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 a hospital mortality for severe sepsis of up to 55%.[1] Sepsis is the most common cause of death in children in the world. Sixty percent of deaths in developing countries occur as a result of communicable disease.[2] 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.

Box 1: Definitions of Sepsis[3]

Systemic Inflammatory Response Syndrome (SIRS): Two or more of the following:

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats/minute
- Tachypnoea (respiratory rate > 20 breaths/min) or hyperventilation ($PaCO_2$ < 4.25 kPa)
- White blood count > 12 x 10^9/l, or < 4 x 10^9/l

Sepsis: 2 or more SIRS criteria in response to infection.

Severe Sepsis: Sepsis associated with hypotension or organ dysfunction or organ hypoperfusion (eg 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.

Circulatory insufficiency in sepsis results from hypovolaemia, myocardial depression and vasoregulatory abnormalities including vasodilatation and impaired regulation of organ perfusion. This, together with increased metabolic rate, causes an imbalance between tissue oxygen supply and demand, leading to global tissue hypoxia.

The interactions between infecting micro-organisms and the immune, inflammatory and coagulation responses in sepsis are complex. Pro-inflammatory and pro-coagulant responses are amplified by ischaemia and hypoxia, and immunosuppression occurs in severe sepsis.[4]

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, reduced urine output as well as tachypnoea and tachycardia.

Signs of SIRS should be picked up on routine observations. These should include temperature, heart 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) is a particularly 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.

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.[5] 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.[6]

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, immediate 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.

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 an Ambubag and mask (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 (see Figure 1).

Intubating critically ill patients has significant risks. They have little oxygen reserve, and despite full pre-oxygenated 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 it is wise to intubate such patients without sedation, using a local anaesthetic agent sprayed through a cannula onto the larynx under direct laryngoscopy.

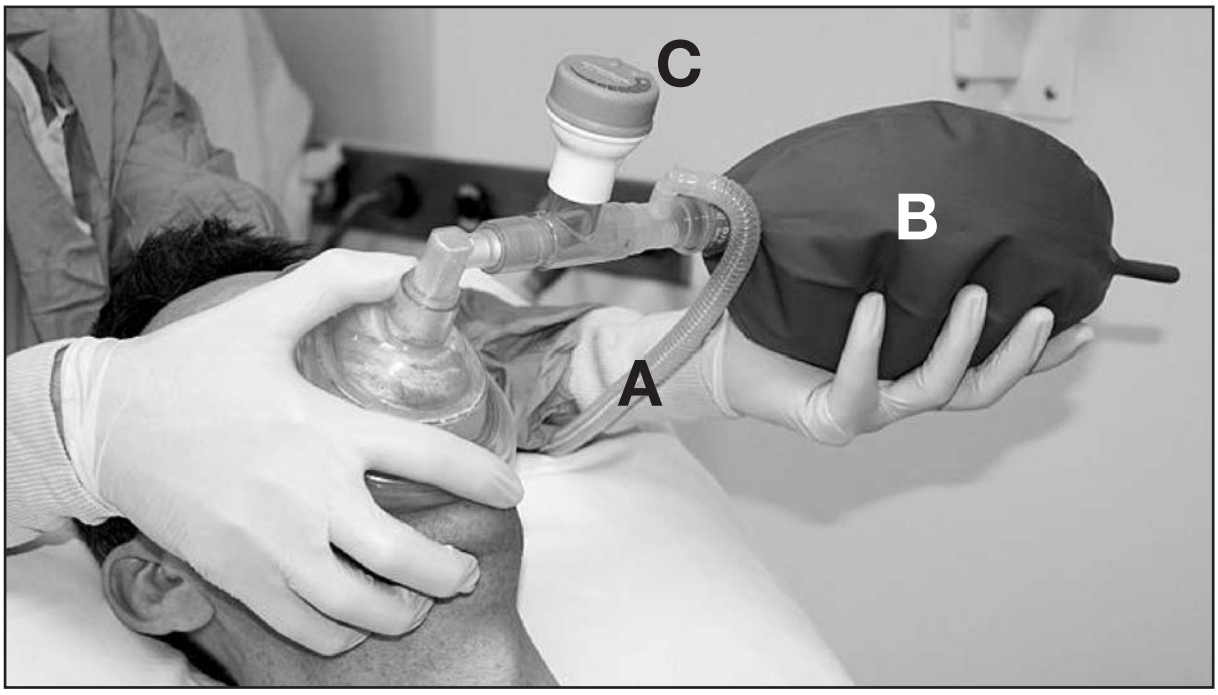

Figure 1: A Waters circuit which has tubing from an oxygen source (A), a reservoir bag (B) and an adjustable pressure limiting (APL) valve (C), is ideal for optimal oxygenation and also gives the facility to deliver a variable level of respiratory support by squeezing the bag, or to apply CPAP by adjusting the APL valve.

Box 2: Intubation checklist for critically ill patients

Monitoring:	As available: SaO_2, ECG, frequent BP, assistant to feel pulses
Assistants:	One or preferably two for cricoid pressure and assistance. Check they know what you expect them to do
Pre-oxygenation:	Deliver as much oxygen as available via facemask and 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:	eg. ketamine & suxamethonium
Resuscitation drugs:	ephedrine 30mg in 10ml (1-3ml boluses) metaraminol 10mg in 20ml (0.5-2ml), epinephrine1mg 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

Circulation

Fluid Resuscitation

Septic patients need a lot of fluid. An initial fluid bolus of 20-30ml/kg 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.[5]

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 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.[7]

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, 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 in implementing the findings of clinical studies into 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 in venous blood and < 1mmol/l in arterial blood. A recent study of patients with an infective diagnosis attending an emergency department, showed that patients with a **venous** lactate level above 4mmol/l 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 and a systolic BP below 70mmHg on presentation was 60%.[8]

Several monitors can measure or calculate cardiac output and fluid status (*see Update 21*).[9] 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.[10] In fact a recent trial in patients with acute lung injury (of whom 25% were septic) showed no advantage in 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).[11] 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 with 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 to improve the perfusion pressure to organs such as 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. If in doubt, an inotrope such as dobutamine may be added.

Patients with low cardiac output have cool peripheries and slow capillary refill. Their systemic vascular resistance may be high or low. Once adequately fluid resuscitated, they need an inotrope to improve cardiac output. Epinephrine 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 noradrenaline but titrating two vasoactive drugs without cardiac output monitoring is not easy. There is some concern over the effects of epinephrine on gut perfusion[11] but a recent Cochrane review concluded that there was not sufficient evidence to recommend one vasopressor over another.[13]

The most common reason why a patient fails to respond to vasopressors / inotropes is that they are under-filled: a fluid challenge is worth trying. Given the difficulty 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. The TRICC study showed that in intensive care patients a restrictive transfusion strategy aiming for haemoglobin of 7-9g/dl was at least as effective

Box 3: Resuscitation goals:

Mean Arterial Pressure (MAP) > 65mmHg

Urine Output > 0.5ml/kg/h

Warm peripheries, capillary refill < 2 seconds

Central Venous Pressure (CVP) 8-12mmHg (7.6mmHg = 10cmH_2O)

Central Venous Oxygen Saturation ($ScvO_2$) > 70% where available

Venous serum Lactate < 4mmol/l

Notes: MAP = diastolic BP + (systolic BP-diastolic BP)/3
i.e. MAP 65 compatible with BPs of 85/55, 95/50, 105/45

Box 4: use of inotropes and vasopressors

These are examples only. 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/hour & titrate according to response
  - for a 50kg person 0.1micrograms/kg/min = 3ml/hour
- If no infusion pumps available:
  - mix 5mg in 500ml. *The infusion rate should be watched continuously.*
  - Paediatric giving sets with 60 drops/ml are helpful, start at 10-50 drops/min
  - Normal 20 drops/ml sets can also be used- divide drops/min by 3
  - For example for a 50kg person:
    - with 60 drops/ml paediatric set 0.1 micrograms/kg/min = 30 drops/min
    - with 20 drops/ml set 0.1 micrograms/kg/min = 10 drops/min.

Dopamine & Dobutamine

- By infusion pump:
  - mix 250mg in 50ml.
  - start around 5 micrograms/kg/min
  - for a 50kg person 5 micrograms/kg/min = 3 ml/hour
- These can also be used without an infusion pump as above.

and possibly superior to a liberal transfusion strategy aiming for Hb 10-12g/dl.[14] However, only 5% of their patients had a primary diagnosis of sepsis, average lactate concentration was less than 2mmol/l, 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. The Rivers protocol included transfusion to Hb>10g/dl, if $ScvO_2$ >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 levels in intensive care remain controversial.[15] 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.[15] 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 long-standing 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. ALI is defined as PaO_2/FiO_2 ratio of 200-300mmHg (26-39KPa). ARDS is more severe with PaO_2/FiO_2 ratio <200mmHg (26KPa).

Box 5: Early Goal-Directed Therapy

Many recommendations in this review and in the Surviving Sepsis Guidelines[6] are based on Rivers' trial of early goal-directed therapy (EGDT) in severe sepsis and septic shock.[5] 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 (p=0.0009, NNT).[7]

Enrolled patients met SIRS criteria (above) and had systolic BP < 90mmHg after 20-30ml/kg of crystalloid, or venous lactate >4mmol/l. The control group received standard therapy to achieve CVP 8-12mmHg, MAP >65mmHg, urine output >0.5ml/kg/h. The experimental group protocol aimed for the same targets plus $ScvO_2$ >70%:

- They were given 500ml crystalloid every 30 mins 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
- 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 7-72hours 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.

Mortality at hospital discharge was 29% in the study group compared to 44% in the control group (p=0.006, number needed to treat = 7).

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.

Mechanical ventilation of patients with ALI/ARDS should avoid high airway pressures and high tidal volumes. The ARDSnet study was the largest randomised controlled trial comparing ventilation strategies including 861 patients.[17] Ventilation with tidal volumes of 6ml/kg and plateau pressures of <30cmH_2O compared to ventilation with tidal volumes of 12ml/kg and plateau pressures <50cmH_20 reduced mortality from 40% to 31% 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 are probably more important than the ventilation mode.

Permitting modest hypercapnia to allow lower tidal volumes and airway pressures is likely to be safe. However, this is limited if the patient has a metabolic acidosis.[6]

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.[18] Increasing PEEP according to FiO_2 as in the original ARDSnet study seems reasonable: minimum PEEP of 5cmH_2O at FiO_2 of 30% up to PEEP of 20cmH_2O or higher with FiO_2 of 100%.

Nursing ventilated patients in the semi-recumbent position (45 degrees) has been shown to reduce the incidence of ventilator-associated pneumonia.[19] Patients may need to be laid flat if hypotensive. Non-invasive ventilation,[20] subglottic drainage and use of heat & moisture exchange filters instead of heated water humidification may also reduce ventilator-associated pneumonia.[21]

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.[22]

Activated Protein C

Recombinant activated protein C has been shown to reduce mortality in severe sepsis[23] but not in low risk patients[24] or in children.[25] Its expensive precludes use in many countries.

Steroids in sepsis

Patients on long term steroid therapy or with known adrenocortical insufficiency will require steroid

replacement during critical illness. Many studies have looked at treatment of septic patients with corticosteroids and this remains controversial.

One multicentre randomised controlled trial (RCT) of 229 patients showed an improvement in mortality in patients with septic shock and relative adrenal insufficiency (blood cortisol level failed to rise appropriately in response to a dose of synthetic adrenocorticotropic hormone, ACTH) when they were given hydrocortisone 50mg 6 hourly and fludrocortisone.[26] The only statistically significant difference without adjusting the data was in ICU mortality (70% control group, 58% treatment group – giving a number needed to treat of 8). This effect was only seen in non-responders to the ACTH test, not in the group as a whole, leading to fears that a proportion of septic patients would be treated with steroids inappropriately. Two smaller RCTs showed improvements in shock reversal with low dose hydrocortisone.[6] Two meta-analyses have shown reduction in mortality, but only in studies of low dose, long duration steroid therapy.[27,28] The interpretation of the ACTH stimulation test remains controversial.

The recent CORTICUS trial, a randomized, controlled study of 500 patients comparing hydrocortisone to placebo in septic shock is not yet published but is thought to show no difference in mortality with low dose steroids in septic shock.[29]

Steroid use in sepsis is controversial, but current practice in many ICUs is to give low dose steroids to patients with vasopressor-dependant septic shock, with or without an ACTH test. This may change once the results of CORTICUS are published. Short courses of high dose steroids should not be used.

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.[30] 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.[30,31] 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,[32] and it is advisable that all ICUs use an enteral feeding protocol describing gradual introduction of feed to a pre-determined 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.[33,34] 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. Some surgeons will not allow feeding until bowel sounds are present which can take several days and hypokalaemia can worsen ileus. They can often be persuaded to allow oral rehydration solution by mouth or nasogastric tube.

The Surviving Sepsis Guidelines recommend stress ulcer prophylaxis with ranitidine. This is unnecessary once enteral feeding is established.[6]

Blood glucose control

Glucose control in ICU remains controversial. Van Den Berghe's study in 2001 showed improvements in ICU mortality in patients with tight glucose control (4.4-6.1mmol/l versus 10.0-11.1mmol/l).[35] 62% of the patients in this study had undergone cardiac surgery, but despite concerns about the relevance of these results to medical ICU patients, tight glucose control has been widely adopted. The Surviving Sepsis Guidelines recommend keeping blood glucose below 8.3mmol/l (150mg/dl).[6]

Van den Berghe's next study, in medical ICU patients, showed that intensive insulin therapy improved some markers of morbidity but not mortality in the randomised group.[36] 19% of patients in the treatment group developed hypoglycaemia, but with no obvious adverse outcome.[37] 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%).[38]

Septic patients are at risk of both hypo- and hyperglycaemia whether or not they are treated with dextrose 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. Very high blood glucose (>11mmol/l) is likely to be harmful, as is severe hypoglycaemia. Clinicians have to balance the potential benefits of tighter glucose control against the risks of undetected hypoglycaemia. 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, by 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) 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 and increase intracranial pressure. 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.

In ventilated patients sedation may be given by intermittent bolus or by continuous infusion, according to a protocol with sedation goals.[6] Daily lightening of sedation ('a sedation hold') allows assessment of neurological function and reduces the duration of mechanical ventilation and ICU length of stay.[39]

Neuromuscular blockers should be avoided if at all possible due to the risk of prolonged muscle weakness (critical illness polyneuropathy).[6] Use of muscle relaxants without adequate continuous sedation is unacceptable.

Both chemical and physical restraint have risks.[40] In one observational study in European ICUs both prolonged sedation and physical restraint without sedation were associated with post traumatic stress disorder.[41] 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, pain and other causes of agitation have been addressed and 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. Treatment of acidosis with sodium bicarbonate does not improve haemodynamics or response to vasopressors.[4] Lactic acidosis should be treated by optimising the circulation.

If available, renal replacement therapy can be with either continuous veno-venous haemofiltration or intermittent haemodialysis.[6] Peritoneal dialysis is appropriate but is contraindicated in the large proportion of patients who have intra-abdominal infection.

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 be used if heparin is not given.[6,42]

Paediatric considerations [6,43]
To recognise a sick child, it is important to know normal values for vital signs in that age group. Listen to the mother - she will tell you if the child is lethargic, not feeding, not passing urine, hot or generally unwell. Weigh the child if possible: formulas for calculating weight according to age usually overestimate the weight of children in developing countries.

Children have less respiratory reserve than adults. They have a high metabolic rate, higher airway resistance and lower functional residual capacity. Babies breathe using their diaphragm and tire quickly. Signs of respiratory distress include tachypnoea, intercostal and subcostal indrawing, cyanosis and tachycardia. All sick children should receive oxygen, and continuous saturation monitoring if possible. They are more likely to need intubation and ventilation and can decompensate very quickly.

Children have a high cardiac output and cardiovascular reserve; they tend to compensate then deteriorate suddenly and rapidly. They become dehydrated easily and respond to hypovolaemia by an increase in heart rate and vasoconstriction. Capillary refill time is a particularly useful sign in children and should be less than 2 seconds. Hypotension is a late, pre-terminal sign. Aggressive fluid resuscitation is vital in the septic child. 20ml/kg boluses should be given over 5-10 minutes, titrated to heart rate and capillary refill, aiming for a urine output of 1ml/kg/h. 60ml/kg of fluid or more may be required. Venous access may be difficult; intraosseous infusion can be lifesaving and should be undertaking if two attempts at IV cannulation are unsuccessful. Inotropes should only be used after adequate fluid resuscitation and dopamine (or dobutamine) is recommended as first line. Hepatomegaly may indicate fluid overload.

Septic children frequently become hypoglycaemic. It is important to check blood glucose early and treat hypoglycaemia with 5ml/kg 10% glucose.

CASE EXAMPLE: POST-PARTUM SEPSIS [44,45]

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 130 and a blood pressure of 140/95. 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° overnight and the next morning she is drowsy and confused and 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 35/min, your saturation monitor is not picking up a signal. Her heart rate is 140/min and blood pressure 70/40. 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 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, but 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 5mg/kg once (with further doses every 24 hours if renal function 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, do **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 X-ray** 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 5l/min O_2, HR 130, BP 80/40, capillary refill 2s, drowsy but now orientated and complaining of abdominal pain, a catheter was inserted draining a small amount of dark urine, 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, white cell count (WCC) $30x10^9$/l, platelets $90x10^9$/l. Na 150mmol/l, K 4.0mmol/l, Cl 110mmol/l, bicarbonate 15mmol/l, urea 10mmol/l, creatinine 80mcmol/l, glucose 6mmol/l. Gram stain 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 of fluid, and 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 a paediatric (60 drops/ml) giving set at 30 drops/minute via 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, 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 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 the 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 improved 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.

Children become hypothermic easily, particularly when large volumes of cold fluid are infused. Even in hot climates it is important to prevent heat loss, warm fluids and check the child's temperature.

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.

Further Reading

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