admission, such as critical illness polyneuropathy and myopathy. This review will discuss the more common disease processes that cause muscle weakness in intensive care.

ASSESSMENT FOR ICU ADMISSION^{1,2}

Regardless of the cause, a systematic approach must be used when assessing and treating a patient with muscle weakness. Timing of intubation and ventilation may be difficult to judge. Impaired conscious level, aspiration, airway obstruction, hypoxaemia or hypercapnoea usually indicate that immediate intervention is needed. Uncertainty about the prognosis and potential for recovery of function in some conditions raises ethical questions about the appropriate level of medical interventions. However most conditions are reversible or controllable and full supportive measures are appropriate. A combination of subjective clinical assessment and lung function tests, in addition to careful consideration of pre-existing physiological reserve and patient wishes, is required to inform management decisions.

Features indicating the need for airway protection and ventilatory support are:

- Rapidly progressive weakness,
- Difficulty swallowing,
- Altered speech,
- New onset shortness of breath at rest,
- More subjective signs include:
 - Rapid shallow breathing,
 - Weak cough,
 - 'Abdominal' breathing – indicating a reliance on diaphragmatic breathing.

- Staccato speech – abrupt speech where each syllable is produced separately, indicating poor expiratory function,
- Accessory muscle use – abdominal muscles, sternocleidomastoid etc,
- Cough or gurgling after swallowing.

Lung function tests may not be available and their use is often limited due to poor technique and variability between individuals. Some patients with Guillain-Barré may be unable to create a seal around the mouth piece due to facial weakness. When available, lung function tests should ideally be monitored 4 hourly. The tests that are considered most useful include:

Test	Values suggesting need for mechanical ventilation
Vital capacity	< 15ml.kg ⁻¹ , < 1litre or reduction by 50% from baseline
Negative inspiratory force	< 30cmH ₂ O
Expiratory force	< 40cmH ₂ O
Nocturnal desaturation	

It is vital to be guided by regular clinical reassessment and the trend of PaO₂ and PaCO₂ on arterial blood gas analysis. Patients with neuromuscular weakness may appear comfortable but be close to decompensation. If intubation is planned in this patient group, previous immobility increases the risk of hyperkalaemia in response to suxamethonium. Consider alternative strategies, such as using rocuronium or awake intubation using local anaesthesia.

The mechanism of ventilatory failure can be subdivided, but different causes often co-exist:

Inspiratory muscle weakness

Segmental lung collapse leads to reduced functional residual capacity (FRC), atelectasis, infection and ventilation-perfusion (V/Q) mismatch.

Expiratory muscle weakness

Inadequate cough to clear secretions and open the distal airways exacerbates the effects above.

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Bulbar weakness

This is failure of the pharyngeal and laryngeal muscles to maintain airway patency and to protect the airways from aspiration and soiling.

Complications of immobility

These include thromboembolic disease, pneumonia and pressure sores.

The differential diagnosis of the causes of muscle weakness is extensive. The most common causes are described below. ICU management is based on careful attention to monitoring physiological function and early intervention to support failing organ systems, before irreversible damage occurs.

NEUROMUSCULAR CAUSES OF WEAKNESS

Guillain-Barré Syndrome (GBS)

Epidemiology

GBS is an acute demyelinating polyneuropathy. It is usually (70%) associated with infection, typically *Campylobacter jejuni* gastroenteritis or respiratory tract infections, but may occur after various other insults such as surgery, vaccination, transplantation and some drugs. Presentation is variable, the classical being an ascending (compared to botulism) flaccid bilateral limb weakness with areflexia. Sensory symptoms are common, including neuropathic pain, but sensory signs are generally absent. It must be suspected in anyone with unexpected limb weakness or sensory deficit.

Pathophysiology

The aetiology is believed to involve antibody cross-reactivity to components of peripheral nervous tissue and various anti-ganglioside antibodies are found in patients with GBS.

Clinical features

Patients typically present with areflexia, weakness ascending from the lower limbs and often hyperpathic pain within a month of a potential cause. Symptoms develop over several days but may be more rapid, suggesting a worse prognosis. The Miller-Fischer variant presents with ataxia, areflexia and ophthalmoplegia.

Investigations

Specific investigations are useful to guide treatment and include CSF examination, which shows a disproportionate increase in protein levels with respect to CSF leucocytes. There is typically CSF pleocytosis of up to 10 cells per mm³. Pleocytosis of 10-20 cells per mm³ may suggest concurrent HIV infection. Electrophysiological tests demonstrate a pattern of peripheral demyelination.

Treatment

The crucial aspect of management is general supportive measures, potentially for several months. In addition, specific treatment by immunomodulation is effective (see below). Bulbar function can be affected and require definitive airway protection with orotracheal intubation or later with tracheostomy. If there has been a period of immobility prior to ventilatory failure, suxamethonium may induce a significant hyperkalaemic response and alternative techniques should be considered.

Autonomic dysfunction in GBS can be very difficult to manage and causes serious morbidity and mortality. Stimulation by laryngoscopy and tracheal suction may precipitate severe cardiovascular instability. Use of topical anaesthetics, judicious use of atropine, where indicated, and small doses of short acting benzodiazepines should be considered. Generally sympathetic activity predominates, with tachycardia and labile blood pressure, but this lability makes treatment difficult and hazardous. If necessary, short acting agents such as esmolol (a β -blocker) are most appropriate to use. Rarely, bradycardia requires temporary pacing.

Intravenous immunoglobulin (IVIg) and plasmapheresis, with albumin replacement, are equally effective in improving outcomes, but are of most benefit when started as soon as possible after onset of symptoms.^{3,4} Plasmapheresis at 50ml.kg⁻¹.day⁻¹, 5 times, over 1-2 weeks, within 4 weeks of onset, increases speed of recovery and improves neurological outcome. There is no benefit in performing more exchanges. Continuous flow plasma exchange machines may be superior to intermittent flow machines, and albumin maybe better than fresh frozen plasma as the exchange fluid. IVIg at 400mg.kg⁻¹.day⁻¹ for 5 days is as effective as plasmapheresis, and there is no additional benefit in combining the two therapies.³

The choice between IVIg and plasmapheresis is based on availability and the limits of the patient's physiology and co-morbidities. IVIg is preferable where the patient has significant haemodynamic instability, sepsis and difficult central vascular access. Plasmapheresis is the treatment of choice when there is concurrent renal failure, congestive heart failure, hyperviscosity or IgA deficiency (risk of anaphylactic reaction with IVIg). Corticosteroids have been shown to be ineffective and in some studies have been associated with a worse outcome.⁴ CSF filtration may be of benefit but is currently considered an experimental treatment.

GBS does not affect conscious level, and the prolonged course will inevitably have psychological consequences. Sedation should be used when necessary, though over-sedation for prolonged periods is likely to worsen psychological as well as physical recovery. Occupational therapy and physiotherapy are of importance in rehabilitation and should start as soon as is practicable. Passive exercise is important to reduce muscle wasting and prevent contractures.

Prognosis

5-10% of cases will be fatal, with deaths usually due to autonomic nervous system dysfunction, pulmonary embolus or pneumonia. Most patients make a virtually full recovery, but 10% cannot walk at one year.

Myasthenia gravis (MG)

Epidemiology

MG has an annual incidence of about 5 per million population and MG prevalence is about 10 per 100000 population. In young Caucasian adults, most cases are female, with a shift to males in the over 50s. Prepubertal presentation is relatively common in Asians.

Pathophysiology

MG is an autoimmune disease, characterised by production of an autoantibody against the post-junctional nicotinic acetylcholine

(ACh) receptors of the neuromuscular junction. Receptor numbers are greatly depleted, resulting in a characteristic fluctuating weakness with fatiguability of bulbar, ventilatory, extra-ocular and proximal upper limb muscles. Reflexes, sensation or other neurological functions are usually intact.

Clinical features

MG should be suspected in any patient with weakness associated with fatiguability, especially in the presence of ptosis, diplopia, poor head control, flaccid dysarthria (nasal, staccato speech), chewing weakness and difficulty swallowing. An uncommon sub-type, characterised by the presence of muscle-specific tyrosine kinase antibodies, may present with ventilatory failure. Motor weakness should improve with rest and increase significantly with administration of a cholinesterase inhibitor, such as edrophonium or neostigmine. Deep tendon reflexes are present, in contrast to GBS.

The combination of one or more of the above and one or more of the following features confirms the diagnosis:

- ACh receptor antibodies.
- Characteristic electromyographic (EMG) studies - increased single fibre 'jitter', decremental response to repetitive peripheral nerve stimulation, reversed by a cholinesterase inhibitor.

Exacerbating factors

With known cases of MG it is important to identify, avoid or minimise factors that may precipitate a myasthenic crisis.

- Lower respiratory tract infections (probably most common)
- Aspiration / airway soiling
- Sepsis
- Surgery
- Reduction of immunological therapy
- Commencement of steroid therapy
- Pregnancy
- Drugs:
 - Neuromuscular blocking drugs - profoundly sensitive to non-depolarising agents, probably resistant to depolarising agents (suxamethonium)
 - Some antibiotics - aminoglycosides especially gentamicin, macrolides
 - Beta-blockers, calcium channel blockers, procainamide, quinidine
 - Quinine
 - Corticosteroids
 - Magnesium
 - Tocolytics
 - Iodinated contrast agents
 - Penicillamine.

Treatment

The most commonly used cholinesterase inhibitor is pyridostigmine. The dose for adults starts at 30mg 4-5 times a day, up to a maximum of 60mg 4-5 times a day. Higher doses run the risk of precipitating a cholinergic crisis, which causes weakness through a depolarising neuromuscular block and may also result in ventilatory failure. The characteristic features of a cholinergic crisis allow it to be clinically differentiated from a myasthenic crisis and include:

- Hypersalivation, lacrimation and sweating
- Miosis (constricted pupils)
- Abdominal pain, nausea, diarrhoea, vomiting
- Bradycardia.

Any concern about cholinergic excess should be managed by intubation and ventilation. Once intubated, anticholinesterases should be stopped to reduce cholinergic complications.

In myasthenic crisis plasmapheresis is effective in improving muscle power, although it may not improve functional outcome.⁵ There is less evidence for the use of IVIg for moderate to severe MG,⁶ however some authorities recommend its use if plasmapheresis is contraindicated or unavailable.

Patients presenting with a crisis may have had significant doses of steroids and other immunosuppressants. Thymectomy is a well established treatment for certain subgroups - this is specialist surgery, requiring careful preoperative planning and optimization of muscle function. A patient in myasthenic crisis is unlikely to benefit from thymectomy acutely.

Noninvasive ventilation (NIV) may be considered as a temporizing measure, as long as the airway is patent and enough bulbar function remains to clear secretions. Patients with MG may do better with NIV than others with neuromuscular weakness, as it provides muscle rest and allows strength to improve. Many eventually need intubation and invasive ventilation.

Prognosis

The general outlook is good, with 90 per cent achieving near normal functional recovery. The side effects of potent immunomodulatory treatment may significantly impact on mortality and morbidity.

Botulism

Epidemiology

Botulism is rare in the developed world. The first recorded cases of food-borne botulism in the UK occurred in 1922, caused by duck paste sandwiches. Eight people were affected and all died. Ten incidents have been reported since, with 11 deaths among the 50 people concerned. Five of the 11 were caused by commercially produced foods. No single food or type of food has predominated; five were vegetarian, four meat, and two fish. Classic food-related botulism is rare, but in recent years, an increase in wound botulism associated with injected drugs (particularly black tar heroin) has been seen.

Pathophysiology

Toxins formed by the microorganism *Clostridium botulinum* interrupt

neuromuscular transmission by cleaving proteins necessary for release of acetylcholine from nerve terminals. This also affects transmission at autonomic ganglia and parasympathetic nerve terminals. The process is permanent. The toxins are either ingested pre-formed (e.g. food poisoning) or formed in vivo (e.g. wound, infant and adult intestinal botulism). The use of botulinum toxin as a biological weapon results in inhalational botulism.

Clinical features

Signs and symptoms of food-borne botulism generally develop within 12-36 hours of ingestion of contaminated food. The severity is proportional to the amount of toxin ingested. The clinical picture is a rapid onset symmetrical descending flaccid paralysis, with multiple cranial neuropathies, in the absence of fever or altered consciousness. Gastrointestinal symptoms including nausea, vomiting, diarrhoea and colicky pain, may precede the neurological signs. These are absent in wound botulism, which has a longer incubation period of up to a week. Parasympathetic dysfunction may present early, with dry mouth and blurred vision associated with dilated, poorly reactive pupils. Further autonomic dysfunction may manifest as gastrointestinal dysmotility, orthostatic hypotension, altered resting pulse, urinary retention, or hypothermia. Diplopia often develops secondary to extraocular muscle weakness. Bulbar weakness may result in flaccid dysarthria, chewing difficulty and dysphagia. The upper limbs, trunk and lower limbs may become weak in a descending pattern. Respiratory compromise occurs due to a combination of upper airway obstruction from weak oropharyngeal muscles and diaphragmatic weakness.

Treatment

Prolonged (30-60 days) ventilatory support is usually necessary, as recovery depends on re-growth of nerve terminals. Trivalent antitoxin may reduce severity, but, due to the irreversible binding of the toxin, it must be given as early as possible.

Prognosis

With improvements in respiratory care, the case-fatality rate has improved from 60% during 1899 to 1949, to 12.5% during 1950 to 1996. The fatality risk for the index case in an outbreak is 25%, with a 4% fatality risk for subsequent cases, after recognition of an outbreak. The public health implications of botulism make it mandatory to report it to the relevant public health body.

MUSCLE WEAKNESS ACQUIRED DURING CRITICAL ILLNESS

Weakness acquired during intensive care may be due to GBS, unmasked myasthenic disorders, spinal cord infarction or electrolyte imbalance. However, it is now recognised that the most common muscular causes of failure to wean from mechanical ventilation in ICU are critical illness polyneuropathy, critical illness myopathy and prolonged neuromuscular blockade.

Electrolyte disorders

Disturbance of biochemical homeostasis is common in the intensive care unit and the principle electrolyte abnormalities contributing to muscle weakness and ventilatory failure are:

- Hypermagnesaemia
- Hypophosphataemia

- Hypo/hyperkalaemia.

Rhabdomyolysis

This potentially devastating cause of muscle weakness must be considered and excluded. Causes include various drugs, trauma, surgery and prolonged muscle compression.

Critical illness polyneuropathy - CIP

Initially described in the early 1980's, this condition is associated with the systemic inflammatory response syndrome (SIRS), sepsis and multiple organ failure. 70% of such patients have electrophysiological features of CIP and 30% have subsequent difficulty weaning from ventilation. It is a widespread axonal peripheral neuropathy, causing weakness and wasting of extremity muscles, distal sensory loss and paraesthesia. The cranial nerves are typically spared. The main differential diagnosis is GBS, which is often excluded on clinical grounds, with electrophysiological studies rarely being necessary.

The prognosis depends on resolution of the antecedent disease, but survivors should recover good function over several months. CIP does not seem to adversely affect long term survival.

Recently, tight glycaemic control has been shown to reduce the development of CIP.

Critical illness myopathy - CIM (Acute myopathic quadruplegia)

This condition is typically associated with severe respiratory disease, such as status asthmaticus. Most cases occur after use of non-depolarising neuromuscular blocking drugs and high dose corticosteroids, although cases also occur independently of these factors. Many other predisposing agents have been identified, such as muscle relaxation induced by other drugs, for example propofol or benzodiazepines.

A flaccid global weakness develops after several days of muscle relaxation but sensation remains intact. Serum creatine kinase may be elevated, especially if measured early in the course of the myopathy. Electrophysiology studies demonstrate normal sensory action potentials, but reduced amplitude of compound muscle action potentials. Muscle histology, which is unnecessary for clinical management, shows myosin loss. Like CIP, CIM may require prolonged ventilatory support, but should not worsen the patient's long term outcome, with muscle function typically recovering over weeks to months.

Where possible the use of high doses of corticosteroids should be avoided, especially when non-depolarising muscle relaxants are being administered. There is little to be gained from differentiation between these two conditions, as management is the same for both. Some authors feel that they represent two ends of a spectrum of disease.

Prolonged neuromuscular blockade

Continuous infusions of neuromuscular blocking agents have been associated with delayed return of muscle strength. This is due to the effects of hepatic and renal dysfunction on the metabolism of steroidal muscle relaxants such as vecuronium. This problem can be significantly reduced by limiting the use of these agents through appropriate

ventilator modes, available on more modern machines and through effective, appropriate sedation. If absolutely essential, infusions should be monitored properly by peripheral nerve stimulation and adjusted to maintain a minimal level of muscle relaxation i.e. 1-2 twitches in response to supra-maximal stimuli in a train-of-four pattern. Alternatively, daily infusion breaks, allowing return of muscle activity before re-paralysing, may be useful.

GENERAL MANAGEMENT

The requirement for ventilatory support may be prolonged and so nutrition, patient positioning, thromboprophylaxis and other preventative measures are especially important. Consideration must also be given to the inevitable psychological impact on the patient and their family.

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Tetanus

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INTRODUCTION

In spite of the World Health Organization's intention to eradicate tetanus by the year 1995, it remains endemic in the developing world. The WHO estimated that there were approximately one million deaths from tetanus worldwide in 1992. This included 580,000 deaths from neonatal tetanus, of which 210 000 were in South East Asia and 152,000 in Africa. The disease is uncommon in developed countries. In South Africa approximately 300 cases occur each year (6 per million population), approximately 12-15 cases are reported each year in Britain (0.2 per million) and between 50 and 70 in the USA (0.2 per million).

Tetanus is caused by a Gram-positive bacillus, *Clostridium tetani*. This is a common bacterium with a natural habitat in the soil. It can also be isolated from animal and human faeces. It is a motile, spore-forming obligate anaerobe. The spore is incompletely destroyed by boiling, but eliminated by autoclaving at 1 atmosphere pressure and 120°C for 15 minutes. It is rarely cultured and diagnosis of the disease is clinical. *Clostridium tetani* produces its clinical effects via a powerful exotoxin. The role of the toxin within the organism is not known. The DNA for this toxin is contained in a plasmid (DNA that is separate from and can replicate independently of the bacteria's chromosomal DNA). Presence of the bacterium does not always mean that the disease will occur, as not all strains possess the plasmid. Bacterial antimicrobial sensitivity has been little investigated.

As infection does not confer immunity, prevention is through vaccination. Tetanus vaccine has been available since 1923. Vaccination is started at 2 months of age with three injections performed at monthly intervals. The second injection confers immunity, with the third prolonging its duration. A booster is given before the age of 5. Similar responses occur in older children and adults. Neonatal immunity is provided by maternal vaccination and transplacental transfer of immunoglobulin. This may be impaired in the presence of maternal HIV infection. Immunity is not life-long. Revaccination at 10-yr intervals is recommended in the USA. In the UK, two boosters spaced 10 years apart are recommended in adulthood, so the recommendations

do not extend to vaccination beyond the third decade. Thus in the UK, after these 5 injections patients are considered immune, and there is no value in giving further prophylactic doses. In the USA, more than 70% of cases and 80% of deaths occur in those over 50. Similar proportions are reported in Europe.

PATHOPHYSIOLOGY

Under the anaerobic conditions found in necrotic or infected tissue, the tetanus bacillus secretes two toxins: *tetanospasmin* and *tetanolysin*. Tetanolysin is capable of locally damaging viable tissue surrounding the infection and optimizing the conditions for bacterial multiplication.

Toxins

Tetanospasmin leads to the clinical syndrome of tetanus. It binds to neural membranes and the amino terminus facilitates cell entry. It acts pre-synaptically to prevent neurotransmitter release from affected neurones. Released tetanospasmin spreads to underlying tissue and binds to gangliosides on the membranes of local nerve terminals. If toxin load is high, some may enter the bloodstream from where it diffuses to bind to nerve terminals throughout the body. The toxin is then internalized and transported intra-axonally and retrogradely to the cell body. Transport occurs first in motor, and later in sensory and autonomic, nerves. Once in the cell body the toxin can diffuse out, affecting and entering nearby neurones. When spinal inhibitory interneurons are affected, symptoms occur. Further retrograde intraneural transport occurs with toxin spreading to the brainstem and midbrain. This passage includes retrograde transfer across synaptic clefts by a mechanism that is unclear.

Toxins and the CNS

The effects of the toxin result from prevention of neurotransmitter release. Synaptobrevin is a membrane protein necessary for the export of intracellular vesicles containing neurotransmitter. The tetanospasmin cleaves synaptobrevin, thereby preventing neurotransmitter release. The toxin has a predominant effect on inhibitory neurones, inhibiting release of glycine and gamma-aminobutyric acid (GABA). The term 'disinhibition' is used as the main effect of tetanus. This

Summary

Tetanus remains an important cause of death worldwide and is associated with a high mortality, particularly in the developing world. With modern intensive care management, death from acute respiratory failure should be prevented, but cardiovascular complications as a result of autonomic instability and other causes of death remain.¹ In this article, the pathophysiology, clinical features and current management of tetanus are reviewed.

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results in a failure of inhibition (relaxation) of muscle groups, leading to increased muscle tone and muscular spasms because the muscles are unable to relax. In normal muscles, when one muscle group contracts there has to be a corresponding relaxation of the opposing muscle group. In tetanus this is prevented and results in intermittent spasms. Interneurons inhibiting alpha motor neurones are first affected and the motor neurones lose inhibitory control. Later (because of the longer pathway), pre-ganglionic sympathetic neurones in the lateral horns and the parasympathetic centres are also affected.

Motor neurones are similarly affected and the release of acetylcholine into the neuromuscular cleft is reduced. This effect is similar to the action of the closely related botulinum toxin, which produces a flaccid paralysis. However, in tetanus the disinhibitory effect on the motor neurone overwhelms any diminution of function at the neuromuscular junction. Medullary and hypothalamic centres may also be affected. Tetanospasmin has a cortical convulsant effect in animal studies. Whether these mechanisms contribute to intermittent spasm and autonomic storms is unclear. The pre-junctional effect on the neuromuscular junction may lead to considerable weakness between spasms, and might account for both the paralysis of cranial nerves observed in cephalic tetanus, and myopathies observed after recovery.

Uninhibited efferent discharge from motor neurones in the spinal cord and brainstem leads to intense muscular rigidity and spasm, which may mimic convulsions. The reflex inhibition of antagonist muscle groups is lost, and agonist and antagonist muscles contract simultaneously. Muscle spasms are intensely painful and may lead to fractures and tendon rupture. Muscles of the jaw, face, and head are often involved first because of their shorter axonal pathways. The trunk and limbs follow but peripheral muscles in the hands and feet are relatively spared.

Disinhibited autonomic discharge leads to disturbances in autonomic control, with sympathetic overactivity and excessive plasma catecholamine levels. Neuronal binding of toxin is thought to be irreversible. Recovery requires the growth of new nerve terminals, which explains the prolonged duration of tetanus.

CLINICAL FEATURES

Tetanus usually follows a recognized injury. Contamination of wounds with soil, manure, or rusty metal can lead to tetanus. It can complicate burns, ulcers, gangrene, necrotic snakebites, middle ear infections, septic abortions, childbirth, intramuscular injections, and surgery. Injuries may be trivial, and in up to 50% of cases the injury occurs indoors and/or is not considered serious enough to seek medical treatment. In 15-25% of patients, there is no evidence of a recent wound.

Presentation

There is a clinical triad of rigidity, muscle spasms and autonomic dysfunction. Neck stiffness, sore throat, and difficulty opening the mouth are often early symptoms. Masseter spasm causes trismus or 'lockjaw'. Spasms progressively extend to the facial muscles, causing the typical facial expression risus sardonius (literally a 'sarcastic smile' - Figure 1), and muscles of swallowing, causing dysphagia. Rigidity of the neck muscles leads to retraction of the head. Truncal rigidity may lead to opisthotonus, which is the severe arching of the back

during a spasm caused by the stronger extensor muscle group (Figure 2). Respiratory difficulty with decreased chest wall compliance may also result.



Figure 1. *Risus sardonius*.



Figure 2. *Opisthotonus* in a 21-month-old with a foot wound.

In addition to increased muscle tone, there are episodic muscular spasms. These tonic contractions have a convulsion-like appearance affecting agonist and antagonist muscle groups together. They may be spontaneous or triggered by touch, visual, auditory or emotional stimuli. Spasms vary in severity and frequency, but may be strong enough to cause fractures and tendon avulsions. Spasms may be almost continual, leading to respiratory failure. Pharyngeal spasms are often followed by laryngeal spasms and are associated with aspiration and life threatening acute airway obstruction.

Generalized tetanus, the commonest form of tetanus, affects all muscles throughout the body. The muscles of the head and neck are usually affected first, with progressive caudal spread of rigidity and spasm to affect the whole body. The differential diagnosis includes orofacial infection, dystonic drug reactions, hypocalcaemia, strychnine poisoning and hysteria.

Local tetanus is seen with lower toxin loads and peripheral injuries. Spasm and rigidity are restricted to a limited area of the body. Mortality is greatly reduced. An exception to this is cephalic tetanus when

localized tetanus from a head wound affects the cranial nerves; paralysis rather than spasm predominates at presentation, but progression to generalized tetanus is common and mortality is high.



Figure 3. Cephalic tetanus with right facial nerve palsy.

Tetanus neonatorum causes more than 50% of deaths from tetanus worldwide but is very rare in developed countries. Neonates present within a week of birth with a short history of failure to feed, vomiting, and 'convulsions'. Seizures, meningitis and sepsis are differential diagnoses. Spasms are generalized and mortality is high. Poor umbilical hygiene is the cause of the disease but it is entirely preventable by maternal vaccination, even during pregnancy.

Autonomic effects

Prior to the introduction of artificial ventilation, many patients with severe tetanus died from acute respiratory failure. With the

development of intensive care and the ability to ventilate patients it became apparent that severe tetanus was associated with marked autonomic instability. The sympathetic nervous system is most prominently affected. Clinically, increased sympathetic tone causes persistent tachycardia and hypertension. Marked vasoconstriction and pyrexia are also seen. Basal plasma catecholamine levels are raised.

'Autonomic storms' occur with marked cardiovascular instability. Severe hypertension and tachycardia may alternate with profound hypotension, bradycardia, or recurrent cardiac arrest. These changes are a result of rapid alterations in systemic vascular resistance, rather than problems with cardiac filling or performance. During these 'storms' plasma catecholamine levels are raised up to 10-fold, to levels similar to those seen in pheochromocytoma. Norepinephrine (noradrenaline) is affected more than epinephrine (adrenaline). Neuronal hyperactivity, rather than adrenal medullary hyperactivity, appears to predominate.

In addition to the cardiovascular system, other autonomic effects include profuse salivation and increased bronchial secretions. Gastric stasis, ileus, diarrhoea, and high output renal failure may all be related to autonomic disturbance.

The involvement of the sympathetic nervous system is established. The role of the parasympathetic system is less clear. Tetanus has been reported to induce lesions in the vagal nuclei, while locally applied toxin may lead to excessive vagal activity. Hypotension, bradycardia, and asystole may arise from increased vagal tone and activity.

Natural history

The incubation period (time from injury to first symptom) averages 7-10 days, with a range of 1-60 days. The onset time (time from first symptom to first spasm) varies between 1-7 days. Shorter incubation and onset times are associated with more severe disease. The first week of the illness is characterized by muscle rigidity and spasms, which progressively increase in severity. Autonomic disturbance usually starts several days after the spasms, and persists for 1-2 weeks. Spasms reduce after 2-3 weeks, but stiffness may persist considerably longer. Recovery from the illness occurs because of re-growth of axon terminals and by toxin destruction.

SEVERITY GRADING

There are several grading systems but the system reported by Ablett is most widely used (Table 1).

Table 1. Ablett classification of tetanus severity

Grade		Clinical features
1	Mild	Mild trismus, general spasticity, no respiratory embarrassment, no spasms, no dysphagia.
2	Moderate	Moderate trismus, rigidity, short spasms, mild dysphagia, moderate respiratory involvement, respiratory rate > 30, mild dysphagia.
3	Severe	Severe trismus, generalized spasticity, prolonged spasms, respiratory rate > 40, severe dysphagia, apnoeic spells, pulse > 120.
4	Very severe	Grade 3 with severe autonomic disturbances involving the cardiovascular system.

Altered cardiovascular physiology

In uncomplicated tetanus, the cardiovascular system mimics that of a normal patient undergoing intense exercise. There is a hyperdynamic circulation, largely because of increased basal sympathetic activity and muscle metabolism, with a lesser effect from raised core temperature. There is low-normal systemic vascular resistance and raised cardiac output, because of extensive vasodilatation in metabolically active muscles.

As the oxygen extraction ratio does not alter in tetanus, the increased demand must be delivered by increased blood flow. Poor spasm control exaggerates these effects. In severe tetanus, patients are less able to increase cardiac performance and are more susceptible to profound hypotension and shock during acute vasodilatory storms. The mechanism is unclear, but may relate to sudden reduction of catecholamine secretion or a direct action of tetanus toxin on the myocardium. Altered myocardial function may occur due to persistently raised catecholamine levels, but abnormal function may occur even in the absence of sepsis or high catecholamine levels.

Altered respiratory physiology

Muscular rigidity and spasms of the chest wall, diaphragm and abdomen lead to a restrictive defect. Pharyngeal and laryngeal spasms predict respiratory failure or life threatening airway obstruction. Poor cough from rigidity, spasms, and sedation leads to atelectasis and the risk of pneumonia is high. The inability to swallow copious saliva, profuse bronchial secretions, pharyngeal spasms, raised intra-abdominal pressure and gastric stasis all increase the risk of aspiration, which is common. Ventilation/perfusion mismatch is also common. Consequently, hypoxia is a uniform finding in moderate or severe tetanus, even when the chest is radiologically clear. When breathing air, oxygen tensions are often between 5.3-6.7kPa (40-50mmHg), with the oxygen saturation commonly falling below 80%.

In artificially ventilated patients, increased alveolar-arterial gradients persist. Oxygen delivery and utilization may be compromised even without super-added lung pathology. Acute respiratory distress syndrome may occur as a specific complication of tetanus. Minute ventilation may be altered by a variety of causes. Hyperventilation may occur because of fear, autonomic disturbance, or alteration in brainstem function. Hypocarbica (PaCO_2 4.0-4.6kPa, 30-35mmHg) is usual in mild to moderate disease. Hyperventilation 'storms' may lead to severe hypocarbica ($\text{PaCO}_2 < 3.3\text{kPa}$, 25mmHg). In severe disease, hypoventilation from prolonged spasms and apnoea occurs. Sedation, exhaustion and altered brainstem function may also lead to respiratory failure. Respiratory drive may be deficient, leading to recurrent life threatening apnoeic periods.

Altered renal physiology

In mild tetanus, renal function is preserved. In severe disease reduced glomerular filtration rate and impaired renal tubular function are frequent. Contributory causes of renal failure include dehydration, sepsis, blocking of the renal tubule with myoglobin (as a result of muscle breakdown) and alterations in renal blood flow secondary to catecholamine surges. Renal failure may be oliguric or polyuric. Clinically important renal impairment is associated with autonomic instability and histology is normal or shows acute tubular necrosis.

MANAGEMENT

Treatment strategies involve three management principles:

- Organisms present in the body should be destroyed to prevent further toxin release,
- Toxin present in the body, outside the CNS should be neutralized, and
- The effects of toxin already in the CNS should be minimized.

Adult tetanus protocol

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1. Start metronidazole intravenously 500mg three times a day.
2. Give tetanus human immune globulin IM 3,000-6,000 IU if available. If not available Equine ATS 10 000 IU IM.
3. Admit to ICU, commence oxygen, obtain IV access and attach monitoring.
4. Alert surgeon to perform radical debridement.
5. Slow loading dose diazepam IV to control spasms. Up to about 40mg may be required. Give a loading dose of 5g magnesium sulphate slowly over 20 minutes IV.
6. Start diazepam 10mg 6 hourly and increase to hourly if required. Titrate to symptoms.
7. Start magnesium 2.5g IV 2 hourly and increase to hourly if required. Titrate to symptoms. Stop diazepam if symptoms controlled by magnesium alone. Anaesthetist to pass nasogastric tube for feeding when patient stabilised.
8. Phenobarbitone up to 200mg IV twice a day for breakthrough spasms using 50mg doses.
9. Tracheostomy if airway compromised by above treatment.
10. Intermittent positive pressure ventilation with muscle relaxants if respiration compromised by treatment or uncontrolled spasms.

Removal of the source of infection

Obvious wounds should be surgically debrided. The surgeon should be encouraged to perform a radical debridement to eliminate as much of the source of infection as possible. Penicillin has been widely used for many years, but is a GABA antagonist and is associated with convulsions. Metronidazole is probably the antibiotic of choice. It is safe and comparative studies with penicillin suggest at least as good results. Erythromycin, tetracycline, chloramphenicol and clindamycin are all accepted as alternatives.

Neutralization of unbound toxin

If available human tetanus immune globulin 3,000-6,000 units is given intra-muscularly (IM). If this is not available (which is often the case in the developing world), then anti-tetanus horse serum (ATS) should be given after sensitivity tests, in a dose of 10,000 units IM. All these injections should be administered within 24 hours of the diagnosis.

Control of rigidity and spasms

The principle of management is to prevent spasms and rigidity with the minimal dose of pharmacological agent, so that the side effects of the drugs themselves do not become life threatening. Administering the correct dose of agent cannot be judged without frequent assessment by the clinician, especially in the early stages. Clinical symptoms may change rapidly.

Avoidance of unnecessary stimulation is mandatory, but the mainstay of treatment is sedation with a benzodiazepine. Benzodiazepines increase GABA activity, by inhibiting an endogenous inhibitor at the GABA-A receptor. Diazepam may be given by various routes. It is cheap and widely used, but long acting metabolites (oxazepam and desmethyldiazepam) may accumulate and lead to prolonged coma. Doses vary between individuals, but a starting dose of 10mg every 6 hours is usual. Higher doses of 20 or 40mg 6 hourly may be necessary. Midazolam has been used with less apparent accumulation.

Additional sedation may be provided by anticonvulsants, particularly phenobarbitone at a dose of up to 200mg IV twice a day. Phenobarbitone has a GABA agonist effect. However, it is a potent respiratory depressant and should be used with caution, starting with low doses of 50mg twice a day.

Phenothiazines, usually chlorpromazine, have often been used. However caution is essential to avoid deep depression of protective airway reflexes and the risk of pulmonary aspiration.

In situations where full intensive care facilities are available, the classical teaching is to proceed to tracheostomy and IPPV when sedation does not control the spasms, or when the necessary sedative dose produces such deep depression of the airway reflexes or respiration, that the patient is no longer safe. However, in many parts of the developing world there is little capacity to perform a tracheostomy or give IPPV. Even if a surgeon is available to perform a tracheostomy, the nursing care demands of a tracheostomy over several weeks puts a major strain on nursing capacity. This should not be undertaken without firstly considering other treatment options.

Magnesium sulphate may offer some new hope in this context. In Sri Lanka, Attygalle and Rodrigo reported a series of 40 patients with tracheostomy, in which IPPV was avoided by using magnesium sulphate.² There has also been a report from the USA where the need for tracheostomy was avoided through the use of magnesium sulphate.³ The dose suggested is 1g increasing to 2.5g per hour in adults, following a 5g loading dose. The therapeutic serum magnesium levels were 2–4mmol.L⁻¹ (normal 1.2mmol.L⁻¹).

Magnesium is a presynaptic neuromuscular blocker. It blocks catecholamine release from nerves and the adrenal medulla. It also reduces receptor responsiveness to released catecholamines, is an anticonvulsant and a vasodilator. It antagonises calcium in the myocardium and at the neuromuscular junction and inhibits parathyroid hormone release, lowering serum calcium. If too large a dose is given, it causes weakness and paralysis with central sedation (although the latter is controversial). Attygalle advises using the presence of patella tendon reflexes as a monitor of a safe serum magnesium level.² Hypotension and bradyarrhythmias may occur. It is therefore mandatory to maintain magnesium levels in the therapeutic



Figure 4. *Opisthotonus modified by treatment with magnesium.*

range. In a series of patients with very severe tetanus magnesium was found to be inadequate alone as a sedative and relaxant, but was an effective adjunct in controlling autonomic disturbance.⁴ The author's experience of using magnesium to manage severe tetanus in rural Africa has been positive, with good outcomes. The future role of magnesium will require further studies, but it offers hopeful new possibilities.



Figure 5. *Seven weeks after admission and treatment with invasive ventilation and magnesium.*

Neuromuscular blocking agents and intermittent positive pressure ventilation may be required for a prolonged period when sedation alone is inadequate. Traditionally, the long acting agent pancuronium has been used and it is cheaper than the more modern non-depolarising muscle relaxants. Vecuronium, atracurium and rocuronium have also been used.

Propofol sedation may allow control of spasms and rigidity without the use of neuromuscular blocking drugs. However, drug levels are closer to anaesthetic than sedative concentrations and mechanical ventilation is likely to be needed.

Control of autonomic dysfunction

Many different approaches to the treatment of autonomic dysfunction have been reported. Most are presented as case reports or small case series. There is a lack of comparative or controlled studies. In general, outcome measures have been limited to haemodynamic data, rather than survival or morbidity.

Sedation is often the first treatment. Benzodiazepines, anticonvulsants, and morphine are frequently used. Morphine is particularly beneficial as cardiovascular stability may be achieved without cardiac compromise. Dosages vary between 20 and 180mg daily. Proposed mechanisms of action include replacement of endogenous opioids, reduction in reflex sympathetic activity and release of histamine. Phenothiazines, particularly chlorpromazine are also used; anticholinergic and adrenergic antagonism may contribute to cardiovascular stability.

β -adrenergic blocking agents, such as propranolol, were used in the past to control episodes of hypertension and tachycardia, but profound hypotension, severe pulmonary oedema and sudden death were all found to occur. Labetolol, which has combined α and β -adrenergic blocking effects has been used, but no advantage over propranolol has been demonstrated (possibly because its α activity is much less than its β activity). In recent years, the short-acting agent, esmolol, has been used successfully. Although good cardiovascular stability is achieved, arterial catecholamine concentrations remain elevated.

Sudden cardiac death is a feature of severe tetanus. The cause remains unclear, but plausible explanations include sudden loss of sympathetic drive, catecholamine-induced cardiac damage and increased parasympathetic tone or 'storms'. Persisting β -blockade could exacerbate these causes because of its negatively inotropic effect or vasoconstrictor activity. This may lead to acute cardiac failure, particularly as sympathetic crises are associated with high systemic vascular resistance and normal or low cardiac output. Isolated use of α -adrenergic block, with long acting agents, cannot therefore be recommended.

Postganglionic adrenergic blocking agents such as bethanidine, guanethidine and phentolamine have been used successfully with propranolol, along with other similar agents such as trimetaphan, phenoxybenzamine and reserpine. Disadvantages of this group of drugs are that induced hypotension may be difficult to reverse, tachyphylaxis occurs and withdrawal can lead to rebound hypertension.

The α -adrenergic agonist clonidine has been used orally or parenterally, with variable success. Acting centrally, it reduces sympathetic outflow, thus, reducing arterial pressure, heart rate, and catecholamine release from the adrenal medulla. Peripherally, it inhibits the release of

norepinephrine from pre-junctional nerve endings. Other useful effects include sedation and anxiolysis.

Magnesium sulphate has been used both in artificially ventilated patients to reduce autonomic disturbance and in non-ventilated patients to control spasms. The dose suggested is 1g, increasing to 2.5g, per hour for an adult.

Supportive intensive care treatment

Weight loss is universal in tetanus. Contributory factors include inability to swallow, autonomic induced alterations in gastrointestinal function, increased metabolic rate (due to pyrexia and muscular activity), and prolonged critical illness. Nutrition should therefore be established as early as possible. Enteral nutrition is associated with a lower incidence of complications and is cheaper than parenteral nutrition. Nasogastric tube feeding should be started as soon as possible. In experienced units, percutaneous gastrostomy may be more suitable as a route for feeding.

Infective complications of prolonged critical illness, including ventilator-associated pneumonia, are common in tetanus. Securing the airway early in the disease and preventing aspiration and sepsis are logical steps in minimizing this risk. As artificial ventilation is often necessary for several weeks, tracheostomy is usually performed after intubation. In experienced hands the percutaneous dilatational method may be particularly suitable for patients with tetanus. This bedside procedure avoids transfer to and from the operating theatre, with the attendant risk of provoking autonomic instability. Prevention of respiratory complications also involves meticulous mouth care, chest physiotherapy and regular tracheal suction, particularly as salivation and bronchial secretions are greatly increased. Adequate sedation is mandatory before such interventions in patients at risk of uncontrolled spasms or autonomic disturbance. The balance between physiotherapy and sedation may be difficult to achieve.

Other important measures in the routine management of patients with tetanus (as with any long-term critical illness), include prophylaxis of thromboembolism, gastrointestinal haemorrhage and pressure sores. The importance of psychological support should not be underestimated.

Venous access is a major problem when diazepam has been used for many days using peripheral veins. An elective placement of a central or femoral line improves general care and outcomes.

COMPLICATIONS

Complications may occur as a result of the disease (e.g. laryngospasm, hypoxia), or as a consequence of treatment (e.g. sedation leading to coma, aspiration or apnoea; ventilator-associated pneumonia; complications of tracheostomy; acute respiratory distress syndrome). Gastro-intestinal complications include gastric stasis, ileus, diarrhoea and haemorrhage. Cardiovascular complications include tachycardia, bradycardia, hypertension, hypotension and asystole. High output renal failure and oliguric renal failure are reported and thromboembolism and overwhelming sepsis also occur.

MORTALITY AND OUTCOME

Fatality rates and causes of death vary dramatically according to the

facilities available. Without doubt the introduction of intensive care treatment will reduce mortality. In developing countries, without facilities for prolonged intensive care and ventilatory support, deaths from severe tetanus exceed 50% with airway obstruction, respiratory failure, and renal failure as prominent causes. A mortality of 10% has been suggested as an acceptable goal in developed countries. Modern intensive care should prevent death from acute respiratory failure, but as a result, in severe cases, autonomic disturbance becomes more apparent. Before ICU care was established about 80% of patients died as a result of early acute respiratory failure. Important complications of ICU care include nosocomial infections (particularly ventilator-associated pneumonia), generalized sepsis, thromboembolism, and gastrointestinal haemorrhage. Mortality varies with patient age. In the USA, mortality in adults below 30 years may approach zero, but in those over 60 years is 52%. In Africa, mortality from neonatal tetanus without artificial ventilation is over 80%.

Severe cases of tetanus generally require ICU admission for approximately 3-5 weeks. Recovery can be expected to be complete, with return to normal function, although some survivors of tetanus may have persistent physical and psychological problems.

CONCLUSION

Tetanus is entirely preventable by vaccination. However it remains

a major health problem worldwide. In developed countries, several cases present every year in the elderly and unimmunised population. Mortality in these cases remains high. Prolonged intensive care support may be necessary, but most treatment is based on limited evidence. Major therapeutic challenges lie in the control of muscular rigidity and spasms, the treatment of autonomic disturbance and the prevention of complications associated with prolonged critical illness. For the developing world tetanus is a major challenge with a high mortality among all age groups. The use of magnesium to avoid long term ventilation is a hopeful development that will need further evaluation. Return to normal function can be expected in those who survive.

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Brainstem death

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Summary

The practice of diagnosing death varies between countries. It is particularly important when futility of treatment is discussed or when patients are considered for organ donation. The clinical features and diagnosis of brainstem death are described.

INTRODUCTION

This article describes the practice behind the diagnosis of brainstem death in the UK. Set definitions and criteria allow this concept to be applied for the purposes of withdrawal of critical care, when it is deemed to be futile. It also allows the harvest of organs in a heart-beating patient, where there is no chance of recovery of neurological function.

However, this practice is not international and has taken time to develop. Neurological death has long been, and still is, a difficult concept to define. There are other contexts for death which are easier to rationalise. The concept of a 'somatic death', where death is undeniable as a result of body decomposition or catastrophic injury such as decapitation is straightforward. A 'cardiovascular' death, in which there is a clear absence of any form of cardiac output or circulation, is also indisputable. But neurological death is more of a problem. This problem initially arose in the late 1950s when advances in critical care left physicians to be faced with patients who were severely brain injured, with no prospect of recovery, but were seemingly kept alive by mechanical ventilation.

Western culture agrees that the death of the brain equates to the death of an individual and should involve an irreversible inability to breathe and an irreversible lack of capacity for consciousness.

However, brain death can be taken to mean death applying to either the whole of the brain, or just the brainstem. Practice in the USA and in many European countries follows the principle of 'whole brain death'. Unlike in the UK, where the concept of brainstem death is used, those countries require confirmation of the loss of all forms of brain function.

Although the actual clinical tests used are the same, it is the role of other, confirmatory, investigations that differ. While a patient with brainstem death can be confirmed dead in the UK, the presence of cortical electrical activity on EEG or intracranial blood flow, as seen on cerebral angiography, would preclude this diagnosis in the USA. Needless to say, many controversies relating to these concepts still persist.

This article concentrates on practice in the United

Kingdom, following criteria proposed by the Conference of Royal Colleges in 1976.

ANATOMY

The brain is made up of three main embryological segments:

1. Forebrain (prosencephalon) - the cerebral hemispheres, thalamus and hypothalamus,
2. Midbrain (mesencephalon),
3. Hindbrain (rhombencephalon) - the pons, medulla oblongata and cerebellar hemispheres.

The brainstem is the physical link between the cerebral cortex and the spinal cord and it consists of the midbrain, the pons and the medulla. Most of the cranial nerve nuclei are contained here. In addition, and of particular relevance to this topic, the pons contains the reticular activating system that is vital for cortical arousal and conscious awareness, whilst the medulla contains centres that control cardiorespiratory function.

PHYSIOLOGY AND PATHOLOGY OF BRAIN INJURY

The brain is particularly susceptible to injury. It has a high metabolic requirement, comprising 20% of the body's oxygen consumption and receiving 15% of the total cardiac output.

Swelling occurs in the injured brain, with the effects of swelling exacerbated by the brain's location in the fixed volume skull. The consequent rise in intracranial pressure opposes cerebral perfusion pressure and limits cerebral oxygen delivery. This in turn contributes towards the secondary brain injury that neurocritical care aims to limit.

Intracranial pressure (ICP) that is raised to a sufficient level, for a sufficient duration, causes brainstem ischaemia and death. This may be associated by coning - a grossly elevated ICP that forces the brainstem downwards through the foramen magnum.

Neuronal tissue has no capability for repair and regeneration, so treatment options are aimed at prevention of brain injuries - both primary and secondary.

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CLINICAL FEATURES OF BRAINSTEM DEATH

In addition to profound reduction in conscious level, there are specific clinical features of brainstem death.

Damage to cranial nerve nuclei within the brain stem may cause specific neurological signs (termed *localising signs*). False localising signs describe palsies of the 3rd (or 6th, which has a long intracranial course) cranial nerve lesions that result from stretching of the nerve as it passes forwards towards the eye. The oculomotor nerve is prone to damage by herniation of the uncus of the temporal lobe or another expanding lesion, as it crosses the free edge of tentorium cerebelli. The defect of ocular gaze is therefore a manifestation of a secondary pressure effect, rather than a direct effect of the brainstem injury (hence the term *false*).

As the brainstem is compressed, pressure and ischaemia cause more systemic changes. Initially, ischaemia of the vasomotor areas within the brainstem causes systemic hypertension in an attempt to restore cerebral perfusion. This, coupled with hypertensive stimulation of the baroreceptor reflex, causes bradycardia (Cushing's sign). This may then be followed by a variety of arrhythmias and ECG abnormalities, mediated by abnormal sympathetic outflow from the brain stem, and hypotension due to systemic vasodilatation.

Hypothalamic and pituitary failure causes a reduction in thyroid hormone synthesis and secretion, which contributes to the cardiovascular changes, whilst a lack of antidiuretic hormone causes craniogenic diabetes insipidus. There may also be loss of thermoregulation usually causing hypothermia.

DIAGNOSIS OF BRAINSTEM DEATH

There is no statutory definition of death in the UK. After *brain death criteria* were proposed by the Conference of Royal Colleges in 1976, courts in England and Northern Ireland adopted them for the diagnosis of death. A Department of Health (UK) guideline defines death as the '*irreversible loss of capacity for consciousness, combined with irreversible loss of the capacity to breathe*'. This essentially defines brainstem death and is equivalent to the death of an individual.

PRECONDITIONS FOR BRAINSTEM DEATH TESTING

1. There must be an identifiable pathology causing irremediable brain damage. This may be intra- or extracranial.
2. The patient must be deeply unconscious.
 - a. Hypothermia must be excluded as the cause of unconsciousness and the patient's core temperature should be over 34°C.
 - b. There should be no evidence that the patient's state is due to depressant drugs. This refers to narcotics, hypnotics and tranquillisers, as well as neuromuscular blocking drugs. A careful drug history is required, whilst drug levels and antagonists may need to be used.
 - c. Potentially reversible circulatory, metabolic and endocrine disturbances must have been excluded as the cause of the continuing unconsciousness. Some of these disturbances may occur as a result of the condition, rather than the cause, and these do not preclude the diagnosis of brainstem death.

3. The patient must be apnoeic, needing mechanical ventilation. This condition must not be secondary to the effect of sedative drugs or neuromuscular blockade. This may require testing with a nerve stimulator to show intact neuromuscular transmission. Alternatively, demonstration of tendon reflexes can also demonstrate intact transmission.

BRAINSTEM DEATH TESTING

In the UK, the tests must be carried out by two doctors who have held full registration with the General Medical Council for more than five years, one of whom should be a consultant. Both should have adequate experience of interpreting the results and neither should be a member of the transplant team.

Two sets of tests should be performed to remove the risk of observer error. The two doctors may perform the tests together or separately and, although no defined time interval has to elapse between the tests, it should be of sufficient duration to reassure the patient's next-of-kin.

The time of death is recorded when the *first test* indicates brain death.

The rules apply to children over the age of two months and cannot be applied to those below 37 weeks gestation. It is rarely possible to apply the criteria to children between these ages.

Once brainstem death has been diagnosed, cessation of the heart beat follows within a short period. This has been confirmed and validated in published series.

THE TESTS

1. **Pupils must be fixed** in diameter and not responsive to incident light. (Cranial nerves II, III).
2. There must be **no corneal reflex** (avoid damaging the cornea). (Cranial nerves V, VII).
3. **Vestibulo-ocular reflexes are absent**. No eye movements occur following the slow injection of at least 50ml ice cold water over one minute, into each external auditory meatus. Note that the normal reflex is deviation of the eyes away from the side of the stimulus. Access to the tympanic membrane should be confirmed by otoscopy. Injury or pathology may prevent this test being performed on both sides – this does not invalidate the test. (Cranial nerves VIII, III).
4. **No motor responses** in the cranial nerve distribution should occur as a result of stimulation of any somatic area. No limb movement should occur in response to supra-orbital pressure. (Cranial nerves V, VII).
5. **No gag reflex** should occur in response to posterior pharyngeal wall stimulation with a spatula. (Cranial nerve IX).
6. **No cough** or other reflex should occur in response to bronchial stimulation by a suction catheter being passed down the endotracheal tube. (Cranial nerve X).
7. **No respiratory movements** should occur in response to disconnection from the ventilator ('apnoea test'). Hypoxia should be prevented by preoxygenation and insufflation of oxygen through a tracheal catheter. This tests the stimulation of respiration by

arterial carbon dioxide tension which should be allowed to rise to 6.65kPa – confirmed by arterial blood gases.

MANAGEMENT OF BRAINSTEM DEAD PATIENT

Relatives, partners and carers need to be kept informed of the patient's condition in a sympathetic and appropriate manner, that is tailored to the individuals concerned. Standard medical care must be continued in those in whom brain stem death has not been conclusively established and may be continued after this, in order to maintain the condition of organs for donation. This may include maintaining fluid and electrolyte balance or haemodynamic parameters.

Initiating mechanical ventilation in those patients thought to have irremediable brain damage, who stop breathing before brain stem death testing can occur, is only justified if it is of benefit to the patient. It is unlawful for this to occur in order to preserve organ function.

ORGAN DONATION

A local transplant coordinator should be contacted early once the potential for organ donation is recognised. Once brainstem death has been established, the priority becomes preserving and optimising the potential transplantable organs.

Respiratory support should be continued, maintaining normal blood gas parameters, but minimising the harmful effects of positive pressure ventilation (e.g. avoidance of excessive positive end-expiratory pressure and excessive FiO_2).

Hypotension is common following brain stem death and can compromise the perfusion of transplantable organs. It may occur as a result of decreased sympathetic tone, diabetes insipidus, cold diuresis

or cardiac dysfunction. It should be treated with fluids, vasopressors or inotropes as appropriate.

Normothermia should be maintained as per standard critical care management, as it may contribute to coagulopathy, acidaemia, cardiac arrhythmias and diuresis. Endocrine support may also be required to reduce the need for inotropes and delay cardiac arrest. Vasopressin, insulin, tri-iodothyronine and methylprednisolone may all be used.

CONTRAINDICATIONS TO ORGAN DONATION

- Positive HIV, Hepatitis B or C, HTLV, syphilis or malaria tests
- Evidence of Creutzfeldt-Jakob disease
- Progressive neurological disease of unknown cause (e.g. Alzheimer's, Parkinson's, motor neurone disease)
- Untreated systemic sepsis
- Uncontrolled hypertension or end-organ damage from hypertension or diabetes mellitus
- Malignancy
- A previous transplant recipient who has received immunosuppressive treatment.

FURTHER READING

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Cultural issues in end-of-life care

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INTRODUCTION

The passage of life to death is a very individual experience for each patient and their family, and is influenced by many different factors. Race, ethnicity, age, religion, spiritual beliefs and socio-economic status influence a patient's wishes and expectations for their end-of-life care.¹ Within the culture of an Intensive Care Unit (ICU) the training, the desire for quality outcomes and the finances available are some of the factors that can influence the delivery of end-of-life care. The spectrum of values, beliefs, habits, customs and traditions that influence end-of-life management is extensive. All aspects are important and need to be addressed in order to deliver compassionate and personalised end-of-life care for each individual.

The ICU is becoming a common place to die, with 22.4% of deaths in the United States occurring after admission to ICU.² With an increasingly ageing population and the ability to provide more and more medical intervention, the number of patients dying on intensive care is likely to rise.^{2,3} While the ICU staff are experienced at caring for the dying, evidence suggests that the process of care surrounding death is not always done well.^{4,5,6} The last few years has seen a growing focus addressing end-of-life management on intensive care. This article looks at some of the issues raised.

THE PATIENT AND FAMILY

The influence of culture, religion and ethnicity

The principle of autonomy, which can be described as the individual's right to self determination about their body, their lifestyle and their health,⁷ how they are treated and their right to receive information about themselves, is widely adopted by most Western countries.^{8,9} There are many legal and advisory documents across different countries to guide end-of-life decision making which address the concept of autonomy. It is important to appreciate that 'autonomy' is not a value held universally 'and as such, may be very foreign or even opposite to the views of patients and families from other cultures'.¹⁰ Even where autonomy is recognised, culture, religion and ethnicity heavily influence who is informed of a patient's diagnosis,

whether the patient themselves is told they are at the end-of-life, and what decisions are made.

Ethnicity

A study looking at differences in care according to race identified that black patients were almost twice as likely to choose to have cardiopulmonary resuscitation, and half as likely to choose withdrawal of care, as some other races.¹¹ Shrank et al identified that African-Americans were more likely to involve extended family, friends and spiritual leaders when making decisions about end-of-life care and that they put a strong emphasis on spirituality, 'healing' and preserving life at all cost.¹² White-Hispanics were more likely to limit end-of-life discussions to immediate family and placed greater importance on quality of life.¹²

Hispanic, Chinese and Pakistani families will actively ensure that their loved one is unaware of their terminal prognosis.¹³ The Vietnamese and Russians believe it is wrong to inform a patient that they have cancer and that such discussions should be held with the family only.¹⁰ Families from these cultures traditionally believe that it is their duty to protect their loved one, keeping them from the burden and anxiety of their diagnosis¹³ and preventing them from losing hope.¹⁰

Religion

Beliefs regarding end-of-life care, including those of withholding and withdrawal of medical intervention, vary widely between different religions.⁸ All health care professionals need to have some insight and knowledge into the beliefs of the major faiths they are likely to encounter, in order to be culturally sensitive to what their patient's wishes may be, and so that discussions and management can be targeted appropriately. However, it is important to appreciate that decision-making within the same religion or culture can vary considerably.¹⁴ Although patients may come from the same cultural background, experiences with immigration, education, acculturation (the modification of the culture of a group or individual as a result of contact with a different culture), medical and other encounters will differ significantly from person to person, influencing and individualising their decision making process.^{10,15,16}

Summary

With an increasingly aged world population and rising expectations of the level of therapy offered for a wide range of illnesses, the ICU is a common place to die. The attitudes of patient, relatives and medical staff vary greatly between countries, cultures and religions. This article provides an overview of the factors we should consider when managing patients with a critical illness, particularly concerning end-of-life care.

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End-of-life customs and rituals

Many religions and cultures have different end-of-life customs and rituals. These play an important role in preparing and dealing with death, for both the patient and loved ones.^{1,15} Customs and rituals vary widely. Muslim families may wish for their dying member to have their head turned towards Mecca.¹⁵ Pacific Islanders request that a window is left open while their family member is dying in order for the soul to be able to leave.¹ The Hindu family may wish to wash the body of their deceased family member themselves.¹⁵ Some ICUs may not be used to dealing with a variety of rituals, however, with some thought and consideration, most rituals can be accommodated, meeting the patient and family's spiritual and religious needs.

An appreciation of each patient's culture, religion, race and ethnicity is important in order to understand how these will influence a patient's response to dying.¹⁵ It is important that the care provided is individualised and that patients are not stereotyped by ethnic or cultural group;^{16,17} this can only be facilitated by asking the patient, or their advocate, about their individual wishes. Examples of relevant questions are:^{10,15,17}

- When a diagnosis is established does the patient wish to be told, or would they prefer that this is discussed with the family instead?
- Does the patient themselves want to make decisions, or do they want this referred to their family?
- How 'aggressive' does the patient want their care to be? Should everything possible be done?
- What are their religious and spiritual views, how important are they and do they have any customs or rituals that must be observed?

It is important to ask these questions in order to be able to provide end-of-life care that is in keeping with the patient's wishes.^{10,15}

Caring for the family

Dame Cicely Saunders, credited as a founder of the hospice movement and a leader in the development of palliative care, stated 'How one dies remains in the memories of those that live on.'

Providing care that focuses on the family, as well as the patient, brings with it many benefits. Increasing family participation,¹⁸ focusing on communication with them^{18,19} and supporting their spiritual and emotional needs,^{19,20} increases satisfaction amongst family members and surrogate decisions regarding end-of-life decision making¹⁹ and the overall ICU encounter.²⁰ In addition, fewer suffer psychological consequences from the experience.¹⁸ Introduction of quality initiative improvements for end-of life care, with family involvement, such as conferences to improve communication about end-of-life care issues, lead to significant reduction in ICU days before death.²¹

Family-centred care, with responsibility for the welfare of the family as well as the patient, is seen as the ideal model for end-of-life management and that 'caring for family members is an important part of caring for the critically ill patient'.²² Reinforcing this as part of the ICU culture is fundamental to improving the quality of end-of-life care and is advocated by many Intensive Care Societies.¹⁴

THE INTENSIVE CARE UNIT

Training in end-of-life care

A general consensus exists that there is insufficient training in end-of-life care for health care professionals¹⁴ and that end-of-life care 'demands the same high level of knowledge and competence as all other areas of ICU practice'.²² A change in culture, to one where end-of-life training is seen to be as important as learning how to manage respiratory failure, is required. Doctors in particular, need improved teaching in palliative care that commences in medical school, but continues throughout their career, with particular attention to improving communication skills. However, specific end-of-life care is important for all health care professionals, so that all care-givers involved in the care of a dying patient are able to deal with the medical, social and psychological issues of end-of-life care.²³

Variation in decision-making between different ICUs: withdrawing and withholding care

The decision to move from curative-led to palliative-led care is always difficult. It requires careful consideration, balancing the risk of unnecessary distress, discomfort and prolongation of suffering against the possibility of withholding or withdrawing intervention in a patient that may survive.¹⁴ Most decisions regarding end-of-life care can be guided by ethical and legal principles, however, what decisions are made, how and when they are reached and the extent to which family and other clinical staff are involved in the decision making process, varies considerably from physician to physician, ICU to ICU and country to country.

A study from Canada, looking at health care worker characteristics, identified the number of years since graduation, the city and province they worked in, the number of beds on their ICU and the consideration of what their colleagues would do, as characteristics that influenced decisions to withdraw treatment.²⁴

The ETHICUS study, a study of end-of life practices in 37 ICUs in 17 European countries, identified that the majority of ICU deaths that occur across Europe do so after a decision has been made to limit treatment being provided.²⁵ Yet within this European sample the decision to limit life-sustaining treatment differed markedly according to country, religion, duration of time on the ICU, diagnosis and patient age.²⁵ Northern European units were more likely to implement limitations to care and take a shorter period of time to reach the decision than Central or Southern European units.²⁵ Atheist, Protestant or Catholic physicians were more likely to withdraw treatment than Greek Orthodox, Jewish or Muslim colleagues.²⁵ Miccinesi et al identified that religion was a determinant of physician attitude towards end-of-life decisions, alongside age, gender and previous experience with dying patients.²⁶ However the strongest determinant of physician attitude was country.²⁶

A number of differences have been identified between countries and their approach to end-of-life care. The United States is most likely to involve ethicists and courts of law in assisting with decision-making. Japan, Turkey, the United States, Southern Europe and Brazil are more likely to continue treatment in a deteriorating vegetative patient with no family or advanced directive. This is in contrast to Northern and Central Europe, Australia and Canada.⁷ Northern and Central

Europe are most likely to involve nurses in end-of-life care decisions, whereas Southern Europe, Japan, Brazil, Turkey and the United States are least likely.²⁷ In the ETHICUS study nurses were involved in around 78% of cases, but only initiated discussion in 2% of cases; however disagreement between carers occurred in only 0.6% of cases.²⁷ The involvement of nurses in end-of-life decisions is an important consideration.¹⁴ Nurses can be excluded from the decision making process,^{27,28} yet it is they who potentially form the closest relationships with patients and their families, and are most likely to be familiar with the values, beliefs and wishes of those concerned.

The process of decision making can vary between two extremes, from paternalism where the doctor makes all decisions, to full patient autonomy, where the patient or their designated surrogate has responsibility for decision making while the doctor remains in an informative role only.²⁹ The 'paternalistic' approach runs the risk of failing to appreciate the patient's wishes, conversely decisions made by patients and family alone can be extremely stressful for those involved.^{18,31}

The 'Study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT)' identified that the majority of physicians did not know their patients' preferences for end-of-life care and that many patients did not receive the end-of-life care that they wished.⁴ Less than 5% of ICU patients retain the capacity to make decisions.³⁰ This highlights the importance of involving those closest to the patient with decisions, to ensure that, where the patient cannot express their preferences, family and friends can help guide to the care that the patient would want.¹⁹ Yet, as mentioned above, this comes at a price. A number of studies have shown that those involved in decisions about a loved one's end-of-life care, can be traumatised by the experience. Many suffer symptoms of anxiety, depression and post-traumatic stress following the episode.^{18,31}

Many studies have shown that patients favour their family as decision makers,^{32,33} others that families do not want to be involved,³⁴ and further papers that having both family and physicians contributing to the decision making process is preferable.^{35,36} It is the shared decision making approach that a consensus of international critical care societies advocate.¹⁴ This approach means that the family need not assume the full burden of the end-of-life care decisions, while allowing the health care team an opportunity to provide information and understanding to the family about the medical issues. In addition, the shared decision making approach allows the family to express what they feel are the patient's wishes and values, so that the health care team can acknowledge and incorporate these into end-of-life care recommendations and decisions.²⁹

Impact on the care providers

Both nursing and medical staff working in critical care are at high risk of burnout (an emotional condition marked by tiredness, loss of interest, or frustration that interferes with job performance).^{37,38} This is especially so when clinicians believe that the care that they are providing is inappropriate.³⁹ Caring for and making decisions pertaining to the end-of-life care of a patient are significant factors that contribute to the risk of burnout,^{37,39} as are the care giver's personal and professional values and beliefs, which may influence the extent of burnout that they experience.⁴⁰

A recent study looking at perceptions of appropriateness of care amongst intensive care nurses and physicians identified that good collaboration between nurses and doctors, involvement of nurses in end-of-life care decisions, and shared decision making between nurses and physicians with regard to symptom control, were variables that were associated with decreased perception of inappropriate care.³⁹ This study went on to suggest that managers should look to promote a culture and environment within the ICU where there is 'self-reflection, mutual trust, open communication, and shared decision making.... in order to improve the well-being of the individual clinicians and, thereby, the quality of patient care.'

CONCLUSION

Providing care for a patient at the end of their life is a key component of good quality care on the Intensive Care Unit, and as a result has been receiving increased attention over the last few years. Ensuring that a patient is free from pain and distress, that family members are supported and that the principle of shared decision making is promoted, are all key aspects of end-of-life care. All intensivists should strive to provide end-of-life care of the highest standard through research, education and quality improvement initiatives, with sensitivity to, and understanding of, the unique cultural needs of individual patients and their families.

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Diabetic ketoacidosis

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DEFINITION

Diabetes ketoacidosis (DKA) is a medical emergency. It is classified by the triad of:

- Ketonaemia (3mmol.L^{-1} and over) or significant ketonuria (more than 2+ on standard urine sticks),
- Blood glucose over 11mmol.L^{-1} or known diabetes mellitus,
- Bicarbonate (HCO_3^-) below 15mmol.L^{-1} and/or venous pH less than 7.3.

The main differential diagnosis is hyperosmolar hyperglycaemic syndrome, alternatively known as hyperosmolar non-ketotic syndrome (HONK). Despite significant overlaps between the two conditions, this article will only address DKA.

As there are important differences between the management of the adult and paediatric populations, the treatment of each group will be discussed separately.

EPIDEMIOLOGY

DKA primarily occurs in patients with type 1 diabetes mellitus, but is being recognised in type 2 diabetes patients.² The true incidence is difficult to establish, but population based studies estimate between 4.6 and 8 episodes per 1,000 patients with diabetes.³

DKA may be the first presentation of diabetes, or may follow a precipitating event. This is most commonly infection, although in a large number of cases no identifiable cause can be found (Table 1).

MORTALITY AND MORBIDITY

Better understanding of the pathophysiology of DKA, with close monitoring and controlled correction of electrolytes has seen a reduction in the overall mortality of DKA in the last 20 years from 7.96% to 0.67%.⁴ The mortality is still high in non-hospitalised patients and in the developing world.

The most common cause of mortality in DKA is cerebral oedema, particularly in children and adolescents. In the adult population, the main causes of mortality

Table 1. Common precipitating events of DKA.

Precipitant	Occurrence (%)
Infections (commonly urinary tract)	30
Non-compliance with treatment	15
New diagnosis of type 1 diabetes	5-15
Other stresses (MI, alcohol, pancreatitis, drugs)	5
No cause found	up to 40

include severe hypokalaemia, adult respiratory distress syndrome, and co-morbid states such as pneumonia, acute myocardial infarction and sepsis.⁵

PATHOPHYSIOLOGY

Diabetic ketoacidosis is a complex metabolic disorder characterised by hyperglycaemia, acidosis and ketonaemia. It usually results from an absolute or relative lack of insulin and is complicated by a corresponding rise in counter-regulatory hormones - glucagon, cortisol, growth hormone and the catecholamines. This hormone imbalance reduces the uptake of glucose by peripheral tissues and increases hepatic gluconeogenesis and glycogenolysis, resulting in severe hyperglycaemia. Enhanced lipolysis increases the breakdown of triglycerides into free fatty acids. Large quantities of ketones are then formed by the β -oxidation of the free fatty acids. Ketones include acetone, 3- β -hydroxybutyrate and acetoacetate. The predominant ketone in DKA is 3- β -hydroxybutyrate.

The secondary consequences of these primary derangements include metabolic acidosis and an osmotic diuresis. Metabolic acidosis is created by the production of H^+ ions by the dissociation of ketoacids. The accumulation of ketoacids leads to an elevated anion gap, which is a key feature of DKA.

There are several mechanisms for dehydration in DKA. These include osmotic diuresis, vomiting and eventually reduction in oral intake due to reduced level of consciousness. Initially, as the blood sugar rises, there is a shift of fluid from the intracellular to the extracellular compartment with subsequent dilution. Once the

Summary

Diabetic ketoacidosis remains a frequent and life-threatening complication of type 1 diabetes. Recent national (UK) guidelines have seen some changes in the management of the condition, and this article reflects the current best practice.¹

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blood sugar levels exceed the renal threshold for glucose of around 12mmol.L⁻¹, glycosuria occurs. This results in an osmotic diuresis, with a loss of water from the extracellular compartment. Electrolyte shifts and depletion are in part due to this osmotic diuresis. As well as losing glucose and water in the urine, there will be urinary loss of ketones, sodium, potassium and phosphates. At presentation these patients are often severely dehydrated with marked serum electrolyte disturbances.

CLINICAL FEATURES

There is a wide spectrum of severity of illness in patients presenting with DKA. Classically patients present with a history of thirst, polyuria and polydipsia, although these are not invariably present. Diabetes mellitus may have been previously undiagnosed.

Other symptoms may include:

- Weakness and lethargy
- Nausea and vomiting
- Abdominal pain
- Weight loss.

Common general physical signs are:

- Evidence of dehydration
- Tachycardia and hypotension
- Kussmaul respiration (deep, laboured respirations to provide respiratory compensation for metabolic acidosis)
- Ketotic breath (fruity acetone smell due to exhaled ketones)
- Temperature is usually normal or low, even in the presence of an underlying infection⁶
- Altered consciousness and confusion.

INVESTIGATIONS

Initial investigations aim to confirm the diagnosis, estimate the severity of the DKA and identify the underlying cause.

Blood glucose

Usually blood glucose is grossly elevated at presentation. Rarely it may be normal or only moderately raised if there has been partial treatment of DKA prior to presentation, as this may reduce the blood glucose but not correct the acidaemia. This is known as euglycaemic diabetic ketoacidosis.

Capillary and laboratory blood glucose should be taken on presentation. It is important to remember that 'near patient' testing of blood glucose may be grossly inaccurate with very high concentrations of glucose. Blood glucose should then be checked hourly. Laboratory testing is only necessary until levels are back within the range of the near patient testing devices.

Ketones

In some settings, portable ketone meters now allow bedside measurement of blood ketones (3-beta-hydroxybutyrate). The

resolution of DKA depends on the suppression of ketonaemia, therefore measurement of blood ketones now represents best practice in monitoring response to treatment.

Urine ketones can be measured on urine dipstick.

Serum urea and electrolytes

These should be measured in the laboratory initially and ideally should then be monitored hourly using venous or arterial blood gas sampling.

Sodium

As discussed above, hyperglycaemia causes a dilutional hyponatraemia. The measured serum sodium level can be corrected by adding 1.6mmol.L⁻¹ for each 5.5mmol.L⁻¹ elevation of glucose over 5.5mmol.L⁻¹. One correction formula is:

$$\text{Corrected Na}^+ = \text{Measured Na}^+ + 0.4 \times ((\text{Plasma glucose (mmol.L}^{-1}\text{)}) - 5.5)$$

Alternatively visit: <http://www.strs.nhs.uk/resources/pdf/guidelines/correctedNA.pdf>

Potassium

In DKA there is a total body deficit of potassium. However, initial serum levels may be within the normal range or elevated because of acidosis and dehydration. Serum levels must be checked regularly because correction of the acidosis and administration of insulin can result in a precipitous drop in serum potassium, via intracellular movement of potassium.

Urea and creatinine

Renal impairment may be present at presentation. Elevated acetoacetate levels may cause a falsely elevated creatinine level if the calorimetric method is used to measure the serum creatinine.

Serum osmolality

This can be calculated as: (2 x Na) + glucose + urea. If a patient in DKA is comatose with an osmolality less than 330mosm.kg⁻¹ then other sources for coma should be sought.

Venous or arterial blood gases

Either venous or arterial blood gas measurement is useful at presentation, 60 minutes, 2 hours and 2 hourly thereafter, until at least 6 hours from commencing treatment.

An elevated anion gap is a key feature of DKA. Anion gap is calculated as:

$$(\text{Serum Na}^+ + \text{serum K}^+) - (\text{serum HCO}_3^- + \text{serum Cl}^-)$$

Normal value: 8-12mmol.L⁻¹

Full blood count

An increased white blood cell count in the range 10-15 x10⁹.L⁻¹ is characteristic of DKA and is not indicative of infection. However a count above 25x10⁹.L⁻¹ should raise concern that an infection is present.

Amylase

Amylase is often raised in the absence of pancreatitis. This may cause diagnostic confusion, especially in the presence of abdominal pain.

Other investigations

Other investigations are necessary to aid diagnosis of any underlying cause and to monitor for complications. They include:

- Blood cultures
- ECG
- Chest Xray
- Mid-stream urine.

Children should be weighed to guide fluid and drug therapy. If this is not possible an estimated weight should be calculated.

Excellent comprehensive guidelines and a pathway poster are available at www.diabetes.org.uk. Follow the links: 'About us' > 'Our policy views' > 'Care recommendations' > 'The management of diabetic ketoacidosis in adults'

MANAGEMENT OF ADULTS IN DIABETIC KETOACIDOSIS

Initial assessment and resuscitation

Patients with DKA may be severely unwell and comatose. The initial approach requires a rapid assessment of Airway, Breathing, Circulation and Disability, administration of oxygen and confirmation of the diagnosis. Intravenous access should be established as soon as possible, blood tests and blood cultures taken, and treatment started with fluid initially and insulin later (see below). A full clinical examination is mandatory, followed by further investigations as above. Precipitating causes should be considered and treated as appropriate.

The focus of treatment of DKA is now on the underlying metabolic abnormality (ketonaemia), which simplifies the treatment of those who present with euglycaemic diabetic ketoacidosis.

The basic principles of DKA management are:

- Rapid restoration of adequate circulation and perfusion with isotonic intravenous fluids,
- Gradual rehydration and restoration of depleted electrolytes,
- Insulin to reverse ketosis and hyperglycaemia,
- Careful and regular monitoring of clinical signs and laboratory tests to detect and treat complications.

Fluid administration and deficits

The most important initial treatment in DKA is appropriate fluid replacement followed by insulin administration. The main aims for fluid replacement are:

- Restoration of circulating volume,
- Clearance of ketones,
- Correction of electrolyte imbalance.

Typical Deficits in DKA are:

- Water 100ml.kg⁻¹
- Sodium 7-10mmol.kg⁻¹
- Chloride 3-5mmol.kg⁻¹
- Potassium 3-5mmol.kg⁻¹

So a 70kg adult presenting with DKA may be up to 7 litres in deficit.

The aim of the first few litres of fluid is to correct hypotension, replenish the intravascular deficit and counteract the effects of the osmotic diuresis, with correction of electrolyte disturbance.

Initially fluid therapy is aimed at rapid restoration of intravascular volume. This is done by judicious fluid boluses of 0.9% saline. Patients in cardiogenic or septic shock will require vasoactive drugs and haemodynamic monitoring. As a guide to fluid replacement, after initial resuscitation with 0.9% saline, a typical fluid regime is suggested in Table 2.

Table 2. Typical fluid replacement regime.

Fluid	Volume
0.9% sodium chloride	1000ml over 1st hour
0.9% sodium chloride with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride with potassium chloride	1000ml over next 2 hours
0.9% sodium chloride with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride with potassium chloride	1000ml over next 4 hours
0.9% sodium chloride with potassium chloride	1000ml over next 6 hours

It is extremely important to remember that this is a guide only. Fluid therapy should be judged by repeated clinical assessment, including blood pressure, urine output and mental status. Special care is required in vulnerable patient groups, such as the elderly, pregnant women, those aged 18-25 yrs (see cerebral oedema), patients with heart or kidney failure and any patient with other serious co-morbidities.

0.9% saline or Hartmann's solution for resuscitation?

There has been much recent debate about the relative merits of these two solutions.^{7,8,9} 0.9% saline can cause a hyperchloraemic metabolic acidosis, which may cause renal arteriolar vasoconstriction leading to oliguria and a slowing of the resolution of acidosis. Whilst using Hartmann's solution may avoid this problem, Hartmann's has other potential physiological disadvantages, although the clinical significance of these effects is debatable. The potential adverse effects of Hartmann's solution in the context of DKA include a lactate load that may increase the blood glucose and a potassium content that should be avoided in hyperkalaemic patients. Even though patients will often need more potassium than the 5mmol.L⁻¹ potassium provided in Hartmann's

solution, the practice of adding potassium to Hartmann's is not licensed. Because 0.9% saline with either 20 or 40mmol.L⁻¹ potassium is readily available it has been recommended as a resuscitation fluid.

When the blood glucose reduces to 14mmol.L⁻¹ intravenous fluid should be changed to 10% glucose. This allows the insulin infusion to be continued, suppressing ketogenesis, while avoiding hypoglycaemia. 0.9% saline may need to be run simultaneously to correct any remaining circulatory volume deficit. Glucose should be continued until the patient is eating or drinking normally.

Insulin therapy

A fixed rate intravenous insulin infusion (IVII) is recommended and is calculated as 0.1units.kg⁻¹.h⁻¹. A standard infusion mix is prepared by adding 50units actrapid insulin to 50mls 0.9% sodium chloride. If the patient normally takes a long acting insulin analogue (e.g. Lantus, Levemir), then this should be continued at their usual dose and time. It is no longer advised to administer a bolus dose of insulin at the time of diagnosis of DKA to allow rapid correction of blood sugar. Intravenous fluid resuscitation alone will reduce plasma glucose levels by two methods. It will dilute the blood glucose and also the levels of counter-regulatory hormones. Excessive insulin therapy causes inappropriately rapid falls in plasma glucose and risks profound hypokalaemia.

The aim is to reduce plasma blood glucose by 3mmol.L⁻¹ per hour. If the blood glucose falls too slowly, the insulin rate should be doubled every hour until the target decrease is met. If the blood glucose falls too quickly, the insulin rate can be halved to 0.05units.kg⁻¹.h⁻¹, but for a short time only, as a rate of 0.1 units.kg⁻¹.h⁻¹ is needed to switch off ketone production. If hypoglycaemia occurs prior to complete resolution of DKA, the insulin infusion should not be stopped, but extra glucose should be added to the IV fluids instead.

Potassium replacement

In DKA there is a total body deficit of potassium. Despite this, at presentation mild to moderate hyperkalaemia is not uncommon. Serum levels will fall once insulin and fluids are started. Supplementary potassium is often required and may be provided by use of intravenous fluids containing between 20-40mmol.L⁻¹ KCl. Serum potassium should be maintained between 4.0-5.0mmol.L⁻¹. If the initial serum potassium is low (<3.3mmol.L⁻¹) then the insulin infusion should be withheld temporarily. Potassium is not routinely given in the first litre of 0.9% saline following resuscitation, unless more than 1L of saline was given in the early resuscitation stage. If the serum K⁺ is above 5.3mmol.L⁻¹ potassium supplements should be omitted and serum potassium should be checked every 2 hours.

Sodium bicarbonate

Sodium bicarbonate is rarely, if ever, necessary. If administered, potential deleterious effects include hypokalaemia, cerebral oedema and reduced tissue oxygenation, the latter by its effects on the oxygen dissociation curve. Acidosis will improve with fluid replacement and insulin. Continuing acidosis usually indicates insufficient resuscitation. Sodium bicarbonate should only be considered in patients with profound acidosis (pH< 6.9) and circulatory failure resistant to inotropes.

Continuing management

Liaise with the Diabetic Specialist team

Involvement of the diabetic specialist team has been shown to shorten patient stay and improve safety.¹ The timing of their involvement will depend on local circumstances. They should be involved in the assessment of the precipitating cause of DKA, its ongoing management, discharge and follow up. They will also assess patients' knowledge and whether further diabetic education and lifestyle advice is warranted.

Location of care

Patients with DKA require close nursing and medical supervision. This may be best provided in a high dependency or intensive therapy environment if facilities are available. Arterial or central venous access may simplify management in patients with severe DKA by allowing regular monitoring of base excess, electrolytes and glucose in particular. Regular clinical assessment is mandatory so as to guide fluid therapy and ensure adequate resolution of shock.

Starting an insulin sliding scale and conversion to subcutaneous insulin

The fixed rate IVII should continued until blood ketones are below 0.3mmol.L⁻¹ and the blood pH is above 7.3. The insulin infusion should then be changed from a constant rate to a sliding scale. An example of a sliding scale is shown in Table 3. Oral diet should be resumed as soon as the patient is able. Subcutaneous insulin regimes may be commenced when the patient is tolerating an oral diet and is biochemically stable (ketones are below 0.3mmol.L⁻¹ and the blood pH is less than 7.3). Ideally give subcutaneous fast acting insulin and a meal and discontinue IV insulin one hour later.

Antibiotic therapy

Occult infections are common precipitants of DKA (Table 1). Evidence of infection should be actively sought and investigations should include blood cultures and urine dipstick testing and cultures.

Table 3. Sliding scale for use in DKA once plasma glucose is less than 10mmol.L⁻¹.

Plasma glucose (mmol.L ⁻¹)	Insulin (units.h ⁻¹)	Additional action
<4	0.5	Increase glucose intake. Repeat reading 30 minutes later
4.0 - 6.0	1	
6.1 - 8.0	2	
8.1 - 10.0	4	
10.0	6	Alert doctor if remains >10mmol.L ⁻¹ after second reading

Suspected bacterial infections should be treated aggressively with appropriate antibiotics. The role for prophylactic antibiotics in patients with DKA is an area of debate. The authors' preference is against this practice, but clinicians should consult local hospital guidelines.

Thromboprophylaxis

Patients with DKA are at increased risk of thromboembolism. Prophylactic heparin has an accepted role in the management of patients with DKA. It should be continued until patients are mobile, with no evidence of dehydration or elevated serum osmolality. Unfractionated heparin or low molecular weight heparin are both suitable treatments.

Nasogastric tube drainage

DKA causes gastric stasis. Aspiration pneumonitis may occur if vomiting is combined with a reduced level of consciousness. Nasogastric tube drainage should therefore be considered in all patients with DKA. It is mandatory in those with markedly impaired conscious level.

Urinary catheterisation

Strict fluid balance is required in the management of DKA. Measurement of urinary output is simplified by urinary catheterisation.

Continuous ECG monitoring

Where available, this is indicated in the presence of significant underlying cardiac disease, significant hyper- or hypokalaemia or severe DKA.

Notes recording

Adequate recording of regular clinical assessments and laboratory test results is vital. This process is made easier by the use of standard ward or high dependency care observation charts and serial results sheets for blood results. Specific DKA care pathway documents should be used if available.

MANAGEMENT OF CHILDREN AND ADOLESCENTS IN DIABETIC KETOACIDOSIS

A full description of DKA management in children is beyond the scope of this edition. Although the pathophysiology behind DKA in children is the same as in adults, there are important differences, particularly concerning presentation and management.

For young people under the age of 18 years refer to the British Society of Paediatric Endocrinology and Diabetes (BSPED) guidelines: <http://www.bsped.org.uk/clinical/docs/DKAGuideline.pdf>

Major considerations for children with DKA

- Smaller size mandates more precise prescription of fluids and electrolytes.
- Cerebral oedema is more common in children, occurring in up to 1%, with a mortality rate of up to 25%.¹⁰ Less aggressive fluid replacement should be employed in children compared to adults.

- Fluid deficit is replaced over 48 hours and is calculated using the following equation:

Fluid requirement over 48 hours = Maintenance (over 48 hours) + deficit - fluid already given

where the deficit (in ml) = Body weight (kg) × % dehydration × 10

- Insulin should be avoided in the first hour of fluid replacement, sodium bicarbonate should be avoided altogether and the rate at which the blood glucose falls should be very carefully monitored and controlled.

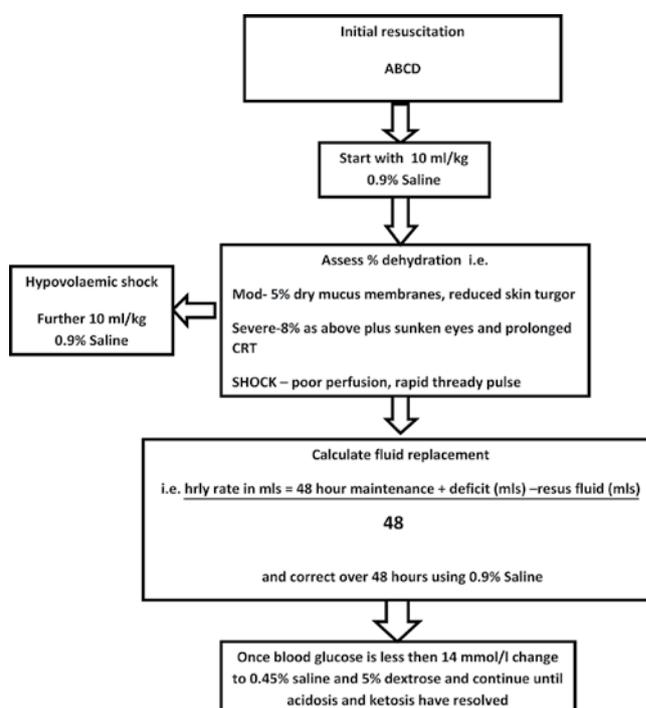


Figure 1. Overview of management of DKA in children (Modified from: Glaser NS et al. Frequency of sub-clinical cerebral oedema in children with diabetic ketoacidosis. *Pediatr Diabetes* 2007; 8: 28-43).

Remember overestimation of fluid loss is dangerous, therefore do not use more than 8% dehydration in calculations.

COMPLICATIONS OF DKA TREATMENT

Cerebral oedema

Monitoring for any signs of cerebral oedema should start at the time of admission of patients with DKA and continue for at least the first 12 hours of treatment. Cerebral oedema typically presents within 2 – 24 hours of treatment for DKA. Early signs are headache, confusion and irritability. Later signs include reduced conscious level and seizures.

As cerebral oedema usually occurs within a few hours of initiation of treatment, there has been speculation that it is iatrogenic. This has been disputed by some since sub-clinical cerebral oedema has been demonstrated before treatment has been started. Recent studies suggest that cerebral hypoperfusion with subsequent reperfusion may be the mechanism responsible.¹

If cerebral oedema is suspected due to an altered level of consciousness, hypoglycaemia must be excluded initially. Intravenous mannitol ($1.0\text{g.kg}^{-1} = 5.0\text{ml.kg}^{-1}$ 20% mannitol) should be given immediately. Fluids should be restricted to two-thirds maintenance and the fluid deficit should be replaced over 72 hours. Patients should be transferred to an Intensive Care Unit for intubation and mechanical ventilation and arrangements should be made for an urgent CT head. If cerebral oedema is present use of intracranial pressure monitoring should be discussed with a neurosurgeon.

Hypoglycaemia

The blood glucose can fall very rapidly as ketoacidosis is corrected, and hypoglycaemia may ensue. This can lead to rebound ketosis, driven by counter-regulatory hormones, which has been shown to lengthen the duration of treatment. Severe hypoglycaemia is also associated with cardiac arrhythmias, acute brain injury and death. Hypoglycaemia should be treated with increased dextrose administration. A decreased insulin infusion rate may be necessary temporarily. Insulin infusions should not be stopped before the metabolic acidosis and ketonuria has resolved, as this will delay recovery.

Hypokalaemia

Potassium levels should be monitored frequently by venous or arterial blood gas analysis, and hypokalaemia should be treated in a standard fashion. If potassium needs to be infused in a concentration of more than 40mmol.L^{-1} , then it must be given via a central line, with continuous cardiac monitoring.

Hypophosphataemia

Hypophosphataemia is common. It seldom requires treatment as levels will correct once oral diet is resumed. The routine replacement of phosphate does not improve the outcome in DKA. However in those with cardiac dysfunction, anaemia or respiratory depression combined potassium and phosphate replacement can be given.

DKA IN PREGNANCY

DKA in pregnancy is of special concern. It tends to occur at lower plasma glucose levels and more rapidly than in non-pregnant patients and usually occurs in the second and third trimesters because of increasing insulin resistance. Fetal mortality rates have previously been reported as high as 30%, rising to over 60% in comatose parturients with DKA.¹¹ However, with improvements in diabetic care, the figure for fetal loss has been reported to be as low as 9% in some countries.¹² Prevention, early recognition and aggressive management are vitally important to try to minimise fetal mortality. It is clear that diabetic and obstetric teams should jointly manage all pregnant patients with DKA. Additional support may be required from the critical care team.

CONCLUSION

DKA is a potentially life threatening complication of diabetes mellitus. An understanding of the pathophysiology of the condition aids appropriate treatment. Initial assessment must involve a rapid assessment of Airway, Breathing, Circulation and Disability.

Immediate adequate intravenous access is required. Initial investigations are aimed at confirming the diagnosis and identifying underlying causes.

The basic principles of DKA management are:

- Rapid restoration of adequate circulation and perfusion with isotonic intravenous fluids.
- Gradual rehydration and restoration of depleted electrolytes.
- Insulin to reverse ketosis and hyperglycaemia.
- Regular monitoring of clinical signs and laboratory tests to detect and treat complications.
- A target rate of correction of hyperglycaemia of 3 to $4\text{mmol.L}^{-1}.\text{h}^{-1}$.

Acute cerebral oedema is a potentially fatal complication that is possibly caused by excessive fluid therapy or too rapid a fall in blood glucose. Early signs of the development of cerebral oedema include headache, irritation and confusion. Prompt recognition and appropriate management may improve prognosis.

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Emergency management of poisoning

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INTRODUCTION

Drug overdose and poisoning is a global public health problem. In the UK it accounts for 120 000 hospital admissions each year (around 1% of the total number) and is a significant proportion of the Emergency Department workload.¹ In 2004 the World Health Organisation estimated that 346,000 people died worldwide from unintentional poisoning, whilst 1 million people died as a result of deliberate self harm, and poisoning accounted for a significant number of these deaths.² Drug overdose is the most frequent presentation of deliberate self-harm and this may complicate medical management. However most patients are young, otherwise medically well and, managed appropriately, the vast majority should recover fully.

GENERAL PRINCIPLES

Many drugs in overdose (e.g. opiates, tricyclics, benzodiazepines) can cause significant depression of cerebral and cardiorespiratory function. Emergency management should always start with a rapid **initial assessment** and **resuscitation** of the airway, breathing and circulation. Careful **history** and **examination** will, in most cases, give an indication as to the likely severity of the overdose and guide subsequent management. Treatment principles include strategies to reduce absorption, increase elimination, general supportive measures and, when available and appropriate, the use of specific antidotes. It is strongly recommended that, in cases where doubt exists regarding the degree of risk, or appropriate management, the Poisons Information Service be contacted. In the UK, they can be reached by dialling **0844 892 0111**, 24-hours-a-day, or information may be obtained via their website www.toxbase.org.

HISTORY

A detailed and reliable account of the drug or drugs taken should be sought; this should include the drug name, amount, preparation type, time of ingestion and the co-ingestion of other substances such as alcohol or recreational drugs, which might influence the patient's clinical state or drug clearance. The presence of vomiting of tablets soon after overdose should be noted but does not preclude significant toxicity.

The medical, social, psychiatric and therapeutic drug history will help to identify high risk patients and also guide subsequent management.

The patient may be uncooperative or unable to give these details and so a collateral and confirmatory history should be acquired from available sources such as drug packets, the ambulance crew, witnesses, a suicide note and the patient's case notes. The MIMS (Monthly Index of Medical Specialties) colour index, BNF (British National Formulary) descriptions or the computerised system 'TICTAC' may aid identification of drugs already removed from packets.

EXAMINATION

The **airway, breathing and circulation** should be reassessed and treated accordingly as a priority. Basic airway manoeuvres, simple adjuncts, supported ventilation and/or cuffed **endotracheal intubation** may be required if the airway and/or breathing is compromised. The patient's level of consciousness may give an indication of the toxicity of the overdose, risk to the airway and guides the level of supportive care needed. It can be expressed on the 'AVPU' scale or as a formal GCS (although not designed for this purpose, it does give a reproducible score which is sensitive to subsequent changes). A GCS equal or less than 8 (or responding to Pain only) increases the risk of airway compromise and endotracheal intubation is indicated unless rapid recovery is anticipated.

Careful attention should be paid to **respiratory function**, particularly with sedative drug toxicity. This should include respiratory rate and tidal volume and the measurement of oxygen saturations using pulse oximetry. A low respiratory rate with decreased oxygen saturations may indicate hypoventilation, but note that a normal saturation does not exclude hypercarbia or indeed hypoxia in carbon monoxide poisoning. If in any doubt, arterial blood gases should be measured. Tachypnoea can be seen with metabolic acidosis (e.g. tricyclics, methanol), anxiety, and stimulant drug overdose and as an early feature of salicylate poisoning (respiratory alkalosis). Supplementary oxygen via facemask should be given to all patients initially, taking account of pulse oximetry (noting the limitations described above).

Summary

This article covers the basic aspects of management of patients who have ingested a poisonous agent. Specific common agents are described in more detail. In particular, the recommendations on the management of paracetamol in the UK have recently been altered in order to make treatment algorithm easier to use and administration of acetylcysteine safer.

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Many drugs exhibit **cardiovascular toxicity** in overdose (e.g. tricyclics, β -blockers, digoxin, lithium). This may manifest as hypotension and or cardiac arrhythmias. Pulse, blood pressure and ECG should be recorded, intravenous access established and initial fluid resuscitation given as appropriate.

General examination may give corroborating evidence of significant ingestions or clues in unknown overdoses. Many drugs (SSRIs, tricyclics, phenothiazines) have serotonergic or anticholinergic effects with pupil dilatation, and extrapyramidal movements, whilst opioid type drugs will cause sedation and pin point pupils.

Temperature, blood glucose (low in β -blocker, ethanol poisoning) and weight should also be recorded. Weight is important in calculating whether the patient is likely to have received a toxic dose and may guide treatment, for example in paracetamol overdose.

Examination should reveal any associated injury (accidental or deliberate self harm) which may require treatment, or the presence of other substances such as alcohol. If their clinical condition allows, an assessment of the patient's mental state should be made.

FURTHER MANAGEMENT

Additional investigations

Samples should be sent for laboratory investigation – urea, electrolytes and blood glucose as a minimum. Blood gases are helpful in providing a rapid assessment of acid-base disturbance as well as assessing adequacy of ventilation in patients with reduced conscious level. Creatinine kinase (CK) should be measured if there is a possibility of rhabdomyolysis or serotonin syndrome is suspected.

Appropriately timed drug levels (e.g. paracetamol, salicylate, lithium) should be taken when indicated. Paracetamol levels should be sent if there is any possibility of paracetamol poisoning – this includes all unconscious patients. Many Emergency Departments measure paracetamol levels in all patients presenting where poisoning is suspected, as paracetamol poisoning is associated with a lack of early clinical signs. There is no need to routinely measure salicylate concentrations in conscious overdose patients who deny taking salicylate-containing preparations and who have no features suggesting salicylate toxicity. Salicylate levels should be measured in all unconscious patients or where poisoning is suspected.

Treatment

Supportive treatment of the cardiorespiratory and neurological systems should be given by standard intensive care methods.

Induced emesis is no longer recommended and is contraindicated in volatile or corrosive substances.³ Drug absorption can be reduced by the use of activated charcoal, given either orally or nasogastrically. A single dose (50g in adults, 1g.kg⁻¹ in children) should be given up to one hour after the ingestion of a substantial amount of toxin (i.e. a dose expected to cause moderate to severe toxicity). After this time adsorption is reduced. Multiple doses of activated charcoal should be considered for the adsorption and enhanced elimination of certain toxins (see Box 1). Certain other substances (including alcohols, ferrous salts and lithium) however, are not readily adsorbed to charcoal and this treatment is not indicated for poisoning with these substances.

An unprotected airway is an absolute contraindication to charcoal administration, as aspiration pneumonitis is a risk.

Box 1. Toxins for which multiple doses of activated charcoal are indicated⁴

- Carbamazepine
- Dapsone
- Digoxin
- Paraquat
- Phenobarbitone
- Quinine
- Slow release preparations such as theophylline
- Amanita phalloides fungus
- Multiple doses may also be considered in life threatening overdose of other drugs (e.g. tricyclic antidepressants).

There is little evidence to support the use of gastric lavage and current literature suggests that this should only be considered in patients who present within 1 hour, who have ingested a substantial amount of a toxin with high lethality.⁵ It is contraindicated if the airway cannot be protected and in the ingestion of hydrocarbons (risk of aspiration and chemical pneumonitis) and corrosives.

If metabolic acidosis due to poisoning persists, despite the correction of hypoxia and adequate fluid resuscitation, then correction with intravenous sodium bicarbonate should be considered. Rapid correction is particularly important if there is prolongation of the QRS or QT intervals on the ECG. In adults an initial dose of 50mmol of sodium bicarbonate may be given and repeated if necessary (as guided by arterial blood gas monitoring).

In cases of severe poisoning, haemodialysis should be considered as a means of extracorporeal toxin removal as well as for management of acute kidney injury.⁶ Seizures should be controlled initially with intravenous diazepam (10–20mg in adults; 0.25mg.kg⁻¹ body weight in children) or lorazepam (4mg in adults; 0.1mg.kg⁻¹ body weight in children).

SPECIFIC POISONS

Alcohol

Blood ethanol concentrations may be used to demonstrate exposure, but are levels not reliable due to individual tolerance and do not exclude co-ingestions or head injury as a cause for symptoms or signs. They should therefore be interpreted with caution.

Clinical features

With increasing blood concentrations, features are progressive from ataxia, dysarthria, and nystagmus, to hypothermia, hypotension, stupor and coma. In severe cases, especially children, convulsions, respiratory depression, cardiac arrhythmias and acidosis may occur.

Specific hazards

These include aspiration of vomit, hypoglycaemia (especially in children), and rhabdomyolysis (especially following a period of unconsciousness).

Treatment

Alcohol is rapidly absorbed from the gut, and therefore gut decontamination is unlikely to be of benefit.

Intravenous thiamine (e.g. Pabrinex®) should be given to chronic alcohol abusers to protect against the onset of Wernicke's encephalopathy. This should be achieved before administration of glucose to treat hypoglycaemia.

Hypoglycaemia should be treated as quickly as possible with oral glucose if the patient is awake, or otherwise intravenous 5% or 10% glucose.

If facilities allow, haemodialysis should be considered if the blood concentration is greater than 5g.L^{-1} , if arterial pH is <7.0 , or if the patient's condition deteriorates in spite of maximal supportive measures.

Paracetamol

In therapeutic doses paracetamol conjugation to inactive metabolites is the major route of metabolism. Oxidation by cytochrome P450 enzymes is a minor route of metabolism and produces N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI binds covalently to sulphhydryl (-SH) groups in glutathione to form a non-toxic conjugate. When larger doses of paracetamol are taken more NAPQI is formed, hepatic glutathione stores are exhausted and NAPQI binds to hepatic cellular proteins, resulting in cellular injury.

Ingestion of as little as 150mg.kg^{-1} (75mg.kg^{-1} in high risk patients, see Box 2) is potentially fatal. Note that for obese patients (weighing $>110\text{kg}$) the toxic dose in mg.kg^{-1} should be calculated using 110kg , rather than their actual weight.

Box 2.

There is increased risk of paracetamol toxicity if the patient:

- is malnourished, has a nutritional deficiency and/or chronic illness and therefore likely to be glutathione deplete e.g. acute or chronic starvation, eating disorders, children with 'failure to thrive', cystic fibrosis, AIDS, alcoholism, hepatitis C.
- has hepatic enzyme induction or evidence of ongoing liver injury e.g. is on long term treatment with enzyme inducing drugs (including phenytoin, phenobarbital, carbamazepine, primidone, rifampicin, rifabutin, efavirenz, nevirapine, St John's Wort), regularly consumes ethanol in excess of recommended amounts. Note enzyme induction with drugs or alcohol may occur within a few days.

Clinical features

There are often none. Mild nausea and vomiting and anorexia may occur, but patients are generally asymptomatic up to 4 hours post ingestion. Right subchondral pain and tenderness, jaundice, vomiting

and acute liver failure may be seen at 24-36 hours. Confusion and encephalopathy develop over 36-72 hours.

Specific hazards

Hepatocellular necrosis is maximal 3-4 days after ingestion, and may be associated with hypoglycaemia, haemorrhage, encephalopathy and death.

Treatment guidelines

Intravenous acetylcysteine is the antidote of choice. It must be started within 8 hours if maximal benefit is to be gained,⁷ however there is evidence that acetylcysteine can improve outcome, even in patients with encephalopathy, so those that present more than 8 hours after ingestion should also be considered for treatment.⁶ Knowledge of the timing of ingestion, and whether there has been a single ingestion or repeated or 'staggered' ingestions (taken over 1 hour or more) is vital. Treatment is dependent on the weight of the patient (this should be measured as estimates are often inaccurate) and an accurately timed paracetamol plasma level for non-staggered overdoses. Acetylcysteine is highly effective especially within 8 hours of a toxic dose and generally should be used if any doubt that a toxic amount of paracetamol has been ingested. Specific management advice for paracetamol poisoning is otherwise based on the duration since ingestion:

Presentation less than 8 hours after ingestion

Consider activated charcoal if more than 150mg.kg^{-1} (75mg.kg^{-1} if high risk) has been taken within the previous hour.

4 hours after ingestion, take a venous blood sample for plasma paracetamol level, as well as baseline biochemistry and haematology (including INR). Plasma concentrations should not be measured less than 4 hours after ingestion, as levels are unreliable before this time.

If the patient is at risk according to the 'plasma paracetamol - time from ingestion graph' (see Figure 1), start acetylcysteine according an appropriate dosing schedule available.

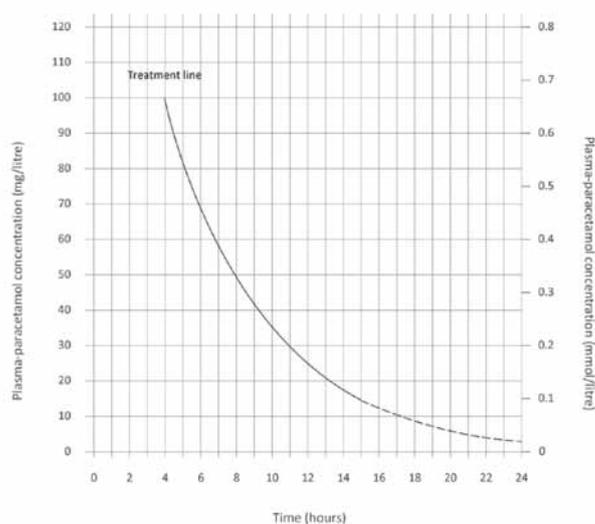


Figure 1. Revised paracetamol overdose treatment nomogram (reproduced courtesy of the College of Emergency Medicine, UK and available at <http://www.collemergencymed.ac.uk/Shop-Floor/Clinical%20Guidelines/Clinical%20Guidelines/Paracetamol%20Overdose/>)

If the patient is not at risk according to the appropriate treatment line, no treatment is necessary.

Adult and paediatric dosing tables for acetylcysteine are available at: <http://www.collemergencymed.ac.uk/Shop-Floor/Clinical%20Guidelines/Clinical%20Guidelines/Paracetamol%20Overdose/>. Note that the College of Emergency Medicine (UK) now recommends that the first infusion is completed over 1 hour (not 15 minutes).

In children under 6 years old where there is absolute certainty that a single dose of less than 150mg.kg⁻¹ body weight (or 75mg.kg⁻¹ in those in high risk group) has been ingested the need for measuring plasma paracetamol concentrations can (according to NPIS advice) “reasonably be considered unnecessary and the child discharged”.

Presentation at 8-24 hours after ingestion

DO NOT wait for the result of the plasma paracetamol level. Give acetylcysteine immediately unless certain that the ingestion has been less than 150mg.kg⁻¹ (75mg.kg⁻¹ in the high risk group). The efficacy of acetylcysteine in protecting against hepatotoxicity declines rapidly during this period.

Take blood urgently for paracetamol level, ALT, creatinine, and INR.

If the patient is determined not to be at risk, when the paracetamol level is reported, INR plasma creatinine and transaminases are normal, and the patient is asymptomatic, acetylcysteine may be discontinued.

If the risk of liver damage is confirmed, continue administration of acetylcysteine, and keep the patient under observation.

Presentation 24-36 hours

Give acetylcysteine immediately unless certain that the ingestion has been less than 150mg.kg⁻¹ (75mg.kg⁻¹ in the high risk group).

Measure plasma creatinine, ALT and INR, paracetamol levels and venous blood gases. The plasma paracetamol concentration is unlikely to be detectable after 24 hours, even after significant overdose. If elevated it suggests either a very large overdose, that the timing of ingestion is not accurate or that the overdose was staggered.

If the patient has evidence of liver injury or raised paracetamol levels continue administration of acetylcysteine, and keep the patient under observation.

Presentation after 36 hours

Unless the patient has hepatic tenderness or is jaundiced wait for lab results before commencing treatment (there is no evidence that delaying treatment with acetylcysteine for a short time affects patient outcome in those presenting more than 36 hours after overdose).

Measure plasma creatinine, ALT and INR, paracetamol levels and venous blood gases.

If the patient has evidence of liver injury or raised paracetamol levels commence treatment with acetylcysteine, keep the patient under observation and discuss with the regional poisons or liver unit according to local guidelines.

Additional notes

- For staggered overdoses, the risk of serious damage is minimal if

<150mg.kg⁻¹ has been ingested in 24 hours (75mg.kg⁻¹ per 24 hours in the high risk group). For all patients who have consumed more than this, consider treatment with acetylcysteine. Plasma levels cannot be interpreted and should not be used to guide treatment in these cases.

- UK guidelines (extrapolated from a 1979 study⁸) suggest that if the INR exceeds 1.3 or transaminase activity has increased to more than twice baseline values then acetylcysteine infusion should be continued at a dose of 100mg.kg⁻¹ over 16 hours until results are acceptable.
- Severe liver injury due to paracetamol poisoning can be associated with renal failure.⁹ Isolated renal failure occurs rarely – mostly in patients who are already glutathione depleted, those who have taken nephrotoxic compounds in addition to paracetamol, those who have become dehydrated, or those who have pre-existing renal insufficiency.¹⁰
- Methionine is an alternative antidote to paracetamol poisoning but it is not recommended for use unless acetylcysteine is not available and there will be a delay in transfer to hospital (animal studies suggest it is less effective¹¹).
- Acetylcysteine commonly causes nausea and vomiting, and can provoke an anaphylactoid reaction.¹² Almost all reactions can be treated effectively by interrupting the infusion and providing symptomatic relief with antihistamine and nebulised β_2 -adrenergic receptor agonists. Once the reaction has subsided the entire dose of acetylcysteine should still be given (at a slower rate of infusion).

Tricyclic antidepressants (TCAs)

Clinical features

Toxicity is due to anticholinergic effects at autonomic nerve endings and in the brain, sodium channel blockade and alpha-1 adrenergic receptor blockade. Peripheral signs include tachycardia, dry skin, dry mouth and dilated pupils. Central signs include ataxia, nystagmus, seizures, drowsiness and coma. There may also be increased tone and hyperreflexia. ECG features include lengthening of the PR, QRS and/or QT intervals and, together with a metabolic acidosis, these increase the risk of ventricular arrhythmias. Rarely, skin blisters are seen, which should be treated as burns. A serotonin syndrome may occur (see Box 3).

Box 3. Serotonin syndrome

An adverse drug reaction that may result from intentional self-poisoning (but more commonly therapeutic drug use or inadvertent drug interactions).

Results from an excess of intrasynaptic 5-hydroxytryptamine (5HT).

Characterized by the triad of:

- altered mental status (confusion, agitation, anxiety, delirium, hallucinations, drowsiness, coma)
- neuromuscular hyperactivity (myoclonus, hyperreflexia, muscle rigidity, tremor)

- autonomic instability (hyperthermia, diaphoresis, tachycardia, hyper/hypotension, diarrhoea, vomiting).

Life threatening complications include coma, seizures, rhabdomyolysis, DIC.

Features occur over a period of minutes to hours.

Treatment is supportive - IV fluids, benzodiazepines to control delirium, cooling measures, haemodialysis/filtration as required.

Dantrolene (1mg.kg⁻¹) may be considered in difficult to control hyperthermia.

5HT₂ antagonists cyproheptadine and chlorpromazine have both been used to treat serotonin syndrome but there are no controlled trials to support the use of either.

Differential diagnosis is neuroleptic malignant syndrome (in NMS onset and resolution of symptoms usually takes days to weeks, rigidity is "lead pipe" and rhabdomyolysis and metabolic acidosis are more common).

Treatment guidelines

- Activated charcoal (50g) by mouth or nasogastric tube is indicated if the patient presents within 1 hour of potentially toxic ingestion. A second dose of charcoal should be considered 1-2 hours later. In patients with features of toxicity provided the airway can be protected.
- Patients who are asymptomatic with normal ECGs at 6 hours are unlikely to develop late problems.
- Arrhythmias should be treated in the first instance by correction of hypoxia and acid/base disturbance.
- Sodium bicarbonate alters the binding of TCAs to the myocardium, and therefore 50mmol should be given intravenously to an adult with ECG changes or arrhythmias, even in the absence of acidosis.
- If cardiotoxicity is unresponsive to sodium bicarbonate consider the use of lipid emulsion (Intralipid).¹³ In both adults and children give an initial IV bolus of 1.5ml.kg⁻¹ of 20% Intralipid followed by 0.25-0.5ml.kg⁻¹.min⁻¹ for 30-60 minutes to an initial maximum of 500ml. This can be repeated in cases of persistent cardiovascular collapse or asystole.
- Convulsions should be treated with diazepam or lorazepam, NOT phenytoin, as the latter, in common with TCAs, block sodium channels and hence potentiates cardiotoxicity.
- Consider glucagon 1mg IV every 3 minutes to treat refractory hypotension and myocardial depression.

Salicylates

An ingested dose of 500mg.kg⁻¹ is potentially fatal. The toxic effects of salicylates are complex and include the direct stimulation of respiratory centres, inhibition of the citric acid cycle and uncoupling of oxidative phosphorylation, and increased metabolism of fatty acids.

Clinical features

Nausea, vomiting, tinnitus, lethargy and dizziness may occur in mild poisoning (usually <125mg.kg⁻¹ body weight ingestion). Dehydration, restlessness, sweating, vasodilation and hyperventilation occur in moderate poisoning (>250mg.kg⁻¹ body weight ingestion). Less commonly haematemesis, renal failure, hyperpyrexia can occur. Presence of CNS signs, e.g. confusion, coma, convulsions are commoner in children, but are an indicator of severe poisoning in all.

Specific hazards

In adults, a mixed respiratory alkalosis and metabolic acidosis is usual. In children less than 4 years, a metabolic acidosis is seen, which increases salicylate transfer across the blood-brain barrier.

Assessment of severity of poisoning

Plasma concentrations of >350mg.L⁻¹ indicate salicylate intoxication. Most deaths in adults are associated with a level of >700mg.L⁻¹. Risk factors for death include age (<10 years and >70 years), acidosis, CNS features, late presentation, and the presence/development of pulmonary oedema.

Treatment guidelines

- Give activated charcoal if >125mg.kg⁻¹ has been ingested within the past hour.
- If >125mg.kg⁻¹ has been ingested, do a plasma salicylate level at least 2 hours (in symptomatic patients) or 4 hours (in asymptomatic patients) after ingestion. A repeat sample (2 hours later) may be needed in patients with suspected severe poisoning, as there may be continued absorption.
- Arterial blood gas analysis is helpful. If a metabolic acidosis is present, and the serum potassium is normal, give intravenous sodium bicarbonate, as below, to correct acidosis and alkalize the urine which increases salicylate excretion. If the potassium is low, correct this **before** giving the bicarbonate.
- Salicylate concentration in adults >500mg.L⁻¹ (3.6mmol.L⁻¹) - give 1.5L of 1.26% sodium bicarbonate (or 225ml 8.4%) over 2 hours
- Salicylate concentration in children (<5years) >350mg.L⁻¹ (2.5mmol.L⁻¹) - give 1ml.kg⁻¹ 8.4% bicarbonate diluted in 0.5L 5% glucose at 2-3ml.kg⁻¹.hr⁻¹.
- Aim to achieve a urinary pH of 7.5-8.5, repeating treatment if necessary to achieve a falling plasma salicylate level.
- The previously used forced alkaline diuresis should not be used as it carries a significant risk of pulmonary oedema.
- In severe poisoning with evidence of cardiac or renal failure, haemodialysis is the treatment of choice.

Ethylene glycol (antifreeze, coolant, brake fluid)

Ethylene glycol is a clear, viscous fluid with a sweetish taste. It is rapidly absorbed from the gut and peak plasma concentrations occur 1 to 4 hours after ingestion. The fatal dose is 100g for a 70kg adult. Inhalation and skin absorption are not serious hazards to health. Toxicity is due to glycolic, glyoxylic and oxalic acids which are products of ethylene glycol metabolism. Glycolic acid is largely responsible for

the metabolic acidosis seen in severe cases. Early administration of the antidote prevents the production of toxic metabolites and minimises the development of complications.

Clinical features

Onset of symptoms is rapid. In the first 12 hours post-ingestion the patient appears inebriated but does not smell of alcohol. Nausea and vomiting, ataxia and dysarthria occur followed by convulsions, coma and severe metabolic acidosis. Between 12 and 24 hours after ingestion, cardiac failure, hypertension, respiratory distress and oliguric renal failure occur. If untreated death from multiorgan failure occurs between 24 and 36 hours after ingestion.

Specific hazards

Calcium oxalate monohydrate crystals precipitate resulting in cerebral oedema and renal failure (calcium oxalate monohydrate crystalluria is diagnostic of ethylene glycol poisoning). Hypocalcaemia occurs as calcium is consumed in the circulation.

As glycol is absorbed over the first few hours, patients develop a high osmolal gap. After this, as glycol is metabolised to acids the osmolal

gap falls whilst the anion gap increases and acidosis worsens. A severely poisoned patient presenting shortly after ingestion may have a normal anion gap and normal pH, however their osmolal gap will be high (see Box 4).

Treatment guidelines

Consider gastric lavage if the patient presents within 1 hour of ingestion. Charcoal is not indicated as it does not adsorb significant quantities of ethylene glycol.

Ethylene glycol concentration levels can be measured but this assay is often not available locally and thus is not often determined early enough to be useful in emergency treatment. However these should be taken and sent (at least 2 hours post ingestion) as they will guide later treatment.

Whether to commence treatment is guided by clinical suspicion and the presence of high osmolar gap or high anion gap metabolic acidosis.

Treatment with an antidote should be commenced if:

- There is suspicion that any amount of ethylene glycol has been ingested and objective evidence of toxic alcohol exposure e.g. high anion gap metabolic acidosis, osmolal gap $>10\text{mosmol.kg}^{-1}$ (without another likely cause).
- There is strong suspicion that $>10\text{g}$ (in adults) or 0.1g.kg^{-1} (in a child) of ethylene glycol has been ingested within the last 12 hours whilst awaiting ethylene glycol levels

Once initiated an antidote should be continued until the plasma ethylene glycol concentration is less than 50mg.L^{-1} .

Both antidotes - ethanol and fomepizole - work by competing with ethylene glycol for alcohol dehydrogenase, which is responsible for the conversion of the ethylene glycol to its toxic metabolites (see table 1 for examples of dosing regimes). Both are also antidotes to methanol poisoning.

Box 4. Calculating osmolal gap

The osmolal gap is the difference between the measured and calculated serum osmolality and provides a means of assessing osmotically active constituents in serum. It is calculated as follows:

$$\text{Osmolal gap} = (\text{Measured osmolality}) - (\text{Calculated osmolality})$$

$$\text{Calculated osmolality} = (2 \times \text{sodium}) + (\text{potassium}) + (\text{urea}) + (\text{glucose})$$

(all measured in mmol.L^{-1})

The normal osmolal gap is about 10mOsm.kg^{-1} .

Table 1. Typical antidote dosing regimes in treatment of ethylene glycol poisoning.

	Ethanol	Fomepizole
Loading dose	2.5ml/kg of 40% v/v orally or 10ml/kg of 10% v/v IV Both given over 30 minutes	15mg/kg IV over 30 minutes
Maintenance	0.375ml/kg/hr of 40% v/v orally or 1.5ml/kg/hr of 10% v/v IV	10mg/kg IV over 30 minutes every 12 hours for next 4 doses then 15mg/kg IV every 12 hours thereafter
Notes	Above doses are for an average adult. Doses vary in children, heavy drinkers, those undergoing haemodialysis	Above doses would be suitable in children also. Continuous infusion is required in those undergoing haemodialysis

Fomepizole does not cause any alteration in the patient's mental state, hypoglycaemia, or respiratory depression, and may be preferable to the use of ethanol in pregnant patients¹⁴ or hepatic disease. The main drawback is cost.

Ethanol is cheaper and often more readily available, and can be given orally or IV. However, adverse effects include hypoglycaemia (particularly in children and malnourished patients), respiratory and CNS depression, and clinical features of alcohol intoxication, potentially making the patient difficult to manage.

Correct metabolic acidosis with IV sodium bicarbonate.

Hypocalcaemia should be corrected with 10-20ml (0.2-0.3ml.kg⁻¹) IV 10% calcium gluconate only if there is evidence of prolonged QTc on ECG or persistent seizures. Routine correction of hypocalcaemia may increase the formation of calcium oxalate crystals.

In severe poisoning with evidence of cardiac or renal failure, haemodialysis is the treatment of choice.

Carbon monoxide (CO)

Toxicity is primarily due to impairment of oxygen delivery and subsequent cellular hypoxia. Carbon monoxide combines with haemoglobin to produce carboxyhaemoglobin, reducing the oxygen carrying capacity of the blood and shifting the oxyhaemoglobin dissociation curve to the left. The half-life of carboxyhaemoglobin is 320 minutes when breathing air. This is reduced to 80 minutes when breathing 100% oxygen.

Clinical features

These are related in the main to tissue hypoxia as a result of impaired oxygen carrying capacity of haemoglobin. Therefore headache, nausea, irritability, agitation and tachypnoea, progressing to impaired consciousness and respiratory failure. A metabolic acidosis and cerebral oedema may develop in severe cases, and progression to multi-organ failure may ensue

Chronic carbon monoxide poisoning is less easy to diagnose, and usually occurs in more than one member of a household, associated with the use of gas heaters in under ventilated areas. The main symptoms are headache and flu-like symptoms.

Specific hazards

Late complications, occurring weeks later in survivors of the acute exposure, may include psychiatric and Parkinson-like movement disorders.

Treatment guidelines

- Remove from exposure.
- Give oxygen in as high a concentration as possible to reduce the half-life of carboxyhaemoglobin and hence improve oxygen delivery to the tissues. Pulse oximetry is unreliable in carbon monoxide poisoning, as it overestimates oxygen saturation.
- Metabolic acidosis generally improves with oxygen therapy. However, if acidosis persists or is severe it can be corrected with sodium bicarbonate.

- If a patient has been exposed to carbon monoxide due to a house fire consider the possibility of concurrent cyanide poisoning and treat accordingly.
- Treat raised intracranial pressure conventionally.
- Use of hyperbaric oxygen should be discussed with the national/regional poisons unit. In the UK, the NPIS does not currently recommend hyperbaric oxygen as "the evidence base is insufficient to support the transport of patients over long distances".

Organophosphates

Organophosphate compounds are a diverse group of chemicals used in a variety of settings including as insecticides, nerve gases, and antihelmintics. Organophosphate poisoning remains a significant issue in developing countries – there are an estimated 300 000 fatalities globally each year.

Clinical features

Organophosphates can be absorbed through skin, inhaled via the lungs or ingested. Poisoning causes nicotinic (muscle weakness, fasciculations, and respiratory muscle weakness), muscarinic effects (hypersecretion, bronchospasm, vomiting and diarrhoea, urinary incontinence), and central nervous system (irritability, seizures, coma) effects.

Treatment guidelines

- Avoid self contamination – wear protective clothing.
- Prevent further absorption by removing source, including soiled clothing.
- Wash patient with soap and water.
- Consider gastric lavage if ingestion within 1 hour.
- If intubation is required avoid suxamethonium because of prolonged effect.
- Give atropine (2mg for adults, 0.02mg/kg for children) IV every 10-30 minutes until adequate atropinisation is achieved. Continuous atropine infusions can be used in doses of 0.02-0.8mg/kg/hr, titrated to effect.
- The dose of atropine required is maximal on day 1 and decreases over the next few days. When the patient improves the dose should be slowly reduced over the next 24 hours. Rebound toxicity may occur due to organophosphates being lipid soluble.
- Oximes (pralidoxime, obidoxime) reactivate phosphorylated acetylcholinesterase before deactivation occurs, and are clinically used to reverse neuromuscular blockade (atropine has no useful effect on the neuromuscular junction). The World Health Organisation recommended dosing regime is 30mg.kg⁻¹ pralidoxime chloride bolus followed by 8mg.kg⁻¹.h⁻¹ infusion. Although the evidence base for this is limited,¹⁵ oxime use is still recommended for use in patients with moderate to severe organophosphorus poisoning.¹⁶
- Benzodiazepines should be given to reduce agitation and control convulsions.¹⁷

SUMMARY

Poisoning is a significant global health problem and a common presentation of deliberate self-harm. Treatment should focus on supportive measures using an ABC approach, with the addition of further interventions to reduce absorption and increase elimination, and where appropriate administration of an appropriate antidote. Whenever possible, reference should be made to national poisoning centre guidelines.

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Management of snake envenomation

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INTRODUCTION

Out of more than 3000 species of snake identifiable world wide, only one tenth of them are dangerous to human beings. There are three major families of venomous snakes:

Elapidae (Land snakes like cobra, krait and coral snakes)

Snakes of this family have short, fixed fangs, which contain venom channels. Their tricolour bands (black, red and yellow/white) encircle the body and they lack laural shields (the shield on the lateral aspect of head separating those shields bordering the eyes from those bordering the nostril).

Viperidae (Russell's viper, bamboo snakes)

These are further classified into pit vipers (crotalinae) and viperine vipers (viperinae). Their fangs are long and movable. Their pupils are vertically elliptical. The ventral plates, caudal to anus, are in a single row. These snakes have a heat sensing pit as a small depression on the side of head for location of prey.

Hydrophilidae (Sea snakes)

These snakes have a flattened tail.

EPIDEMIOLOGY

Although a major public health problem in many countries the epidemiology of snakebite is still fragmentary, mainly due to lack of statistical data. This is compounded by the fact that the majority of victims come from rural areas, out of reach of available medical facilities. It is estimated that snakebites may exceed 5 million per year, out of which approximately 100 000 develop severe sequelae. The incidence also shows a distinct seasonal pattern, with a higher frequency in summer and during rains when the reptiles come out of their shelters. Epidemics of snake bite following floods, as human and snake populations are concentrated together, have been noted in Pakistan, India and Bangladesh.

Snakebite is observed in all age groups, the majority (90%) affecting 11 to 50-year-olds with males affected twice as often as females. Most bites occur between midnight and early morning and a large number of

Summary

Snake bites are common in many areas of the world and may be fatal. The common types of venomous snake are described, along with guidance on differentiation of bites by clinical presentation.

Table 1. Medically important snakes.

Region	Types
North America	Eastern Diamond Rattlesnake (<i>Crotalus adamanteus</i>), Western diamond rattlesnake (<i>C. atrox</i> , <i>C. viridis</i>), Bothrops atrox (<i>fer-de-lance</i>)
Central and South America	Bothrops jararaca & tropical rattlesnake (<i>C. durissus</i> , <i>C. terrificus</i>)
Britain	European adder (<i>Vipera berus</i>)
Europe	Long nosed viper (<i>V. ammodytes</i>)
Africa	Night adder (<i>Causus</i> species), Puff adder (<i>Bitis arietan</i>), Mambas (four species of <i>Dendroaspis</i>)
Africa and Asia	Cobra (<i>Naja</i> species), Saw-scaled viper (<i>Echis carinatus</i>)
Part of Asia	Russell's viper (<i>V. russelli</i>) Malayan Pit viper (<i>Agkistrodon rhodstoma</i>) Sharp-nosed pit viper (<i>A. acutus</i>) Mamushi Pit viper (<i>A. halys</i>) Haliu viper (<i>Trimeresurus flavoviridis</i>) Kraits (<i>Bungarus coeruleus</i> , <i>B. multicinctus</i>)
Pacific-Australian area	Tiger snake (<i>Notechis scutatus</i>) Death adder (<i>Acanthophis antarcticus</i>) Taipan (<i>Oxyuranus scutellatus</i>) Papuan black snake (<i>Pseudechis Papuanus</i>) King brown (<i>Pseudechis australis</i>)

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bites occur in fields, as most individuals are unable to spot the snake due to tall grass and crops. Fortunately every bite does not result in complete envenomation and more than half of victims escape without serious poisoning. However, if sufficient venom is injected during the bite to cause serious poisoning, the mortality can be high.

PATHOPHYSIOLOGY

Snake venom is a very complex chemical poison, containing multiple proteins and peptides, in addition to carbohydrates and metals, which exerts toxic and lethal effects on the skin and the hematological, nervous, respiratory and cardiovascular systems (Table 2). Different species have differing proportions of these agents. The picture may be further complicated by the release of endogenous mediators such as histamine, bradykinin and adenosine. Therefore snake venoms cannot be classified purely as 'neurotoxic' or 'cardiotoxic', although they may have a predominantly specific action. The effects may be conveniently, though arbitrarily, classified into vasculotoxic for vipers, neurotoxic for elapids and myotoxic for sea snakes.

Viper venom

This is primarily vasculotoxic. It causes rapidly developing swelling of the bitten part. Local necrosis is mainly ischaemic, as thrombosis blocks the local blood vessels and causes dry gangrene. Systemic absorption is via the lymphatics. Some vipers such as *Vipera berus* (European Viper) cause vomiting, abdominal pain, explosive diarrhoea and shock within a few minutes of the bite, which resolves spontaneously within half an hour. Persistence of shock may however be fatal. Several viper venoms result in intracranial haemorrhage due to direct endothelial damage by 'haemorrhagin' (a venom component), which interestingly does not affect coagulation. In contrast other viper venoms (*Crotalus*, *Bothrops*) do affect coagulation and a very small amount of venom can cause complete fibrinogen consumption. This feature can also differentiate various species of vipers, which can help in instituting appropriate antivenom therapy.

Elapid venom

Local necrosis causes a picture like 'wet gangrene' with a characteristic putrid smell due to direct cytolytic action of the venom. Systemic absorption occurs through venous channels. These result in primarily neurotoxic features, causing selective neuromuscular blockade of the

muscles of the eyes, tongue, throat and chest leading to respiratory failure in severe poisoning.

Sea snake venom

The effects are both myotoxic and neurotoxic, resulting in clinical and pathological changes typical of segmental myopathic lesions in skeletal muscles. Muscle pains may be last for several months unless treated.

CLINICAL FEATURES OF SNAKEBITE

The clinical presentation of a snakebite victim varies with the size and species of snake, the number and location of bites, and the quantity of venom injected. As many 30% of Pit viper bites and 50% of elapid bites result in no envenomation, sometimes referred to as 'dry bites'. The venom channel is recessed above the tip of the fang and the venom injected may be reduced by poor penetration or glancing blows, causing venom to be lost over skin and clothing. The volume of the venom available to a particular snake may also be reduced by previous bites. The age and health of the victim are also important determinants in the clinical presentation. However, whether the snake is poisonous or non-poisonous and regardless of the venom injected, the commonest symptom following snakebite is fright, which may lead to a vasovagal episode (faint).

Usually the minority of victims who receive a venom dose large enough to cause systemic poisoning will already have signs of this by the time they seek medical help. Differentiation of viperine from elapid systemic poisoning is usually obvious from simple clinical evaluation. A persistent bloody ooze from the fang marks may suggest the presence of snake venom anticoagulant. In difficult cases the presence of pain out of proportion to the size of the wound suggests snake envenomation whereas mild pain is more normally caused non-venomous snakes, arthropod bites (centipedes, spiders), bacterial fasciitis or myonecrosis.

Local manifestations

After envenomation, local swelling starts within few minutes. Fang marks may be difficult to see. Local pain with radiation and tenderness and a small reddish wheal are first to develop, followed by oedema, swelling and the appearance of bullae, all of which can progress quite rapidly and extensively. In most viper bites paraesthesia commences around the wound, and tingling and numbness over the tongue,

Table 2. Snake venom components and their effects.

Component	Pit viper	Coral snake	Effect
<i>Enzymes</i>			
Proteinases	Heavy	Minimal	Tissue destruction, coagulation, anticoagulation
Hyaluronidase	Moderate	Moderate	Hydrolysis of connective tissue stroma
Cholinesterase	Minimal	Heavy	Catalyzes hydrolysis of acetylcholine
PhospholipaseA	Heavy		Haemolysis may potentiate neurotoxins
Phosphomesterase	Minimal	Heavy	Unknown
Phosphodisterase	Moderate	Moderate	Hypotension
<i>Non-enzymes</i>			
Neurotoxins	Minimal	Heavy	Flaccid paralysis

mouth and scalp may follow. The local bite may become necrosed and gangrenous. Russell's viper has been reported to cause Raynaud's phenomenon and gangrene in a limb other than the one bitten. Secondary infection including tetanus and gas gangrene can also result. Since the venoms are largely absorbed by the lymphatics, lymphangitis may appear early. Petechiae or purpura may also be present due to the anticoagulant effect of some venoms. These characteristic changes are useful clinically - for example, if after a known Crotalid bite the victim demonstrates no local changes over several hours of observation, he can be released from the hospital as significant envenomation is unlikely.

In contrast Elapid snakebites are associated with minimal local changes.

Systemic manifestations

Cobra and vipers produce symptoms within a few minutes to several hours after the bite. Sea snake bites almost always produce myotoxic features with 2 hours, so that the bite can be reliably excluded if no symptoms are evident within this period. Although snakes are classified into predominantly neurotoxic, hemorrhagic and myotoxic types on the basis of their venoms, each species can result in any kind of manifestations.

Viper bites

75% cause envenomation, 35% mild, 15% severe. Pit viper venom can involve virtually every organ system. Nausea and vomiting are common and, if present early, suggest severe envenomation. Weakness, sweating, fever, chills, dizziness and syncope may occur. Some patients complain of a minty, rubbery or metallic taste in their mouths with increased salivation. Tingling or numbness in the tongue, scalp, face and digits are indications of moderate to severe envenomation, as are fasciculations of the face, neck, back or the bitten extremity. Systemic anticoagulation can lead to gingival bleeding, epistaxis, haemoptysis, haematuria, haemetemesis and rectal bleeding or malena. Intra-abdominal or intracranial haemorrhages may occur. Visual disturbances may result from retinal haemorrhages. There may be tachycardia or bradycardia, often accompanied by hypotension. Delayed shock may occur due to excessive blood loss and haemolysis. Severe envenomation can result in pulmonary oedema as a result of destruction of the intimal lining of the pulmonary blood vessels and pooling of the pulmonary blood. The venom itself and associated hypotension along with haemoglobin, myoglobin and fibrin deposition in renal tubules, can contribute to nephrotoxicity.

Elapid bites

The venom of elapid bites is primarily neurotoxic. Neurotoxic features are a result of selective d-tubocurarine like neuromuscular blockade, which results in flaccid paralysis of muscles. Ptosis is the earliest manifestation of cranial nerve dysfunction followed closely by double vision. Paralysis usually then progresses to involve the muscles of swallowing, but not strictly in that order.

Generally muscles innervated by cranial nerves are involved earlier. However the pupils are reactive to light until the terminal stages. The muscles of the chest are involved relatively late, with the diaphragm being most resistant. Respiratory paralysis is therefore often a terminal event. Even prior to respiratory failure, airway obstruction due to vomit or secretions can result in sudden death.

Reflex activity is generally not affected and deep tendon jerks are preserved until late. Symptoms that suggest severe envenomation include repeated vomiting, blurred vision, paraesthesiae around the mouth and hyperacusis (increased sensitivity to sound), headache, dizziness, vertigo and signs of autonomic hyperactivity. Tachycardia, hypotension and ECG changes may occur. Tetanic contraction of heart following a large dose of cobra venom has also been documented.

Sea snakes

Muscle pain is the most common presentation. Muscle necrosis may result in myoglobinuria and severe sea snake poisoning causes myoglobinuria and respiratory failure within a few hours. Coagulopathy is not a feature of coral snake bites.

In severe systemic poisoning following either elapid or viper bites, the electrocardiogram may show T-wave inversion and ST segment deviation. In sea snake bites, an ECG is especially valuable in detecting hyperkalemia, which can result from damage to muscles. Tall, peaked T-waves in the chest leads may appear within a few hours of bite and give early warning of impending death or acute kidney injury.

Unusual presentations of snake envenomation

- *Naja nigricollis* (spitting cobra) can eject venom from a distance of 6-12 feet. The venom is aimed at victim's eyes resulting in conjunctivitis and corneal ulceration. It may also cause anterior uveitis and hypopyon. A dull headache may persist beyond 72 hours.
- Occasionally a recently killed snake or snakes with severed heads can eject venom into those handling them.
- Rarely recurrence of snake envenomation manifestations may occur hours or even days after an initial good response to the antivenom. This may be due to ongoing absorption of the venom.

MANAGEMENT OF SNAKE BITE

The management of snake envenomation is controversial. It can be divided into first aid and prehospital care, specific antivenom therapy and supportive therapy.

First aid and prehospital care

Reassurance and immobilisation of the affected limb, with prompt transfer to a hospital are of prime importance. The application of a 'constriction band' to delay absorption and venom spread has been advocated during transit to hospital for bites to a limb. A firm, but not tight, ligature may be applied just above the bite. The tension is correct if one finger can pass between the limb and the bandage. This will impede lymphatic drainage, but not arterial or deep venous flow. It should preferably not be released until the administration of anti-snake venom. If the limb becomes oedematous the band should be advanced proximally. However, the band should not be left in place for too long, due to the risk of venous thrombo-embolism and distal ischaemia. An increase in local envenomation has also been reported subsequent to release of the band. Venous or arterial tourniquets are contraindicated.

The site of the bite should be cleaned and covered with a handkerchief

or dressing. Incision and mechanical suction of the bite (intended to open the puncture wound so that suction can be more effective) may be beneficial when performed by a health care worker within a few minutes of the bite, in a victim who is more than 30 to 60 minutes from hospital. The incision should be parallel to the axis of the extremity and should be only approximately 6 mm long and 3mm deep and cross cuts or multiple cuts should be avoided.

Mechanical suction (e.g. the 'extractor' device found in a Sawyer first aid kit) is preferable to mouth suction, in order to avoid wound contamination with oral flora and to prevent possible envenomation of the rescuer through breaks in their oral mucosa. Suction should be maintained for about 30-60 minutes for maximal benefit, but due care should be taken as laceration of nerves, tendons and vessels has been reported following suction by untrained rescuers.

Application of cooling measures such as ice packs or cryotherapy, at the site of bite were initially advocated, but have not been proven to be effective and this practice is not now recommended.

Antitetanus toxoid should always be given following snakebite. There is controversy about use of drugs as part of first aid care. It has been suggested that NSAIDs may be beneficial to relieve local pain but may precipitate bleeding, especially if the venom is vasculotoxic. Paracetamol and/or codeine may be useful, however there are no clear-cut recommendations for the use of sedatives.

If the snake has been killed, it should be taken to hospital, otherwise it should be left alone, since attempts to find or kill it may result in further bites. The snake, even if judged to be dead, should be handled very carefully, since decapitated heads can bite for up to one hour!

Patient assessment

Evaluation should begin with the assessment of the airway, breathing and circulatory status. Oxygen should be administered to every envenomated patient and a large bore intravenous line with normal saline or Ringer's lactate established in the unbitten limb. Cardiac monitoring and pulse oximetry, if available, is indicated. Attempts should be made to determine whether a venomous snake has actually bitten the patient, and the severity of envenomation should be assessed. (Table 3)

During the initial evaluation, several locations on the bitten extremity (at the bite site and at least two sites more proximal) should be marked and the circumferences should be measured every 15 minutes until

swelling is no longer progressing and every 1-4 hours thereafter. The extremity should be placed in a well-padded splint for at least 24 hours.

Laboratory investigations

Although lab tests are of little value in the diagnosis of snake envenomation, nevertheless they are useful for monitoring the patient and deciding about specific interventions and prognosis. They should include a full blood count, electrolytes, glucose, creatinine, serum amylase, creatinine phosphokinase (CPK), prothombin time (PT), partial thromboplastin time (PTT), fibrinogen and fibrin degradation products (FDPs). Commonly hyperkalaemia and hypoxaemia with respiratory acidosis may be seen, particularly with neuroparalysis. Urine examination may reveal haematuria, proteinuria, haemoglobinuria or myoglobinuria. Arterial blood gases and urine examination should be repeated at frequent intervals during the acute phase to assess progressive systemic toxicity.

Blood changes include anaemia, leucocytosis (raised white cell count) and thrombocytopenia (low platelet count). The peripheral blood film may show evidence of haemolysis, especially in viperine bites. Clotting time and prothrombin time may be prolonged and a low fibrinogen may be present. Blood should be typed and crossmatched on the first blood drawn from the patient, as both direct venom and antivenom effects can interfere with later crossmatching. Some specialised centers can identify the species of snake involved.

Non specific ECG changes such as bradycardia and atrioventricular block with ST and T segment changes may be seen.

Recently electroencephalogram (EEG) changes have also been reported in many patients of snake envenomation. They may manifest within hours of bite without any clinical features suggestive of encephalopathy.

Antivenom therapy

Anti snake venoms (ASV) are prepared by immunising horses with venom from poisonous snakes, extracting serum and purifying it. The WHO has designated the Liverpool School of Tropical Medicine as the international collaborating center for antivenom production and testing. Antivenoms may be species specific (monovalent) or effective against several species (polyvalent) (Table 4).

The correct use of antivenom is the most important component of hospital care and not every bite, even with a poisonous snake, merits its use. Administration of antivenom should be selective and based

Table 3. Assessment of severity of envenomation.

No envenomation	Absence of local or systemic reactions. Fang marks +/-
Mild envenomation	Fang marks. Moderate pain, minimal local oedema (0-15cm), erythema +, ecchymosis +/-, no systemic reactions
Moderate envenomation	Fang marks +, severe pain, moderate local oedema (15-30cm), erythema and ecchymosis +, systemic weakness, sweating, syncope, nausea, vomiting, anaemia or thrombocytopenia
Severe envenomation	Fang marks +, severe pain, severe local oedema (>30cm), erythema and ecchymosis +, hypotension, parasthesia, coma, pulmonary oedema, respiratory failure

on the severity of clinical symptoms. The main concern about the empirical use of antivenom is the risk of allergic reactions, its relative scarcity in some centers and the cost. Moreover, in a study of Elapid envenomation, all victims with neuromuscular paralysis survived without receiving any antivenom. Shemesh et al did a preliminary evaluation of the possibility of reducing the dose of anti-venom or totally avoiding it in some viper species.⁹ They concluded that about half of bitten patients in their study did not show systemic symptoms and therefore did not require antivenom treatment. They further observed that antivenom treatment based on systemic symptoms was effective and the dose required was also less than the fixed amount advocated for each patient, thereby reducing the incidence of serum sickness.

Administration of antivenom

Antivenom should be given within 4-6 hours of the bite and the dosage required varies with the degree of envenomation. Serum sensitivity should be tested by injecting 0.2ml of antivenom subcutaneously. If a severe reaction occur within 15 minutes, antivenom is contra-indicated. Epinephrine should be readily available in a syringe for moderate reactions that may occur despite negative tests for sensitivity.

The initial dose should depend upon an estimate of amount of envenomation (Table 5). However no upper limit has been described and up to 45 vials have been successfully used in a patient. In children and small adults (body weight < 40kg) up to 50% higher dose of ASV should be administered, to neutralise the relatively higher venom concentration.

ASV is administered intravenously, either in an undiluted form at a rate of not more than 1ml per minute, or diluted in 500ml of IV fluid and administered as rapidly as tolerated over 1-2 hours. Additional infusions containing 5-10 vials (50-100ml) should be repeated until

progression of swelling in the bitten part ceases and systemic signs and symptoms disappear. However it is not advisable to infiltrate ASV at the local site. Delayed reactions may occur following anti-venom therapy and their frequency of occurrence is proportional to the amount of antivenom administered. Therefore all patients receiving ASV should be observed for several days.

Role of anticholinesterase agents

Since Elapidae snakes result in primarily neurotoxic features as a result of selective d-tubocurarine like blockade, the post-synaptic toxin of the venom leads to pathophysiological changes resembling those of myasthenia gravis. This prompted use of anticholinesterase agents, such as neostigmine, in addition to a conventional antivenom therapeutic regimen with dramatic results. However the use of anticholinesterase drugs alone, without ASV, has also been recommended.

Table 5. Dose of antivenom.

Envenomation	Dose
Mild	5 vials (50ml)
Moderate	5-10 vials (50-100ml)
Severe	10-20 vials (100-200ml) or more

Neostigmine can be given as 50-100mcg.kg⁻¹ 4 hourly or as a continuous infusion. Edrophonium can also be used in dose of 10mg in adult or 0.25mg.kg⁻¹ in children over 2 minutes. If the response is positive then one can switch over to long acting preparations like neostigmine. However prospective studies are required to fully establish the efficacy of neostigmine with or without ASV. Glycopyrrolate 0.2mg preceding neostigmine can be given, as unlike atropine it does not cross blood brain barrier.

Table 4. Types of antivenom.

Name of Antivenom	Species
Polyvalent Wyeth Labs [Antivenin (crotalidae) polyvenom] United States	All North American pit vipers
King cobra antivenom	King cobra (<i>Ophiophagus hannah</i>)
Polyvalent Naja naja serum (common cobra) antislake venom CRI, Kausali, India	<i>Vipra russelli</i> (Russell's viper) <i>Bunqarus ceruleus</i> (common krait) <i>Echis carinatus</i> (saw scaled viper)
Mono specific Echis carinatus antivenom, India	Indian species
Tiger snake antivenom, Australia	Sea snakebite & Afro-Asian elapids
Green pit viper antivenom	<i>Trimeresurus albolabris</i> , <i>Trimeresurus monticola</i>
Bothrops antivenoms, Brazil	
Monospecific antivenom from South African Institute for Medical Areas (SAIMR), Northern Nigeria	<i>Echis pyramidum leakeyi</i>
Poly specific German & French antivenoms	

Storage of ASV: Liquid -between +20 & +80C, Lyophilized - cool & dry place.

Supportive therapy

The patient should be moved to an appropriate area of the hospital - ICU will be required for severe envenomation. Fasciotomy should be undertaken in patients with compartment syndrome and debridement should be performed for necrotic tissue. Coagulopathy should be corrected with fresh frozen plasma and platelets. Blood transfusion should be given to replace blood loss from haemolysis and bleeding. Ventilatory support and haemodialysis may be necessary for pulmonary and renal complications, due to severe envenomation. Corticosteroids are of no proven value and in fact may interfere with the action of ASV. However, corticosteroids may be used for hypersensitivity reactions to ASV. Prophylactic antibiotics are of no proven value. If infection occurs broad spectrum cover, such as ciprofloxacin and clindamycin, should be used.

Intravenous immunoglobulin therapy has also been used for envenomation and it may improve coagulopathy, but has no effect on neurotoxicity. Certain reports on the evaluation of intravenous immunoglobulin suggest that it may reduce the need for repeat antivenom therapy for envenomations associated with coagulopathy.

A compound (2-hydroxy 4-methoxy benzoic acid) isolated and purified from anatamul (*Hemidesmus indicus*), an Indian herb, has also been observed to have potent anti-inflammatory, antipyretic and antioxidant properties, especially against Russell's viper venom.

Analgesia should be given - opioids may be required.

OTHER ENVENOMATIONS

Scorpion venom poisoning

There are more than 1,400 species of scorpion in the world, but the number of medically important species is limited. The venom of the Bark scorpion (*C. exilicauda*) contains at least five distinct neurotoxins that stimulate depolarization of the neuromuscular junction and autonomic nervous system, via release of acetylcholine, norepinephrine and epinephrine. It may also have cardiotoxic effects.

Most stings are minor although serious envenomations can occur in children. The sting is followed by the onset of intense local pain with hyperesthesia (increased skin sensitivity to touch) but local swelling and ecchymosis are absent. Systemic symptoms, when present, reflect sympathetic, parasympathetic and neuromuscular

excitation. Tachypnoea, respiratory distress, wheezing, stridor, muscle fasciculations and spasm follow initial restlessness and anxiety. There may be convulsions, paralysis and involuntary voiding of stools/urine, priapism (persistent penile erection) and anxiety. Other systemic features may include hypertension, supraventricular tachycardia and hyperpyrexia.

The majority of stings can be treated with mild analgesics and cold compresses. In the event of severe envenomation, the patient should be resuscitated and appropriate symptomatic treatment should be instituted. A goat-derived antivenom is available in Arizona. Most adults can be safely treated at home, but children should always be admitted and any child less than a year old, or with neurological findings, should be admitted to ICU.

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