Update in
Anaesthesia

Management of sepsis with limited resources

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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 Guidance using 'bundles' of care are useful, but some aspects become outdated soon after publication.

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 sepsis*[5]

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 ($PaCO_2$ < 4.25kPa)
- White blood count > 12 x 10^9.L^{-1}, or < 4 x 10^9.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.

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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 patients[7] (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 questionned 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 ($ScvO_2$). This may be a useful marker of oxygen delivery. A $ScvO_2$ 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 SaO_2. 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 ($ScvO_2$) > 70%

Serum lactate < 4mmol.l^{-1}

Notes:

$$MAP = \text{diastolic BP} + \frac{(\text{systolic BP} - \text{diastolic BP})}{3}$$

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 trial[17]) 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 trial[19]) 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 $ScvO_2$ 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 $ScvO_2$ 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 Xray, 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 Guidelines[9] 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 $ScvO_2$ > 70%:

- They were given 500ml crystalloid every 30 minutes until CVP 8-12,
- If MAP < 65mmHg they received norepinephrine (if MAP >90mmHg vasodilators),
- If $ScvO_2$ < 70% they were transfused to Hb >10g.dl^{-1},
- Then, if $ScvO_2$ < 70%, they received dobutamine (stopped if MAP < 65 or HR > 120)
- Then, if $ScvO_2$ < 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 $ScvO_2$ 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. $ScvO_2$ 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 finding 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 <30cmH_2O compared to ventilation with tidal volumes of 12ml.kg^{-1} and plateau pressures <50cmH_20 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 <30cmH_2O 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 FiO_2 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 adrenocorticotropic 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 Guidelines[9] 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 (thrombocytopaenia, 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 apyrexial 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 5$L.min^{-1}$ from an oxygen concentrator, insert two 14G cannulae and start fluid resuscitation with Hartmanns 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 amoxycillin 2g 6 hourly, metronidazole 500mg 8 hourly and gentamicin 5$mg.kg^{-1}$ 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 Hartmanns. Observations are: RR 25, SaO_2 100% on 5$L.min^{-1}$ O_2, 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 39ºC.

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) 30x10^{9}.L^{-1}, platelets 90x10^{9}.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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