

Disclaimer:

The Great Ormond Street Paediatric Intensive Care Training Programme was developed in 2004 by the clinicians of that Institution, primarily for use within Great Ormond Street Hospital and the Children's Acute Transport Service (CATS). The written information (known as Modules) only forms a part of the training programme. The modules are provided for teaching purposes only and are not designed to be any form of standard reference or textbook. The views expressed in the modules do not necessarily represent the views of all the clinicians at Great Ormond Street Hospital and CATS. The authors have made considerable efforts to ensure the information contained in the modules is accurate and up to date. The modules are updated annually.

Users of these modules are strongly recommended to confirm that the information contained within them, especially drug doses, is correct by way of independent sources.

The authors accept no responsibility for any inaccuracies, information perceived as misleading, or the success of any treatment regimen detailed in the modules.

The text, pictures, images, graphics and other items provided in the modules are copyrighted by "Great Ormond Street Hospital" or as appropriate, by the other owners of the items. Copyright © 2004-2005 Great Ormond Street Hospital. All rights reserved.

Great Ormond Street Hospital for Children



NHS Trust

22: SIRS, Severe Sepsis & MODS

Author: Mark Peters 2005

Updated: Lara Jackman & Joe Brierley February 2007

Updated: Janani Pallewala & Simon Nadel April 2011

Associated clinical guidelines/protocols:

- Antibiotic guidelines – microbiology "orange book"
- BAL
- Meningococcal septicaemia
- CVVH guidelines
- CATS guidelines (www.cats.nhs.uk): sepsis

Fundamental Knowledge:

List of topics relevant to PIC that will have been covered in membership examinations.

They will not be repeated here.

Information for Year 1 ITU Training (basic):

Year 1 ITU curriculum

- Definitions SIRS, sepsis, severe sepsis syndrome and MODS (shock per se, covered in separate module)
- Basics of Pathophysiological response to infection
- Clinical course of Sepsis, severe sepsis & MODS
- Individual organ support

ITU management of following clinical syndromes:

- Meningococcal sepsis
- Gram negative sepsis
- Toxin mediated disease: Toxic Shock Syndrome, rheumatic fever
- Herpes Simplex

Curriculum Notes for Year 1:

This module focuses on the systemic inflammatory response to infection.

We aim to outline current thinking about the pathophysiology of this process (or processes) but also to focus on practical aspects of clinical care for patients with sepsis-induced organ failure.

Definitions/Terminology

- **SIRS (Systemic inflammatory response syndrome):** The presence of at least 2 of the following 4 criteria, one of which must be abnormal temperature or leukocyte count:
 1. **Core temperature** >38.5 C or <36 C
 2. **Tachycardia:** mean heart rate >2 SD above normal for age in the absence of external stimulus/drugs **or** unexplained

persistent elevation over 0.5-4 hrs **or** bradycardia (mean HR <10th centile for age in the absence of external vagal stimulus/heart disease/drugs) **or** unexplained persistent depression over 0.5 hrs

3. **Mean respiratory rate** > 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anaesthesia
4. **Leukocyte count** elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils

- **INFECTION:** Suspected or proven infection caused by any pathogen or a clinical syndrome associated with a high probability of infection
- **SEPSIS:** SIRS in the presence of, or as a result of suspected or proven infection
- **SEPTIC SHOCK:** Sepsis & cardiovascular organ dysfunction
- **MODS (Multi Organ Dysfunction Syndrome):** Presence of altered organ function in the acutely ill patient such that homeostasis cannot be maintained without intervention.

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus 40 mL/kg in 1 hr

- **HYPOTENSION:** Mean BP < 5th percentile for age or systolic BP 2 SD below normal for age

OR

- Need for vasoactive drugs to maintain BP in normal range (dopamine >5g/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)

OR

- Two of the following:
 - Unexplained **metabolic acidosis:** base deficit >5.0 mEq/L
 - Increased arterial **lactate** >2 times upper limit of normal
 - **Oliguria:** urine output <0.5 mL/kg/hr
 - **Prolonged capillary refill:** >5 secs
 - Core to peripheral **temperature gap** >3°C

Respiratory

- PaO₂/FIO₂ <300 in absence of cyanotic heart disease or preexisting lung disease

OR

- PaCO₂ >8.6 KPa or 2.7 KPa over baseline PaCO₂

OR

- Proven need for >50% FIO₂ to maintain saturation >92%

OR

- Need for non-elective invasive or non-invasive mechanical ventilation

Neurological

- Glasgow Coma Score ≤ 11

OR

- Acute change in mental status with a decrease in Glasgow Coma Score ≥ 3 points from abnormal baseline.

Hematological

- Platelet count $< 80,000/\text{mm}^3$ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic haematology/oncology patients)

OR

- International normalized ratio > 2

Renal

- Serum creatinine ≥ 2 times upper limit of normal for age or 2-fold increase in baseline creatinine

Hepatic

- Total bilirubin ≥ 70 micromol/L (not applicable for newborn)

OR

- ALT 2 times upper limit of normal for age

A new approach to the description of sepsis has been proposed that utilises many more clinical features to produce a 'staging system' that can be summarised as '**P.I.R.O**':

Mitchell M. Levy, MD: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250 –1256

- **P**redisposition,
- **I**nfection,
- **R**esponse, and
- **O**rgan dysfunction.

Pathogens

Varies with age and immunisation status. For example:

- Group B Streptococci, Listeria and enteric organisms e.g. E.coli, in neonates
- Streptococcus pneumonia and Neisseria meningitides in older children
- Also viruses and fungi, and other gram negatives and gram positives, particularly in (immunocompromised patients)
- Staphylococcus aureus and Group A Streptococcus may affect children at any age

Referral to PICU

There are no very reliable predictors of which children with clinical evidence of sepsis can be anticipated to deteriorate into severe sepsis / septic shock.

Questioning should seek out **specific evidence of established organ dysfunction** including:

- Reduced blood pressure
- Clinical evidence of coagulopathy
- Depressed Glasgow Coma score
- Disproportionately high respiratory rate
- Reduced urine output
- Requirement for supplemental oxygen
- Poor perfusion
- Tachycardia
- Unexplained base deficit/high lactate (>2)

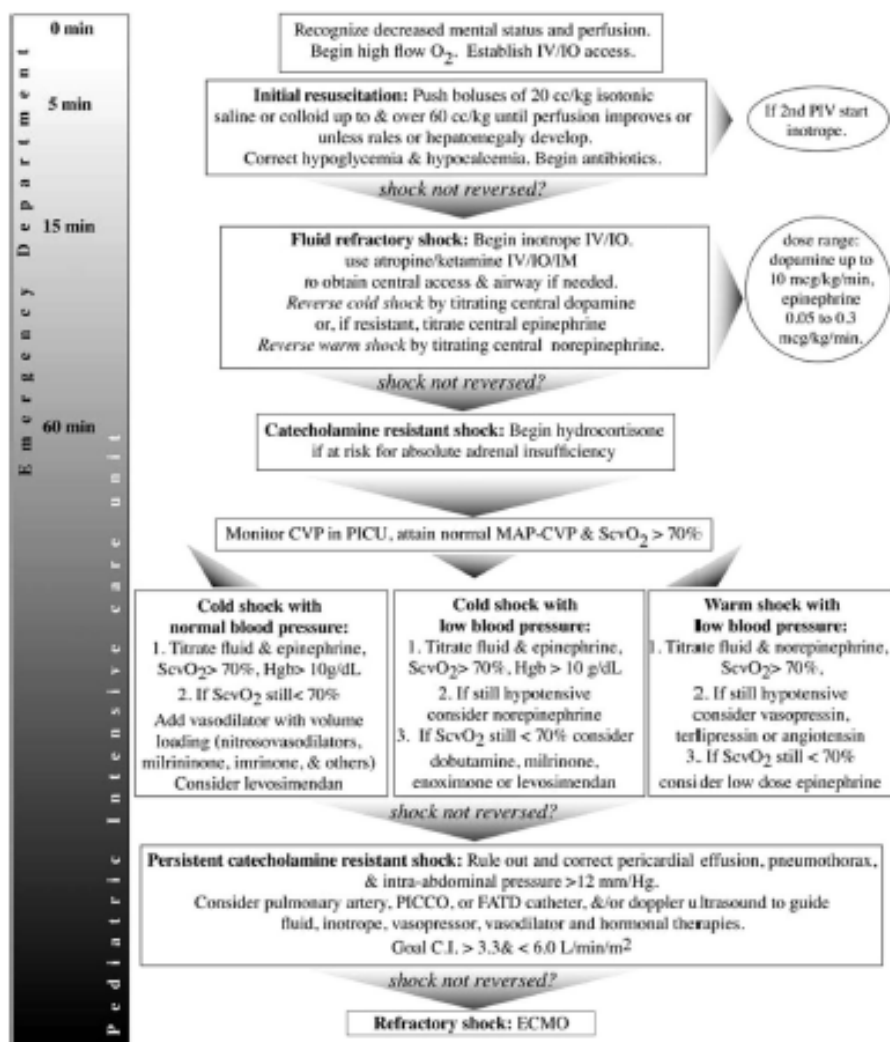
If any of these are significantly abnormal then the child should be considered an intensive care case & advice given according to the flow chart below.

NOTE: The pattern of development of organ dysfunction is not consistent. It is a common error to be falsely reassured by soft signs including:

- Only mild tachycardia
- Base deficit
- Ability to talk with objective evidence of organ dysfunction
- White cell count not elevated

As the pattern of presentation may be more misleading in immunodeficiency, the threshold for intervention should probably be lowered in this group

In severe meningococcal (and other forms of sepsis), the presence of neutropenia & thrombocytopenia on the first FBC is a reliable sign of severe disease *regardless of the clinical condition.*



(2007 update of the 2002 American College of Critical Care Medicine Clinical Guidelines for Hemodynamic Support of Neonates and Children with Septic Shock)

Immediate Action for the Child Presenting in Septic Shock

1. **Early identification of septic shock** with careful clinical examination & initial laboratory tests is critical. Look carefully for signs of organ dysfunction but remember signs may change over time.
2. **Rapid, aggressive correction of deranged physiology**
3. **Specific treatment of infection**

The immediate care of a child with suspected septic shock must address "A, B, C followed by specific therapy.

Follow the flow chart – *paying close attention to the elapsed time* (Grade E).

In septic shock the majority of cases present with an inadequate circulation as the overriding priority.

The relatively low functional residual capacity of infants and young children, however, means that respiratory support may be required earlier in the clinical course than might be anticipated from adult data.

Circulation

If the child is shocked you should not persist with attempting peripheral (or central) venous access for more than 90 seconds. Initial resuscitation via an intra-osseous needle is easy and effective.

You will not be criticised for siting an IO line early & it will improve your chances of securing central venous and arterial lines later.

First choice site for CVL is **FEMORAL**. Remember, many of these children will be severely coagulopathic & hence neck lines carry an increased risk of complications. Remember the differences between mixed venous vs central venous saturations.

Aggressive fluid resuscitation is of fundamental importance to survival of septic shock in children (Grade C). After a fluid bolus has been given, assess the effect it has had on HR, BP, CVP, urine output, metabolic status and peripheral perfusion.

Administration of >40 ml /kg in the first hour is associated with a significant reduction in mortality (Grade E).

R. Phillip Dellinger et al: Surviving Sepsis Campaign: Crit Care Med 2004;**32**:858-873

Large fluid deficits typically exist, and initial volume resuscitation usually requires 40 – 60 ml/kg in the first hour but can be much higher.

Children can delay a reduction in blood pressure by vasoconstriction & increasing heart rate. Therefore, blood pressure by itself is not a reliable end-point for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow.

Choice of resuscitation fluid: There is ongoing debate about the use of colloid versus crystalloid. Current accepted practice is to use 0.9% saline for the initial bolus which may be followed either by further crystalloid or colloid boluses.

Hepatomegaly occurs in children (especially infants) who are fluid overloaded & can be a helpful sign of the adequacy of fluid resuscitation.

In the absence of CVP monitoring the effect of hepatic compression or leg elevation on BP & HR can give a rough guide to the consequences of further fluid administration.

Fluid Refractory Shock: shock persists despite $\geq 40\text{-}60\text{ml/kg}$ fluid resuscitation

Cold shock: low cardiac output and high systemic vascular resistance leading to prolonged capillary refill time, diminished peripheral pulses and mottled extremities

Warm shock: normal/high cardiac output with low systemic vascular resistance leading to rapid capillary refill time and bounding peripheral pulses

Do not delay starting inotropes until central venous access has been obtained as they may also be infused via a peripheral vein/intraosseous needle. When choosing a vasoactive agent, consider the effect it will have on:

- Systemic vascular resistance
- Pulmonary vascular resistance
- Contractility
- Heart rate

While this is happening the need for respiratory support must be reassessed frequently; a semi-elective induction is likely to be much safer than an emergency induction.

In paediatrics the major consensus guidelines differ slightly. The goal is to provide a drug that will be an appropriate first line in both the 'warm' & 'cold' shock scenarios. While dobutamine may be given peripherally, it carries a risk of worsening hypotension in 'warm' shock. As clinical distinction of these two entities is very unreliable, & for simplicity, **dopamine** is recommended as the first line drug in all scenarios. New literature may recommend peripheral adrenaline or dopamine.

Dopamine at 5-15µg/kg/min is the first choice vasoactive drug to children presenting in septic shock (Grade E).

There are two exceptions that should be considered:

1. In individual cases with striking evidence of profound vasodilatation (flash capillary refill, low diastolic pressure with wide pulse pressure) **noradrenaline** may be the most appropriate choice.
2. Children with the most profound cardiovascular collapse secondary to sepsis (e.g. following resuscitation from cardiac arrest or with very poor or intermittent pulse volume) should be receive an **adrenaline** infusion.

Vasodilators or inodilators should not be used early in resuscitation from septic shock and should not be used in the absence of cardiac output monitoring (Grade E).

Fluid and Dopamine Refractory Shock

Further therapy should be guided to the clinical problem as per the flow chart.

Consideration should be given to whether increasing *blood pressure* or *cardiac output* are the clinical priorities. Ideally this requires continuous assessment of blood pressure, cardiac output and systemic vascular resistance.

This information is rarely available in the first hour of resuscitation & therefore proxy measures such as $SVCO_2$ (> or < 70%) may be used as an indication of the adequacy of cardiac output. In principle adrenaline is the key component of resuscitation for cold shock & noradrenaline for warm shock.

In adults evidence exists (Grade B) for adopting the following goals during the first 6 hours of resuscitation from sepsis-induced hypoperfusion:

- CVP (8-12 mmHg)
- MAP >65 mmHg
- Urine Output >0.5ml.Kg⁻¹
- **SVC or Mixed Venous Oxygen Sat $\geq 70\%$**

These may therefore be considered appropriate in older children. The principle of tailoring resuscitation to relevant physiological goals such as $SVCO_2$ is likely to be applicable to children of all ages.

Catecholamine-Resistant Shock: shock persists despite use of adrenaline or noradrenaline. In these situations, consideration should be given to use of an inodilator or vasopressin, depending on the circumstances.

Steroids

Research is in progress to determine how steroids may be used in the management of sepsis. Currently, hydrocortisone replacement is

recommended only for children with shock refractory to high dose inotropes. Children at risk of adrenal insufficiency include those with:

- **Chronic diseases requiring steroid medication**
- **Pituitary or adrenal disease**
- **Purpura fulminans**
- **Lack of the normal hyperglycaemic stress response.**

A suitable dose of hydrocortisone has also yet to be determined but current guidelines recommend a dose of 2-8 mg/kg/day titrated to the resolution of shock.

Vasodilators

In situations of low cardiac output and increased systemic vascular resistance, vasodilators may be of benefit.

Milrinone: A type III phosphodiesterase inhibitor which improves cardiac output and reduces SVR. However may cause hypotension requiring further fluid boluses and will also accumulate in renal failure.

Levosimendan: Increases calcium/actin/tropomyosin complex binding sensitivity (desensitisation occurs in sepsis). Not routinely used but may improve myocardial contractility in sepsis.

Vasopressors

May be useful in warm shock where SVR is low. First line agents are dopamine or noradrenaline.

Vasopressin: action is independent of catecholamine receptor stimulation and efficacy is not affected by receptor down-regulation. May be used in vasodilatory septic shock to increase SVR, improve blood pressure and urine output. However use may not always be associated with improvement in cardiac output.

There are also reports of the use of phenylephrine and inhibitors of nitric oxide but these are not routinely recommended.

Airway and Breathing

All children presenting in septic shock require high flow oxygen via a reservoir mask & prompt anaesthetic/ intensivist review (Grade E).

Any of the following indicate an impending need for assisted ventilation:

- Fluid refractory shock
- Hypoxia
- Severe respiratory distress
- Fluctuating/decreasing GCS

- Signs of raised intracranial pressure

Induction agents can worsen hypotension (direct myocardial depression and vasodilation). This may occur with propofol, thiopentone, benzodiazepines and inhalational agents. Anticipate this and reduce the risk of this occurring by:

- 1) **Aggressive volume replacement**
- 2) Pre-oxygenation
- 3) Intravenous atropine 10-20 µg/kg
- 4) Adrenaline bolus prepared and available (0.05-0.1 ml/kg 1 in 10,000)
- 5) Range of ETT sizes (a snug fit may be needed for adequate ventilation in the face of pulmonary oedema). *Consider a cuffed tube even in infants.*
- 6) Use of optimal drugs for induction (dictated by availability and your experience), good combinations include:

KETAMINE 1-2 mg/kg and suxamethonium (2mg/kg) or atracurium (0.5mg/kg)
or
FENTANYL 5-10µg/kg and suxamethonium or atracurium

Etomidate: has previously been considered useful as a 'cardiostable' induction agent. However its use may increase mortality in septic shock, possibly by impairment of endogenous corticosteroid synthesis and therefore should not be used in this setting.

NB: Children with a significant coagulopathy should be orally intubated.

All children in septic shock must be ventilated with PEEP (Grade D).

There is a significant risk of pulmonary oedema (cardiogenic & non-cardiogenic). In severe cases it may be impossible to achieve adequate recruitment & oxygenation in the absence of PEEP. Bag-valve ventilation is therefore NOT adequate.

Antibiotics

- Commence broad spectrum antibiotics e.g. 3rd generation cephalosporin until causative organism has been identified.
- Consider anaerobic cover
- Additional cover in children who are immunocompromised, have indwelling lines, have hospital acquired infections.

Other considerations

- **Electrolytes:** correct hypoglycaemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia.
- **Glucose control:** tight control of blood glucose with insulin infusion may reduce mortality in intensive care patients. This is currently being studied and is not yet part of established practice.

- **Raised intracranial pressure:** may occur due to intracranial infection or cerebral oedema secondary to capillary leak. If suspected, neuroprotective measures should be instituted.
- **Coagulopathy:** should be corrected with FFP, cryoprecipitate and platelets.

Key Textbooks:

Detailed knowledge of specific features of infection with any of the above pathogens in critically ill children should be part of any intensivist's core knowledge. This is outside the scope of this module. The most complete text is Feigin, Cherry, Demmler and Kalpan: 'Textbook of Pediatric Infectious Disease' 5th Edition 2004 (Copy available in the ICU consultants' office). It is recommended that each time you meet an infection for the first time you read the relevant section in this or similar text.

References:

Definitions

- Mitchell M. Levy, MD: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; **31**:1250 –1256

Pathophysiology

- Pathan N, Faust SN, Levin M: Pathophysiology of meningococcal meningitis and septicaemia. *Arch Dis Child*. 2003 Jul; **88(7)**: 601-7

Management

- Goldstein, B. et al: International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005, Jan; **6(1)**:2-8
- Brierley, J. et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009, Vol 37. No. 2
- Rooney, Z. & Nadel, S.: Optimizing intensive care management in paediatric sepsis. *Current Opinion in Infectious Diseases* 2009; **22**:264-271
- R. Phillip Dellinger et al: Surviving Sepsis Campaign: Guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;**32**:858-873
- Carcillo JA et al: Role of early fluid resuscitation in pediatric septic shock. *JAMA* 1991; **266 (9)**: 1242-5
- Carcillo and Fields: Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med* 2002; **30**: 1365-1378
- Emanuel Rivers et al: Early Goal-Directed Therapy In The Treatment Of Severe Sepsis and Septic Shock. *N Engl J Med* 2001; **345**:1368-77
- The Safe Study Investigators: A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. *N Engl J Med* 2004; **350**: 2247 -2256

- Morris C, McAllister C: Etomidate for emergency anaesthesia: Mad, bad and dangerous to know? *Anaesthesia* 2005; **60**: 737-740
- Annane D: ICU Physicians should abandon the use of etomidate! *Intensive Care Medicine* 2005; **31**: 325-326
- Annane D et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; **288**: 862-871
- Pizarro CF et al: Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med.* 2005; **33(4)**: 855-9
- Sarthi M et al: Adrenal status in children with septic shock using low-dose stimulation test. *Pediatr Crit Care Med.* 2007; **8(1)**: 23-8
- Sharhar T et al: Vasopressin a World of Complexity. *Paediatr Crit Care Med.* 2006 May; **7(3)**: 281-2

Information for Year 2 ITU Training (advanced):

Year 2 ITU curriculum

- More pathophysiological response to infection
- Relationship between perfusion failure, sepsis and endothelial activation to MODS. Occult infection.
- Myocardial dysfunction associated with severe sepsis & MODS
- Outcome prediction – multiple scoring systems
- Overview of research into modulating therapies: rBPI, APC, steroids, anti-endotoxin, anti TNF

•

ITU management of following clinical syndromes:

- Pneumococcal sepsis
- Kawasaki Disease
- Opportunistic infections: PCP, CMV, Candida, Aspergillosis & mucor
- Haemorrhagic sepsis: varicella,

Curriculum Notes for Year 2:

Potential Adjuvant Therapies for Sepsis:

CVVH / Plasmfiltration

CWH is effective in maintaining fluid, electrolyte & acid–base balance. Our preference is to consider using CVVH early after admission to help limit oedema & fluid overload by allowing space for the required blood products. There are no level 1 or 2 data demonstrating efficacy, but there are clear advantages in the ease of fluid, electrolyte & acid-base management. Controversy over high flow vs low flow CVVH.

There are unresolved issues about the most appropriate techniques. We have used the Melbourne trial protocol (36hrs slow continuous PF) in cases complicated by other conditions in which PF is likely to be beneficial e.g. acute SLE & sepsis. Care must be taken to ensure appropriate replacement of plasma proteins (see trial protocol).

Lung Injury

As part of MODS these cases are at risk of ARDS. The primary aim of ventilation is to oxygenate and control CO₂ levels.

HFOV should be considered if a high PEEP and FiO₂ >0.6 are required.

Intravenous Immunoglobulin

A meta-analysis of IVIG therapy in severe sepsis (very poor quality) has been published on the Cochrane database, suggests significant mortality benefit.

The study population is likely to have little relevance to our practice.

Pentoxifylline

A xanthine derivative & phosphodiesterase inhibitor shown to have many potential benefits in human & animal models of sepsis including:

- Suppression of inflammatory mediator synthesis eg. TNF- α , IL-1, IL-10
- Inhibition of neutrophil function
- Prevention of endothelial cell dysfunction

Two small Polish RCTs conducted by the same principal investigator suggest that pentoxifylline (5 mg/kg/hr for 6 hrs on 3 & 6 successive days respectively) may improve survival without significant adverse effects, in preterm neonates (<36/40) with late-onset sepsis (\geq 72 hrs of life).

Larger studies are in progress but currently we reserve pentoxifylline for very occasional cases of sepsis-induced MODS in which the cause has been removed (e.g. post NEC resection) but the infant remains 'stuck' in MODS. We don't!!

Recombinant Activated Protein C

This endogenous protein has anti-inflammatory, anti-coagulant & pro-fibrinolytic properties.

It has been shown to reduce mortality (6% ARR) from sepsis-induced organ failure in adults (*PROWESS* Trial) but with a significant increase in major bleeding complications (3.5% treatment group vs 2% placebo group), with a similar incidence of bleeding complications in the paediatric '*EVAO*' trial.

The single-arm, '*ENHANCE*' trial in paediatric patients with severe sepsis was conducted to collect further data relating to disease state & safety prior to the design of a placebo-controlled RCT. Compared with adults, blood as opposed to lung was the commonest focus, with a higher percentage of gram negative infections, serious bleeding events & intracranial haemorrhage.

The '*RESOLVE*' trial was a blinded, RCT undertaken to further evaluate safety & efficacy of this preparation in children with severe sepsis. Due to the relatively low mortality rate in children with sepsis, a novel composite primary endpoint comprising the resolution of sepsis-induced organ failure over 14 days, was used. **This trial was stopped for futility after an interim analysis showed that it was highly unlikely that there would be an improvement with treatment over placebo in this primary endpoint.**

ECMO

Occasionally a child will demonstrate such severe cardiovascular depression that escalating doses of inotropes are ineffective in maintaining adequate systemic perfusion. At this stage & *prior to complete cardiovascular collapse*

the case should be discussed with the ECMO team. Survival is at least 50% in appropriately selected cases.

Rarely ECMO may be considered for unresolved sepsis-associated acute lung injury.

Investigations include ECHO, cranial USS (where appropriate) & EEG.

If myocarditis is considered as the cause of refractory shock, early referral to an ECMO centre should be considered.

Genomic Polymorphisms and Sepsis

It is well established that susceptibility and immune response to sepsis varies widely between individuals. Recent advances in molecular genetics have enabled investigators to identify a number of genetic polymorphisms in genes relevant to the host immune response to sepsis, including those encoding components of innate immunity and pro- and anti-inflammatory cytokines. In the future it is hoped that it may be possible to utilise this information to tailor therapy to individuals based on their genetic profile & predict more accurately individual outcomes.

References:

Pathophysiology

- Bone RC. Immunologic Dissonance: A Continuing Evolution in Our Understanding of the Systemic Inflammatory Response Syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MODS) 15th October 1996 125 volume 8, Pgs 680-687
<http://www.annals.org/cgi/content/full/125/8/680>
- Bone RC: Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med* 1996; **24(7)**: 1125-1128
- Seely and Christou: Multiple organ dysfunction syndrome: Exploring the paradigm of complex nonlinear systems. *Crit Care Med* 2000; **28**: 2193-2200
- Mervyn Singer, Vincenzo De Santis, Domenico Vitale, William Jeffcoate: Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. *Lancet* 2004; **364**: 545-48
- Fidler KJ et al: Increased incidence and severity of the systemic inflammatory response syndrome in patients deficient in mannose-binding lectin. *Intensive care Med.* 2004 Jul; **30(7)**: 1263-5
- Dahmer MK et al: Genetic polymorphisms in sepsis. *Pediatr Crit Care Med.* 2005 May; **6(3 Suppl)**: S61-73
- Lin MT, Albertson TE: Genomic Polymorphisms in sepsis. *Crit Care Med* 2004 Feb; **32(2)**: 569-79

Management

- Haque K, Mohan P: Pentoxifylline for neonatal sepsis. *Cochrane Database Syst Rev.* 2003; **4**: CD004205

- Bernard GR et al: Efficacy and Safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344**: 699-709
- Goldstein B et al: ENHANCE: Results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. *Pediatr Crit Care Med* 2006; **7(3)**: 200-211
- (See also editorial section same edition pp 277-278 for commentary)
- Nadel et al RESOLVE, Lancet 2007

Outcome

- MJ Peters, RI Ross-Russell: Early severe neutropenia and thrombocytopenia identifies the highest risk cases of severe meningococcal disease. *Pediatr Crit Care Med* 2001; **2**: 225-231
- R Booy, et al: Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child*. 2001 Nov; 85(5):386-90 correspondence:
<http://adc.bmjournals.com/cgi/content/full/85/5/386>