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Sepsis in the intensive care unit

Sean R Bennett

Abstract

Sepsis remains a major cause of mortality in intensive care. The past 15 years has seen a more uniform, world-wide approach to the management of sepsis, severe sepsis and septic shock with improved survival. Recognizing the early symptoms and signs of sepsis are key: the confused, hypoxic, hypotensive patient with pyrexia, tachycardia, tachypnoea and leucocytosis. Examination must include search for a source of infection and early drainage or debridement. Next to take appropriate cultures, give fluids and broad-spectrum antibiotics. If the picture does not improve over the next 6 hours step-up the treatment to include urine output monitoring, blood gases for base excess, lactate, haemoglobin and glucose. These will guide the management of vasopressors, insulin, fluids, transfusion and bicarbonate. If the hypotension persists (septic shock) the patient should be moved to intensive care. The most recent recommendations include the withdrawal of starch based colloids, dobutamine in place of dopamine and a higher threshold for the use of steroids. This should be instituted within 24 hours of the start of sepsis. Advanced care includes mechanical ventilation using the ARDSnet protocol. Prevention by screening, stopping cross infection and appropriate use of antibiotics remains the first priority.

Keywords Intensive care; sepsis; septic shock; severe sepsis

Introduction

Sepsis covers a wide range of conditions which usually do not require admission to the intensive care unit (ICU) unless it becomes severe. When this occurs patients will often need ICU and broadly account for about 30% of admissions according to the patient population. This will impact on the type of septic problems such as community-acquired infection versus nosocomial or hospital-acquired infection. A medical ICU will have far more community-acquired infections than an ICU admitting elective surgical patients. Whatever the source, infection leading to sepsis remains a major intensive care problem that has a mortality of at least 38%.¹

Definitions

Sepsis is infection with systemic manifestations (Box 1).

Severe sepsis is when sepsis induces significant organ dysfunction or tissue hypoperfusion (Box 2). **Septic shock** is when there is induced hypotension that persists despite adequate fluid resuscitation.² Systemic inflammatory response syndrome (SIRS) is a syndrome of two or more of the general variables shown in Box 1. It does not mean the patient is septic. Thus sepsis can be defined as, 'SIRS with evidence of infection'.

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Sepsis is a response not a disease. Defining the level of response and managing each level as it manifests provides the opportunity to start treatment early and influence outcome.

Pathophysiology

The normal immune and physiological response is to eradicate pathogens. In sepsis, there is an imbalance in the normal regulation. This may be caused by continual activation by the pathogen. There are high levels of circulating anti-inflammatory cytokines and impaired immune function. We see rapid lymphocyte apoptosis, delayed apoptosis of neutrophils and enhanced necrosis of cells. The coagulation system is also affected. There is increased coagulation and diminished fibrinolytic activity in conjunction with the excessive inflammatory response. The loss of homeostatic balance among these systems results in generalized coagulopathy and microvascular thrombosis which can lead to acute organ failure and death.³

Various treatments aimed at modifying this response or using biomarkers to direct treatment and predict outcome have been

Systemic manifestations associated with sepsis

General variables

- Core temperature $>38.3^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- Heart rate >90 bpm
- Tachypnoea (may not feel respiratory distress but a rate >30 pm)
- Significant oedema or positive fluid balance (>20 ml/kg over 24 hours)
- Hyperglycaemia-plasma glucose >7.7 mmol l^{-1} . Diabetics are higher risk

Inflammatory variables

- Leucocytosis (WBC count $>12,000$ μl^{-1})
- Leukopenia (WBC count <4000 μl^{-1})
- Plasma C-reactive protein: 2 SD above the normal value
- Plasma procalcitonin: 2 SD above the normal value (not routine in all hospitals)

Haemodynamic variables

- Arterial hypotension: SBP <90 mmHg; MAP <65 mmHg

Organ dysfunction variables

- Arterial hypoxaemia: SaO_2 $<93\%$ on air or $(\text{PaO}_2/\text{FiO}_2 <300)$
- Acute oliguria: urine output <0.5 ml/Kg/hr or <45 ml in 2 hours, despite fluid resuscitation
- Creatinine increase: >44 $\mu\text{mol l}^{-1}$ in 24 hours
- Coagulation abnormalities: INR >1.5 or APTT >60 seconds
- Ileus (absent bowel sounds)
- Thrombocytopenia: platelet count $<100,000$ μl^{-1}
- Hyperbilirubinaemia: plasma total bilirubin >34 $\mu\text{mol l}^{-1}$
- Hyperlactatemia >4 mmol l^{-1}
- Decreased capillary refill

WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure.

Box 1

Signs of organ dysfunction associated with severe sepsis

- Sepsis-induced hypotension
 - Lactate greater than 4 mmol l⁻¹
 - Urine output <0.5 ml/kg/hr for >2 hours, despite fluid resuscitation
 - ALI with PaO₂/FiO₂ <250 in the absence of pneumonia as infection source
 - ALI with PaO₂/FiO₂ <200 in the presence of pneumonia as infection source
 - Creatinine >176 mmol l⁻¹
 - Bilirubin >34 mmol l⁻¹
 - Platelet count <100,000 µl⁻¹
 - Coagulopathy INR >1.5
- ALI, acute lung injury; INR, international normalized ratio.

Box 2

tried. Antithrombin III and activated protein C are two such proteins that have been tested in clinical practice but are not currently recommended.

Modern approach

15 years ago a collaborative approach to the 'septic patient' was started by the Society of Critical Care Medicine, the European Society of Intensive Care Medicine and the International Sepsis Forum. Together they formed the 'Surviving Sepsis Campaign' www.survivingsepsis.org which published a four phase plan to tackle sepsis world-wide.

Phase I

- Awareness amongst professionals, governments, health agencies and the public.
- Early and accurate diagnosis.
- Appropriate treatments and interventions.
- Educating all healthcare professionals about diagnosis, treatment, and management of sepsis.
- Improving access to ICU care for septic patients.
- Developing global standards of care.

Phase II

- Publication of guidelines following the Barcelona meeting in 2003.

Phase III

- Translating the guidelines into clinical practice. Establishing a world-wide database that would enable the campaign to achieve its aim of a 25% reduction in mortality.

Phase IV

- Maintaining the database and refining treatments and publishing results.

In compliance with phase IV, results from the database from 218 centres world-wide have been published showing significant improvement in survival when protocol compliant.⁴

Though well known amongst intensivists, the campaign is less well known to doctors working more widely in the hospital. As most patients come from the wards or via 'accident and

emergency' and there is an emphasis on the first 6 hours of care, it is important that all doctors are aware of what are the best current guidelines for treating sepsis.⁵ In particular 'time zero' for the protocol starts on admission to the 'accident and emergency' department and not when the patient arrives on the ICU. Some of the management seems prescriptive and care bundles are used. Both are inevitable in the drive for global standards and making treatment protocols that are easy to use, remember and audit.

Diagnosis

Recognizing a septic patient is easy once the diagnosis has been considered. However, the longer the patient remains untreated or receives inadequate treatment the worse the prognosis.

History

The patient may have another underlying condition such as arthritis, diabetes, ischaemic heart disease, etc., but that is not the cause of feeling 'unwell'. Ask about fever, chills, lethargy, confusion, weakness, bowel habit, appetite, headache, etc. The doctor needs to cover all the systems. For example, lung infection will cause shortness of breath and purulent sputum, urinary tract infection may cause dysuria and pungent smelling urine and abdominal infection will cause pain.

Physical signs of infection

Look at the whole patient (Figure 1): pyrexia, tachycardia, tachypnoea, pain and swelling. At this stage identifying site specific infection is crucial in the choice of antibiotics and obtaining cultures.

Diagnostic criteria for suspected sepsis:⁵ these define whether the patient has sepsis or not and if it is uncomplicated or severe. This will determine the treatment plan. The patient that is septic without the criteria for 'severe sepsis' should have cultures taken (blood, screening and site specific), antibiotics, fluids and supplemental oxygen according to SaO₂ values. The patient with severe sepsis moves into a more advanced paradigm.

Management of severe sepsis

A patient suspected of severe sepsis should be managed in at least a higher dependency area where there is access to central venous pressure monitoring and supplemental oxygen therapy.

Diagnostic: full screening swabs must include urine, sputum, drains, and pus from any apparent source.

Also blood cultures from vascular lines and direct from a peripheral vein. The successful isolation of a pathogen is more likely if cultures are taken prior to antibiotic therapy.

Antibiotics: antibiotic prescribing should be according to hospital protocol. But the principle is to start broad-spectrum antibiotics early. This should continue for 3–5 days or until there is a culture or other evidence of the source at which time de-escalation to narrow spectrum should begin. Overall therapy should be for 7–10 days unless it is determined that infection was not the source of the illness.

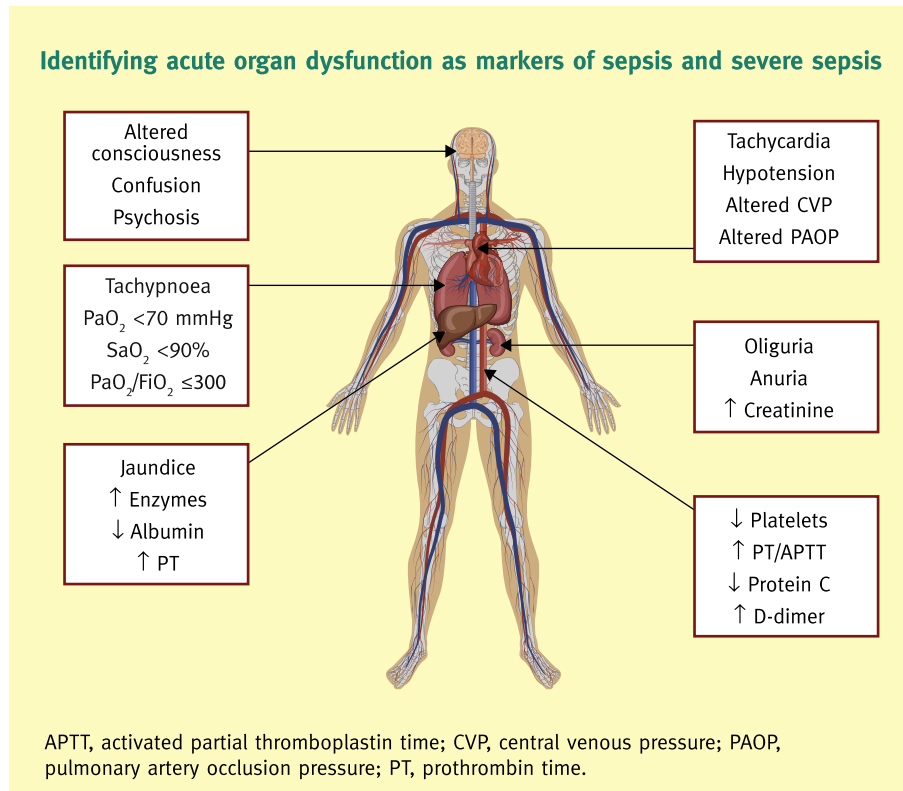


Figure 1

Source control: any collection should be drained or debrided and invasive devices such as catheters should be removed or changed. This may need to be repeated during the illness.

Fluid therapy: the goal of fluid therapy is to increase circulating volume and ensure that if vasoconstrictors are going to be used that the patient is adequately filled. Thus a central venous pressure (CVP) of 8+ mmHg with spontaneous breathing or 12 mmHg in the ventilated patient should be targeted. A fluid challenge can be useful. It requires some clinical awareness of the patient's condition. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with hypovolaemia should be 20 ml/kg of crystalloids over 5–10 minutes. With greater amounts consider albumin. A target of 30 ml/kg of crystalloid or colloid observing the blood pressure and central venous pressure response will determine how treatment will continue. Albumin showed no advantage compared to crystalloid in a study of over 7000 patients.⁶ A meta-analysis of dextrans, starches and gelatins versus crystalloid showed no mortality difference.⁷ However, the CHEST study showed increase renal dysfunction with the use of starches.⁸ Caution is required where cardiac failure is possible and echocardiographic assessment is recommended.

Management of septic shock

The difference between severe sepsis and septic shock is that of response and time. The patient who fits the criteria for severe sepsis but after adequate fluid therapy (maximum 6 hours)

remains hypotensive or hypoperfused (lactate >4 mmol l⁻¹) should be considered as septic shock and managed accordingly. This may proceed quicker than a 6 hours time frame. The important point is that the patient is not left with inadequate perfusion pressure for long periods. This stage of management requires intensive care (Box 3).

Cardiac assessment

Although guidelines recommend both CVP monitoring and central venous saturations (ScvO₂) to achieve therapeutic goals, recent data may change this. The ProCESS trial showed no difference in the use of early invasive monitoring.⁹ A similar result came from the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial which was presented but not yet published at the European Society of Intensive Care Medicine meeting in Barcelona in 2014. As no harm was shown, the Surviving Sepsis Campaign protocol remains but is being reviewed. Nevertheless mixed venous oxygen saturation (SvO₂) from the tip of a pulmonary artery catheter (PAC) or CVP gives information on oxygen supply and demand and is a surrogate marker of adequacy of cardiac output. Generally a cardiac index of >2.5 l min⁻¹ is considered adequate. However, for individuals this may be too high or too low. The PAC will also give information on the systemic vascular resistance. This can then guide vasopressor therapy. However data do not show improved outcomes with the PAC and their use has declined.

Using 65% ScvO₂ as a guide; a lower value should prompt an increase in oxygen transport by either increasing cardiac output

Management requiring intensive care

Fluid therapy

- Crystalloids as the initial fluid of choice hydroxyethyl starches are withdrawn. Albumin when patients require substantial amounts of crystalloids
- Target a CVP of >8 mmHg (on a ventilator >12 mmHg)
- Fluid challenge technique be applied looking for haemodynamic improvement: dynamic (pulse pressure, stroke volume variation) or static (arterial pressure, heart rate)

Vasopressors

- Maintain MAP >65 mmHg
- Noradrenaline the vasopressor of 1st choice
- Vasopressin 0.03 units/min may be added. Other drugs such as phenylephrine and metaraminol are rarely used

Inotropic therapy

- Adrenaline remains the 1st line inotrope in conjunction with noradrenaline
- Dobutamine can be used but causes tachycardia

Steroids

- Hydrocortisone (200 mg/24 hours) for adult septic shock only when hypotension fails to respond to adequate fluids and vasopressors

Blood and blood products

- Packed red blood cells should be given to maintain a haemoglobin of 7–9 g/dl

Mechanical ventilation

- If required the patient should be ventilated according to the ARDSnet protocol. Tidal volumes <6 ml/kg and plateau pressure <30 cm H₂O

Glucose control

- Blood glucose maintained below 9 mmol l⁻¹

Bicarbonate

- Bicarbonate should not be used to correct hypoperfusion. However if cardiac performance is affected by acidosis it should be used

Box 3

or increasing oxygen carrying capacity i.e. correct anaemia. A higher value is re-assuring and allows a reduction in inotropes or avoidance of transfusion. Measuring precise oxygen delivery and targeting supra-normal values is no longer common practice.

Other surrogates for cardiac output are the lactate, base excess and urine output. There is no doubt that seeing the base excess correct is a good sign but it lacks specificity. Should a negative base excess be corrected with bicarbonate? Not if the sole aim is to correct an indicator of tissue perfusion. But if the clinician feels that myocardial performance is compromised then it should be considered.

Case study: a ventilated patient starts with a base excess of -2.0 and pH 7.34. He deteriorates over the next 12 hours and the base excess gradually increases to -11 and pH 7.10 despite escalating inotropes. At this point the patient receives 100 ml of 8.4% bicarbonate and appears adequately fluid resuscitated and inotropes stabilize. Both function and filling are echo guided. This only causes an immediate change in the base excess to -10 and pH 7.15. No further buffer is given and over the subsequent 12 hours the base excess returns to 0 and pH 7.36. The base excess provides useful information on tissue perfusion and shortly after this the patient was extubated. Once the pH is below 7.15 in the acute setting the heart will be affected.

Urine output is good sign of renal perfusion and therefore cardiac output. However, response is slow and can be affected by other factors.

Echocardiography is the best bedside tool for monitoring cardiac function and filling. Most ultrasound platforms are multimodal. That is the same machine that is used for vascular access or chest ultrasound can be used for cardiac ultrasound. All that is needed is the correct probe. Echocardiographic assessment of the left ventricle (LV) has led to increased awareness of the impact of sepsis on LV function. It is common to see young patients who would have an ejection fraction (EF) of >50% having an EF of <30%. Post-event the cardiac function recovers. They do not have ischaemic or valvular heart disease. Baron showed that 60% of patients ventilated with septic shock showed impaired LV function which was partially correctable with dobutamine. There was functional recovery and it did not affect survival.¹⁰ Echo will also show right ventricular dysfunction which carries a much worse prognosis and influences the CVP readings. Simple measures of LV dimensions can guide filling requirements. Measuring the inferior vena cava (IVC) in response to fluid challenges and respiratory variation adds to the information on filling. In over 80% of patients this information can be obtained by transthoracic echo.

Vasopressor and inotropes

Although there are various studies on which inotrope or vasopressor to use, there is little real science that separates them. Noradrenaline is the drug in common use and nursing staff are familiar with it. It is known that excessive use of any vasoconstrictor can cause splanchnic and renal hypoperfusion. However, noradrenaline has the most favourable profile in the event of sepsis and adequate filling pressures. Vasopressin appears as second choice as it has been shown that plasma levels are low in septic patients. Adrenaline is the first choice inotrope with dobutamine second, which has tended to replace dopamine. Adrenaline should be considered alongside noradrenaline but cannot be used outside of intensive care and when central venous access is not available. If less potent inotrope support is required off the ICU then dopamine has a relatively good cardiac safety profile despite concerns about its effects on other hormones of which the clinical significance is unknown.

Steroids

The use of steroids in septic shock has varied over the years. However, there is support from a Cochrane Review for the use

of steroids if hypotension persists despite fluids and pressor therapy¹¹ (commonly hydrocortisone 200 mg over 24 hours for 7 days). However, a European study which confirmed a beneficial effect on reversal of shock failed to show a mortality benefit using low-dose steroids.¹² Hydrocortisone is preferred to dexamethasone due to its mineralocorticoid effect. The Sepsis Campaign has recommended restricted use of steroids.

Blood and blood products

Transfusion policies have varied in the trials in septic patients. Thus an optimal haemoglobin is not known. In River's study¹³ a target haematocrit (Hct) of 30% was used. In other studies a haemoglobin range of 7–9 g/dl has been compared with higher haemoglobins and shown no detriment with the lower values. Thus a target of 7–9 g/dl or Hct 21–27% is recommended although higher values may be desired in specific patient groups.¹⁴ The use of fresh frozen plasma and platelets is for the bleeding patient or if a surgical intervention is planned, in which case platelets are given if the count is $<50,000/\text{mm}^3$. Current guidelines do not recommend the use of cryoprecipitate for measured values of fibrinogen degradation products.⁶ However, both fresh plasma and cryoprecipitate are used when faced with coagulopathy.

Mechanical ventilation

During the past 15 years there has been a move towards protective lung ventilation strategies. Many septic patients will require mechanical ventilation. Non-invasive ventilation is desirable but is less effective in sepsis compared to other respiratory diseases. Half of these patients will have an acute lung injury, caused by the effects of septicaemia. At this time they are vulnerable to barotrauma caused by ventilation-modes used in the operating room. This in turn will result in acute respiratory distress syndrome (ARDS) which carries a very high mortality and morbidity especially in patients over 45 years of age. The basic principle is to use low tidal volumes, $<6 \text{ ml/kg}$, keep inspired plateau pressures $<30 \text{ cm H}_2\text{O}$, recruitment strategies and allow permissive hypercapnia, the so called 'ARDSnet strategy'.¹⁵ Though precise values for the PaCO_2 are not established it is considered reasonable to allow a respiratory acidosis of around pH 7.25.

Glucose control

Van den Berghe presented her work on tight blood glucose control in 2000 at the European Society of Intensive Care Medicine and showed a 50% reduction in sepsis related mortality in a postoperative, intensive care population.¹⁶ Following this, nearly all intensive care patients received additional artificial calories and intense insulin therapy. It seemed intuitively correct that running high blood glucose was a bad thing in the presence of bacteraemia. However, subsequent studies showed far less dramatic findings and many found hypoglycaemia a problem. In 2009 the NICE-SUGAR study with over 6000 patients comparing 'tight glucose control' (normal values) with 'glucose kept below 10 mmol/l' found increased mortality and more episodes of hypoglycaemia in the 'tight' group.¹⁷

Nutrition

When and how? Feeding septic patients remains controversial. Because the source of sepsis is so variable it is difficult to compare like with like. A survey of 454 ICUs in 310 German hospitals specifically looking at feeding in septic patients found that patients fed with parenteral or mixed parenteral/enteral nutrition had a greater than 57% mortality compared with enteral alone which was 38%.¹⁸ However a multicentre Italian study showed an excess mortality in septic patients receiving enteral immune-nutrition compared to parenteral nutrition and the study was stopped.¹⁹ The current position does not recommend specific immune-nutrition.

Administration of bicarbonate

This was considered in the section on cardiac assessment.

Infection control and prevention

The best approach to sepsis is to prevent it in the first place. It is the role of everyone involved with patients to stop infection before it starts and to prevent its spread. Thought needs to be given to the likely pathogens to make this effective. The design and organization of the unit has a crucial role.²⁰ Side rooms are optimal for patients as long as staffing allows proper care. Design should also consider washing facilities so that everyone is able to hand-wash effectively. It is now accepted that methicillin-resistant *Staphylococcus aureus* (MRSA) must be screened for and that screening is effective in reducing the incidence of MRSA infections.

While MRSA can be screened for and is becoming less prevalent other pathogens are on the increase. Of note in ICU are the multi-resistant Gram negative organisms. Mainly, *Acinetobacter* spp., extended spectrum-lactamase producing Gram negatives (ESBL), *Stenotrophomonas maltophilia* and gentamicin-resistant *Pseudomonas aeruginosa*. The ESBL enzyme is found in many pathogens such as *Klebsiella pneumoniae*, *Escherichia coli*, *Salmonella* and *Pseudomonas*. These pathogens are widespread and important decisions on treatment start with distinguishing between colonization and infection. Choice of antibiotics needs to involve microbiology and the infection control team. Treatment will often need to be prolonged (3 weeks or more) and involve isolation. Indeed antibiotic treatment is key to infection prevention across the hospital and ideally should be done by the infection control team in accordance with strict hospital guidelines.

Clostridium difficile is a significant problem on the ICU. Reported cases in the UK since 1990 have increased from 2500 to 65,000 by 2007. Most cases occur in patients over 65 years; 2–3% of adults are carriers, the percentage is much higher in babies. Most patients acquire the infection in hospital by ingesting the spores. The spores survive the gastric acid and then proliferate in the antibiotic reduced flora of the large intestine. Here toxins are produced which can cause colitis ranging from mild diarrhoea to pseudomembranous colitis. In the vulnerable patient this can be a lethal condition and always leads to prolonged isolation on the ICU. Again hand hygiene, cleaning, isolation and careful control of antibiotic prescribing limit its spread and prevalence.

Invasive catheters and central lines have always been inserted in a semi-sterile way. They can become a source of bacteraemia

for the patient. Awareness of the problem and improving the general approach to line insertion has been achieved by various bodies most recently by Matching Michigan. Work done in Michigan showed that sepsis from lines was a problem and that by instituting a package of care or bundle to cover all aspects of line insertion then this problem could be reduced.²¹

Extracorporeal membrane oxygenation (ECMO)

Previously sepsis was a contraindication to ECMO. This is now changing in the very sick. Also viral disease, such as that seen with H1N1 and *Coronavirus* though not strictly sepsis, has created a lot of interest in using ECMO to bring down the very high mortality associated with it. As a treatment option it remains in a few specialized centres but the number of centres is increasing.

Conclusion

The 'Surviving Sepsis Campaign' has increased awareness and made available a package of care that is practical and achievable. Care bundles and the sepsis resuscitation bundle are shown in Box 4. They should not detract from managing patients

individually but have value as an 'aide memoir' and provides a format that can be accurately audited.

This article includes additional relevant aspects of care, some more advanced which deserve wider acceptance on the ICU.

In the UK we now have the 'UK Sepsis Group' which calls for sepsis being a government priority and a national registry. However the clinical management is clear and it is up to individual intensive care doctors to deliver this standard of care.

Recognition, cultures, debridement, treatment and advance treatment for none responders within 24 hours. ◆

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Surviving Sepsis Bundles for severe and septic shock

Severe sepsis resuscitation bundle

Aim to perform these tasks within the first 6 hours of identification of severe sepsis.

- Measure serum lactate
- Obtain blood cultures prior to antibiotic administration
- Administer broad-spectrum antibiotic, within 1–3 hours of admission
- In the event of hypotension and/or a serum lactate >4 mmol l⁻¹
 - Give 30 ml/kg of crystalloid or approximately 15 ml/kg colloid
 - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) >65 mmHg
- If hypotension persists despite fluid resuscitation (septic shock) and/or lactate remains >4 mmol l⁻¹
 - Achieve a central venous pressure (CVP) of >8 mmHg
 - Achieve a central venous oxygen saturation (ScvO₂) $>65\%$

Sepsis shock management bundle

Aim to achieve below as soon as possible but within 24 hours of diagnosis of septic shock.

- Add second line inotrope or vasopressor
- Maintain glucose control <9 mmol
- Maintain a median inspiratory plateau pressure (IPP) <30 cm H₂O for ventilated patients.
- Administer low-dose steroids for septic shock (hydrocortisone 200 mg/24 hours)

N.B. Activated protein C (drotrecogin alfa) is no longer available due to safety concerns.

Box 4

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