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CLINICAL REVIEW

Sepsis in children

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This clinical review has been developed for *The BMJ* in collaboration with BMJ Best Practice, based on a regularly updated web/mobile topic that supports evidence-based decision making at the point of care. To view the complete and current version, please refer to the Sepsis in children (http://bestpractice.bmj.com/best-practice/monograph/1201.html) topic on the BMJ Best Practice website.

Sepsis is a clinical syndrome resulting from a dysregulated systemic inflammatory response to infection.[1] It is characterised by a generalised pro-inflammatory cascade, which may lead to widespread tissue injury.[2] It encompasses a clinical spectrum of severity, including severe sepsis, septic shock, and multi-organ failure.[3] Sepsis is a leading cause of morbidity and mortality in children worldwide.[4]

International consensus guidelines define sepsis as the presence of systemic inflammatory response syndrome plus suspected or proven infection.[3] A more pragmatic definition of sepsis has been proposed—that sepsis is a systemic response to infection with the presence of some degree of organ dysfunction.[5] This definition is not currently widely accepted, but new criteria are under discussion and due to be published later in the year.

What is the epidemiology?

Global data on sepsis in children are incomplete, but it is estimated that infection accounts for most deaths (almost 60%) in children aged under 5 years.[4] The World Health Organization has stated that the four big causes of death in children worldwide are infectious diseases: pneumonia (1.9 million deaths/year), diarrhoea (1.6 million deaths/year), malaria (1.1 million deaths/year), and measles (550 000 deaths/year).[6]

The largest epidemiological reports of the incidence of severe sepsis in children come from US cohort studies. Two of these studies describe the annual incidence of severe sepsis in children (defined as under 20 years old) in acute medical admissions to hospitals in seven US states.[7 8] These studies show a rising annual incidence of severe sepsis over this time period (0.56 to 0.89 cases/1000 children, across all age groups).[8] The incidence of severe sepsis in these cohorts was significantly higher in younger age groups (incidence in the neonatal age group and infants aged <1 year was 9.7 and 2.25 cases per 1000 children, compared with 0.23 to 0.52 in children aged 1 to 19 years). Severe sepsis was also more common in children with comorbidities. Despite the rising incidence of severe sepsis, the case fatality rate has fallen from 10.3% to 8.9%.[8]

Recently published studies describe the prevalence of severe sepsis among patients in paediatric intensive care units: the prevalence of severe sepsis in US paediatric intensive care units has been reported as 7.7% of admissions in one large, multicentre, cohort study using data from 42 units. This is consistent with other epidemiological data from the US, and confirms a rising prevalence of severe sepsis with a falling risk of mortality.[9]

A large international prevalence study (Sepsis PRevalence, OUtcomes, and Therapies (SPROUT)) of severe sepsis in paediatric intensive care units around the world has recently been published. The study found that the global prevalence of severe sepsis in paediatric intensive care units was 8.2% (95% confidence interval 7.6% to 8.9%).[10]

What causes sepsis?

Sepsis is the systemic response to infection. The primary aetiology can therefore be attributed to both the infecting pathogen and the host response. While any infection may precipitate sepsis, the most common pathogens are bacteria, viruses, and fungi. The type of pathogen varies according to host factors, including age, comorbidity, and geographic location. Typical or important pathogens by patient group are listed in box 1.[7 11-14]

The normal host response to infection is an inflammatory process aimed at localising and controlling the infection. The inflammatory response is triggered when innate immune cells (such as macrophages) recognise the invading pathogen. For example, lipopolysaccharides of Gram negative bacteria are recognised by receptors on innate immune cells. Following binding to these sites, the immune cells are activated to secrete pro-inflammatory cytokines, which are responsible for recruiting polymorphonuclear cells to the site of infection. These polymorphonuclear cells release pro-inflammatory cytokines leading to vasodilation and vascular permeability (capillary leak). In the normal host response, this pro-inflammatory response is regulated and localised by a simultaneous anti-inflammatory response. Sepsis occurs when this normal, pro-inflammatory host response exceeds its usual homeostatic

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The bottom line

- The initial clinical presentation of sepsis in children may be non-specific (especially in younger age groups)
- Given the time critical nature of severe sepsis and septic shock, when sepsis is suspected on clinical grounds it is usually best to start investigations and treatment for sepsis, including fluid resuscitation, and to continue with these until sepsis has been excluded
- Progression to organ failure and shock is often rapid, so early recognition and treatment is crucial
- Apart from antibiotics, there are currently no specific treatments of proved value
- Other treatment after antibiotics is supportive and should be delivered according to internationally recognised, consensus based guidelines

Box 1: Typical or important pathogens in sepsis

Early onset neonatal sepsis

Defined as neonatal sepsis occurring in the first 72 hours of life[15]

- Group B streptococci, and Gram negative bacilli (especially *Escherichia coli*) are by far the most common causative pathogens in early onset neonatal sepsis[16]
- *Staphylococcus aureus* and coagulase negative staphylococci, *Haemophilus influenzae*, and enterococci make up most of the rest of the bacterial causes of early onset neonatal sepsis
- Infection caused by *Listeria monocytogenes* is rare but has a disproportionate proclivity for pregnant women and their fetuses.[17] The organism may be responsible for early or late onset neonatal sepsis

Late onset neonatal sepsis

Defined as neonatal sepsis occurring after the first 72 hours to one month of life[18]

- Coagulase negative staphylococci are now the most common cause of late onset neonatal sepsis owing to the high incidence in vascular catheter associated infection in neonatal inpatients
- May also be caused by the same organisms responsible for early onset neonatal sepsis

Infants and young children

- *Streptococcus pneumoniae* remains a major cause of invasive bacterial infection in childhood
- *Neisseria meningitidis* occurs in a bimodal age distribution, affecting young children and adolescents. It is less common since uptake of vaccination
- Both *Staphylococcus aureus* and group A *Streptococci* may cause severe sepsis in previously well children
- *Haemophilus influenzae* type b is an important cause of sepsis worldwide, but it is rare in the developed world because of vaccination
- *Bordetella pertussis*, although rare, may cause a severe illness in young infants before primary vaccination
- Data on specific infecting organisms in resource poor settings are less robust, but diarrhoea and pneumonia are the most common infections (and causes of death)[4]

Infants and children in hospital

- Cause of hospital acquired infection depends on local bacterial epidemiology
- Coagulase negative *Staphylococci* are usually associated with vascular catheter infection
- Meticillin resistant *Staphylococcus aureus* (MRSA) is less common in the UK compared with the US
- Gram negative organisms such as *Pseudomonas aeruginosa*, *Klebsiella* species, *E coli*, and *Acinetobacter* species.

Asplenic or functional asplenia

- Salmonella sepsis, including salmonella osteomyelitis in sickle cell disease
- Other encapsulated organisms (for example, *Streptococcus pneumoniae*, *Haemophilus influenzae*)

Mosquito-borne disease

- Malaria (*Plasmodium falciparum*), dengue virus, and *Burkholderia pseudomallei* (meliodosis) are important causes of severe sepsis in endemic areas

Other organisms

- Fungal (for example, *Candida* species, *Aspergillus* species) and viral (for example, influenza, respiratory syncytial virus, human metapneumovirus, varicella, and herpes simplex virus) pathogens account for as many as 5.3% and 2.9% of severe sepsis in children, respectively[8]

constraints and becomes a generalised process, resulting in inflammation remote from the infection source.

While this model of sepsis is intuitive, the results of emerging research suggest that it may be an oversimplification and that the pathophysiology includes processes such as endothelium dysfunction, cell death, bioenergetic derangement, and immunoparalysis.

Data suggest significant heterogeneity in patients' host responses. This heterogeneity applies to the balance of pro- and anti-inflammatory processes, and the nature of humoral and cellular changes.[19]

Can sepsis be prevented?

Primary prevention

The principal method of primary prevention is immunisation. For many community acquired paediatric infections, immunisation has been highly successful and cost effective. Immunisation has resulted in the global eradication of smallpox and a significant reduction in the prevalence of many infectious diseases (such as poliomyelitis, rubella, tetanus, diphtheria, and measles). Advances in biotechnology have led to new and improved vaccines, including vaccines for *Haemophilus influenzae* type b, *Neisseria meningitides* (type C), and *Streptococcus pneumoniae*.[20]

A new group B meningococcal vaccine has been licensed in Europe. In 2015, the meningococcal B vaccine will be

introduced to the routine childhood vaccination programme in the UK.[21]

Immunisation programmes are key public health initiatives in all global regions, but global inequality exists in terms of access to existing vaccine products. The World Health Organization's Global Vaccine Action Plan is a framework to reduce deaths from infection through improving access to vaccines across the world.[22]

Primary prevention is also relevant within the realm of healthcare associated infections. Since these infections are related to specific interventions (such as insertion of a vascular catheter), there are opportunities to reduce the risk of infection through improvements in clinical practice (such as improved handwashing practices, protective isolation, and universal precautions). An example of a successful initiative in this area is the reduction of venous catheter bloodstream infections in adult and paediatric intensive care units through bundled clinical and non-clinical interventions.[23]

Screening

Screening for sepsis in the asymptomatic population is not useful. However, screening for maternal colonisation with group B streptococci in pregnancy has been shown in some settings to reduce the burden of group B streptococci disease in newborns.

Screening for group B streptococci is controversial and is not practiced in all parts of the developed world. For example, there is no screening programme in the UK as there is a concern that current screening tests do not adequately identify carriers of group B streptococci whose babies will go on to have invasive group B streptococci disease.

US guidelines for the prevention of early onset neonatal sepsis due to group B streptococci were introduced in 2002, recommending the universal screening of all pregnant women between 35 and 37 weeks' gestation. The aim of the screening was to identify women at risk of transmitting group B streptococci to the newborn; these women were to receive intrapartum antibiotics.[24] Dramatic reduction in early onset neonatal sepsis due to group B streptococci was achieved after the introduction of this programme.[25] The guidelines and the effects of the screening programme are regularly reviewed and updated. The latest version of the guideline continues to recommend universal screening between 35 and 37 weeks' gestation.[26]

Secondary prevention

Long term antimicrobial prophylaxis with antibiotics, antivirals, or antifungals is recommended in immunocompromised patients with premorbid conditions (such as leukaemia). Children with cystic fibrosis and other respiratory diseases may be given antimicrobial prophylaxis (such as co-trimoxazole). There is currently insufficient evidence to support the use of prophylactic antibiotics for the prevention of infections in children with indwelling central venous catheters.[27]

How is sepsis diagnosed?

Sepsis should be considered as a time critical emergency, as the disease may progress rapidly to organ failure, shock, and death. Prompt and early recognition of the condition is therefore imperative. Timely antibiotics and other supportive therapies have been shown to improve outcome, and early aggressive treatment should be initiated once sepsis is suspected. In general, sepsis should be suspected in any acute illness or in the neonatal population (including preterm infants) if there is any change from the patient's normal pattern of observations.

While laboratory tests (such as blood cultures and biomarkers) are helpful in securing or supporting the diagnosis, the diagnosis has to be made initially using clinical judgment. Clinical suspicion is not always consistent with standardised criteria. Diagnostic criteria from international consensus guidelines are primarily considered to be research criteria designed to facilitate meaningful research (box 2). Clinical suspicion of sepsis, however, is usually a clinical judgment (for example, a specific clinical pattern recognition or particular clinical syndrome). Research criteria and clinical judgment do not always agree: up to a third of patients with clinical sepsis do not fulfil research diagnostic criteria.[28]

Therefore, given the time-critical nature of severe sepsis and septic shock, when sepsis is suspected on clinical grounds, it is usually best to initiate sepsis investigations and treatment and to continue until sepsis has been excluded.

Clinical features of sepsis

The typical presentation varies according to the age of the child. Whereas older children may present with a focus of infection, infants and neonates usually present with non-specific symptoms and signs. In older infants and children, sepsis typically presents with features of systemic inflammatory response syndrome (defined in box 2), the most common feature of which is fever.[3]

Clinical diagnosis of sepsis must occur earlier in the care pathway than formal classification allows, and, in practice, the clinician should consider sepsis or septic shock if a child has a suspected or proven infection and has at least two of the following:

- Core temperature <36°C or >38.5°C (<97°F or >101°F)
- Inappropriate tachycardia (according to local criteria or advanced paediatric life support guidance)
- Altered mental state (such as sleepiness, irritability, lethargy, floppiness)
- Reduced peripheral perfusion or prolonged capillary refill.

If in doubt, an experienced paediatrician should be consulted.[30]

Fever is defined as elevated body temperature above the normal daily variation (that is, above 37.5°C (99.5°F)).[31] For the diagnosis of sepsis, consensus criteria state that the core temperature must exceed 38.5°C (101°F); however, a lower threshold is required in neutropenic patients, in whom sepsis should be considered if the core temperature is >38°C (>100°F).

In young infants and term and preterm neonates, the symptoms and signs of sepsis are often vague and non-specific. Sepsis in this age group often manifests initially as a change in the normal trends of observations for that child. For example, a preterm infant in a neonatal intensive care unit may demonstrate new onset bradycardic episodes, apnoeas, or feed intolerance as the first signs of sepsis. A useful rule of thumb is to consider sepsis with a low diagnostic threshold if an infant or neonate has developed a new sign or symptom, or the observations have started to veer from the normal pre-existing trends. In older children, it is also worth keeping a low threshold for diagnosis of sepsis if an acute illness has not been fully explained.

In all age groups, if sepsis has progressed, the patient may develop severe sepsis or septic shock. Septic shock may manifest in two main clinical pictures: cold shock and warm shock (box 3).

In both shock states, the patient will show clinical signs of shock outside the cardiovascular system, the most important of which

Box 2: Definitions for sepsis in children* (from the International Consensus Conference on Pediatric Sepsis[3])

Infection

Suspected or proved infection with any pathogen

Systemic inflammatory response syndrome

Generalised inflammatory response, defined by the presence of ≥2 of the following criteria (abnormal temperature or white cell count must be one of the criteria):

- Abnormal core temperature (<36°C or >38.5°C)
- Abnormal heart rate (>2 standard deviations above normal for age, or <10th centile for age if child is aged <1 year)
- Raised respiratory rate (>2 standard deviations above normal for age, or mechanical ventilation for acute lung disease)
- Abnormal white cell count in circulating blood (above or below normal range for age, or >10% immature white cells)

Sepsis

Systemic inflammatory response syndrome in the presence of infection

Severe sepsis

Sepsis in the presence of cardiovascular dysfunction, acute respiratory distress syndrome, or dysfunction of ≥2 organ systems

Septic shock

Sepsis with cardiovascular dysfunction persisting after at least 40 mL/kg of fluid resuscitation in one hour

Refractory septic shock

Fluid refractory septic shock—Shock persisting after ≥60 mL/kg of fluid resuscitation

Catecholamine resistant septic shock—Shock persists despite treatment with catecholamines (that is, dopamine or adrenaline (epinephrine) infusion, or both, or noradrenaline (norepinephrine) infusion)

Classification of neonatal sepsis

Neonatal sepsis is defined as the clinical syndrome of sepsis or isolation of a pathogen in the bloodstream, or both, in an infant in the first 28 days of life.[29] Symptoms and clinical signs are often less apparent or more subtle than in older children. Sepsis in newborns is usually classified in terms of timing of onset in relation to birth:

Early onset neonatal sepsis—Sepsis occurring in the first 72 hours of life[15]

Late onset neonatal sepsis—Sepsis occurring after the first 72 hours of life[18]

Classification by age group

For the purposes of consistent classification, the following age groups are used for referencing normal ranges of physiological variables and laboratory values[3]:

Newborn—0 days to 1 week

Neonate—0 days to 1 month

Infant—1 month to <2 years

Toddler and preschool—≥2 years to <6 years

School-age child—≥6 years to <13 years

Adolescent and young adult—≥13 years to <18 years.

Note that preterm infants are not classified in this age scheme.

*The following standardised definitions were initially developed by the International Consensus Conference on Pediatric Sepsis to standardise entry criteria for large multicentre clinical trials. Clinical diagnosis of sepsis must occur earlier in the care pathway than classification allows

Box 3: Cold and warm septic shock

Cold shock

- A more common presentation of sepsis in infants and young children[32]
- Clinical appearance is characterised by constricted peripheral systemic vasculature, resulting in cold peripheries and prolonged capillary refill time
- Blood pressure is usually preserved (or may even be high) unless the patient is moribund, but the patient is usually tachycardic
- Underlying problem is a low cardiac output, secondary to impaired myocardial contractility, resulting in low cardiac output and peripheral vasoconstriction

Warm shock

- Clinical appearance is characterised by vasoplegia, in which the systemic vascular resistance is low, so the capillary refill time is brisk ("flash" capillary refill) and pulses are usually felt to be full or bounding
- Pulse pressure is high (usually due to a low diastolic blood pressure) and the patient is usually tachycardic
- Often a high cardiac output state, but the patient will be in shock in part due to enlargement of the circulation (through dilation of the systemic vasculature) beyond the scope of the cardiac output
- A more common presentation in older children (and adults) and may be more common in hospital acquired sepsis[32]

is impaired neurological function. This may manifest as irritability in infants and neonates, apnoeas in neonates and preterm infants, and drowsiness, obtundation, or delirium in older children.

Children often maintain normal blood pressure even in late stages of shock; hypotension is therefore often a terminal sign in septic shock.

Purpura fulminans is a widespread non-blanching purpuric rash classically seen in meningococcaemia but may also be associated with severe sepsis from *Pneumococcus*.

Decreased urine output is common in acutely ill children and often reflects a degree of dehydration (due to decreased intake, excessive fluid losses, or both). This is not a specific finding in sepsis, but is commonly present, especially if there has been a prodromal viral illness before the onset of sepsis.

The UK based National Institute of Health and Care Excellence (NICE) has developed a traffic light system based on clinical signs, which helps physicians assess the probability of serious illness in young children presenting with fever (www.nice.org.uk/guidance/cg160/resources/cg160-feverish-illness-in-children-support-for-education-and-learning-educational-resource-traffic-light-table2).

Investigations

No single laboratory test will confirm or refute the diagnosis of sepsis, but many can provide supporting or additional useful information. Box 4 lists the investigations to consider.

Other clinical symptoms and signs will direct the clinician to specific microbiological samples. For example, bronchoalveolar lavage sample for microscopy and culture may be considered in a child in an intensive care unit with a suspected ventilator-associated pneumonia; blood for meningococcal PCR analysis may be considered to help confirm the diagnosis in equivocal clinical cases of meningococcal sepsis; serum serology or PCR for respiratory or opportunistic viruses (such as adenovirus, cytomegalovirus, herpes simplex virus) may be considered in immunocompromised children with sepsis (such as a neutropenic child receiving chemotherapy for leukaemia). However, clinicians should consult local protocols regarding sample collection and testing. Consider ordering herpes simplex virus PCR (blood and cerebrospinal fluid) if neonatal herpes simplex infection is a possibility.

Despite adequate microbiological sampling, in many children with sepsis the pathogen will not be identified. This is known as culture-negative sepsis.[37]

There is growing interest in the use of biomarkers for the diagnosis and monitoring of sepsis and septic shock. A key issue (particularly in intensive care units) is the problem of distinguishing sepsis from systemic inflammatory response syndrome without infection, where clinical signs may not be helpful. The two biomarkers most frequently used for this purpose are C reactive protein and serum procalcitonin. Serum procalcitonin shows the most potential in this area, showing greater accuracy for diagnosis of sepsis in one study compared with C reactive protein in neonates and older children.[38] However, it is not as readily available as C reactive protein, and, for this reason, C reactive protein is more commonly used. Current practice varies from institution to institution regarding the use of serum procalcitonin or C reactive protein, and clinicians should continue to use clinical judgment when diagnosing sepsis. Serum procalcitonin is not currently considered to be the standard of care in the UK or Europe. A study of multiple candidate biomarkers in paediatric patients with septic shock used classification and regression tree analysis to identify a series of 12 biomarkers in order to risk stratify patients for the purposes of clinical decision making and stratification in clinical trials in the future.[39]

Box 5 shows the differential diagnosis of severe sepsis.

How is sepsis managed?

Management of sepsis in children first requires prompt recognition. Attention needs to be paid to education and training of healthcare staff in the recognition of warning or adverse signs of sepsis in children and neonates to enable appropriate triage and rapid treatment. Child death reviews suggest failure to recognise severe sepsis and septic shock with delayed or inappropriate treatment at first contact with healthcare services.[40 41] A standard ABC (airway, breathing, circulation) approach with particular emphasis on early administration of antibiotics and fluid resuscitation is key in the management of children with sepsis and septic shock.

Treatment according to American College of Critical Care Medicine guidelines and bundles

A care bundle is a set of protocols distilled from evidence based practice guidelines. The aim of using a care bundle is to achieve reliability in delivering all key elements of care in a healthcare system. Compliance with guidelines or care bundles is associated with improved outcomes.[42]

The American College of Critical Care Medicine (ACCM) published clinical practice parameters for haemodynamic support of paediatric and neonatal shock in 2002 and updated these in 2007 in the ACCM guidelines for the haemodynamic support of paediatric and neonatal septic shock (ACCM-PALS).[43] These guidelines were drawn up by expert consensus based on extensive reviews of available literature. Several units have reported improved survival in severe sepsis associated with greater compliance with ACCM-PALS guidelines.

One study in the tertiary accident and emergency department at Boston Children's Hospital looked at delivery of the five elements of care within an hour and hospital length of stay (early recognition of severe sepsis, vascular access, antibiotic administration, administering intravenous fluids, and vasopressors for fluid refractory shock). Those who received the care bundle recommended by the ACCM guidelines had a significantly shorter intensive care length of stay (mean 5.5 *v* 6.8 days) and hospital length of stay (mean 6.8 *v* 10.9 days).[44]

Adherence to all five elements of care in this study was low at 19%. In a UK pre-intensive care unit audit, adherence to the ACCM-PALS guideline was only 38%.[45] Reasons for poor compliance are multifactorial.[46] The same team at Boston Children's Hospital subsequently reported improvement in compliance with their five component bundle from 19% to 100% using process focused quality improvement methodology. They observed a reduction in mortality from 4.8% to 1.7%.[47]

The management of children with severe sepsis and septic shock is complex and time critical. Care bundles may aid by simplifying and streamlining the process required for the delivery of therapies to the child with severe sepsis in a timely fashion.

The Surviving Sepsis Campaign (SSC) (www.survivingsepsis.org/Pages/default.aspx) suggests making systems change within institutions through incremental steps based on the LEADER approach developed in conjunction with the Institute for Healthcare Improvement:

- Learn about sepsis and quality improvement
- Establish baseline process and outcome measures to demonstrate need for improvement
- Ask for buy-in from institutional leadership and stakeholders
- Develop institution-specific sepsis care bundle protocols

Box 4: Diagnostic tests for sepsis

First tests to order

Full blood count with differential—Abnormal white blood cell count for age (high or low) is one of the diagnostic criteria for systemic inflammatory response syndrome. A low or normal cell count is a feature of the initial phase of illness in severe sepsis and should raise the suspicion of the diagnosis if there are clinical signs that suggest sepsis. Thrombocytopenia (platelet count <80 000/μL or a decrease by 50% from the highest value in the past three days) in the context of sepsis is indicative of disseminated intravascular coagulation if associated with coagulopathy.

Serum glucose—Moderate hypoglycaemia is a blood glucose level of 2.0-3.0 mmol/L and severe hypoglycaemia is a blood glucose level <2.0 mmol/L.[33] Hyperglycaemia is common as part of the stress response to sepsis. It can also occur as a side effect of corticosteroid treatment. Hypoglycaemia may also occur as a result of depleted glycogen stores.

Blood culture—Many infants and young children with sepsis have a primary bacteraemia, so blood culture is often important. This should be undertaken as soon as possible after the clinical diagnosis of sepsis, and ideally before antibiotics are administered, but empirical antibiotic treatment should not be withheld while awaiting results if sepsis is suspected.

The sensitivity of blood culture is proportional to the volume of blood taken. When using a neonatal aerobic culture bottle in neonates, a minimum of 1 mL of blood from venepuncture or freshly inserted vascular catheter (arterial or venous) is likely to be adequate to diagnose bacteraemia.[34] When standard aerobic culture bottles are used, a minimum of 4 mL of blood is required for a valid negative culture at 48 hours. Depending on the institutional preference, multiple cultures may be preferred, but it is important to avoid delay in administering antibiotics. Two sets of cultures are sometimes recommended to encourage clinicians to take the culture from an indwelling line (for example, central line) and a peripheral site.

Blood culture results should be reviewed every 12 to 24 hours; most positive results will be detectable within 48 hours, and many will be positive within 24 hours.[35]

Urine analysis and urine culture—Urine analysis (urine sample for nitrites, microscopy, Gram stain, and culture) should be considered in all neonates with sepsis (although in the first week of life, a positive result in urine culture may simply reflect a severe bacteraemia). It should be considered in older children with symptoms suggestive of a urinary tract infection. Urine analysis may not be possible until after fluid resuscitation.

Blood gases—Although children rarely have arterial blood gases taken in the emergency department, it is often possible to obtain clinically useful information from capillary or venous blood gases.

- A large base deficit is a key marker of severe sepsis and may be the first marker to give a clue to the severity of illness
- Hypercarbia or hypoxaemia is supportive of a diagnosis of respiratory dysfunction.[3]
  Hypoxaemia—P/F ratio (arterial oxygen pressure/fractional inspired oxygen) <300 (in absence of cyanotic heart disease or pre-existing pulmonary disease)

  Hypercarbia—Arterial carbon dioxide pressure >65 mm Hg, or 20 mm Hg above baseline level
- A high fractional inspired oxygen requirement is indicative of sepsis related respiratory failure[3]
- Pulse oximetry should be ordered as a high requirement for fractional inspired oxygen is indicative of sepsis-related respiratory failure.

Serum lactate—Increased serum lactate level is indicative of inadequate oxygen delivery which, in the context of sepsis, is suggestive of septic shock.[3] Lactate is most reliably assessed using an arterial sample; venous and capillary lactate should be interpreted with caution.

Serum electrolytes—Serum electrolytes are often deranged in sepsis. They should be measured at baseline and regularly until patients improve.

Serum creatinine—Increased serum creatinine (that is, serum creatinine >2 times upper limit of normal or increase in serum creatinine >2 times baseline level) is indicative of sepsis related renal failure.[3]

Liver function tests—Increased bilirubin levels (outside the neonatal age range) or increased alanine aminotransferase is suggestive of sepsis related liver dysfunction.[3]

Coagulation studies—In the context of sepsis and thrombocytopenia, abnormal results (international normalised ratio >2; prolonged activated partial thromboplastin time, decreased fibrinogen level, increased D dimer levels) are indicative of disseminated intravascular dissemination.[3 36]

C reactive protein—May be useful for the diagnosis and monitoring of sepsis and septic shock. It is not as specific as serum procalcitonin, but more commonly available. Current practice varies regarding the use of C reactive protein, and clinicians should continue to use clinical judgment when diagnosing sepsis.

Chest radiography—Infants and small children with respiratory distress in the context of suspected sepsis should undergo chest radiography to assess for pneumonic changes (such as lobar consolidation in bronchopneumonia).

Tests to consider

Lumbar puncture—If meningitis with no sepsis is suspected and there is no purpuric or petechial rash, clinicians should consider a lumbar puncture (for cerebrospinal fluid protein and glucose concentrations, microscopy with Gram stain, and bacterial culture) to exclude meningitis when the child is stable and can safely undergo the procedure.[34] Lumbar puncture is usually contraindicated in children with severe sepsis until the patient is stabilised, as performing a lumbar puncture in severe sepsis may lead to collapse. A positive culture result for cerebrospinal fluid may confirm bacterial meningitis and provide information on the type of pathogen, including sensitivities to antibiotics; protein levels may be increased; glucose levels may be low

Meningococcal polymerase chain reaction (PCR) analysis—This may help confirm the diagnosis in equivocal or suspected clinical cases of meningococcal sepsis, but it is not widely available

Bronchoalveolar lavage culture—Bronchoalveolar lavage sample for microscopy and culture may be considered for a child in an intensive care unit with a suspected ventilator associated pneumonia.

Herpes simplex virus PCR (blood and cerebrospinal fluid)—Neonatal herpes simplex infection (either in the central nervous system or disseminated) is rare, but an important consideration in children with severe sepsis. Consider ordering if neonatal herpes simplex infection is a possibility.

Emerging tests

Serum procalcitonin—This biomarker may be useful for the diagnosis and monitoring of sepsis and septic shock, but the test is not commonly available. It not currently considered to be the standard of care in the UK or Europe.

Emerging biomarkers—Other biomarkers (such as CD64, interleukin 18, mass spectrometry, specific mRNA expression) are considered emerging and are not widely used or validated yet.

- Educate stakeholders
- Remediate errors and anticipate obstacles along the way.

The SSC bundles are available online. (www.survivingsepsis.org/Bundles/Pages/default.aspx).

Paediatric Sepsis Six initiative

The Paediatric Sepsis Six initiative is an example of a care bundle designed to facilitate prompt recognition of severe sepsis, and delivery of an initial six elements of care in a time-critical manner. Developed by the UK Sepsis Trust Paediatric Group, the Paediatric Sepsis Six is modelled on the adult Sepsis Six programme. The adult programme has been shown to improve adherence to resuscitation bundles and early goal directed therapy guidelines, and is associated with reduced mortality.[30]

The Paediatric Sepsis Six does not replace existing ACCM-PALS guidance; it is an operational solution to improve adherence to the guideline. It is designed to empower medical and nursing staff to recognise sepsis early and initiate treatment rapidly. The aim, through education, is to engender a culture

Box 5: Differential diagnosis of severe sepsis

Congenital heart disease

Duct dependent congenital heart disease may mimic early or late onset neonatal sepsis. Differentiating signs include signs of congestive cardiac failure (in left sided obstructive lesions, such as coarctation or aortic stenosis) or profound, refractory cyanosis (in cyanotic lesions such as transposition of the great arteries, or pulmonary atresia)

Differentiating tests: chest radiography may reveal evidence of pulmonary oedema and cardiomegaly in obstructive cardiac lesions; echocardiography will reveal detailed cardiac anatomy

Systemic inflammatory response syndrome (SIRS) without infection

SIRS and organ dysfunction can result from multiple other stimuli, including cardiopulmonary bypass, trauma, pancreatitis, and burns. It is difficult to differentiate SIRS from sepsis, but non-infectious SIRS will usually have a history of some other insult

Haemophagocytic lymphohistiocytosis

May be primary (often associated with an inherited immunodeficiency) or secondary (for example, triggered by a viral illness); the clinical features often mimic severe sepsis, with fever, shock, and multiorgan failure in severe cases. Diagnostic criteria include hepatomegaly, which may be a differentiating sign

Neuroleptic malignant syndrome

Characterised by hyperthermia, generalised rigidity (which may be a differentiating sign), and autonomic dysregulation (for example, sweating and labile blood pressure). Onset of the syndrome occurs as an idiosyncratic complication to use of antipsychotic drugs

Malignant hyperthermia

Characterised by extreme hyperthermia, tachycardia, rigidity, and rhabdomyolysis after exposure to a stimulating agent (usually anaesthetic agents)

where sepsis is an emergency requiring urgent intervention. Included in the toolkit is an integrated monitoring system for recording adherence.

The clinician should consider sepsis or septic shock if a child has a suspected or proven infection and has at least two of the following:

- Core temperature <36°C or >38.5°C (<97°F or >101°F)
- Inappropriate tachycardia (according to local criteria or advanced paediatric life support guidance)
- Altered mental state (sleepiness, irritability, lethargy, floppiness, decreased conscious level)
- Reduced peripheral perfusion or prolonged capillary refill.

If in doubt, a clinician experienced in the recognition of sepsis in children should be consulted. The following interventions should be initiated within 1 hour of presentation:

- Supplemental oxygen should be given
- Intravenous or intraosseous access should be obtained and blood tests ordered including blood cultures, blood glucose (low blood glucose should be treated), and arterial, capillary, or venous blood gases. Full blood count, serum lactate, and C reactive protein should also be ordered for baseline assessment
- Intravenous or intraosseous antibiotics should be given with broad spectrum cover as per local policies
- Fluid resuscitation should be considered. The aim is to restore normal circulating volume and physiological parameters. Isotonic fluid (20 mL/kg) should be titrated over 5 minutes and repeated as necessary. Caution should be taken to avoid fluid overload by examining for crepitations (rales) and hepatomegaly
- Experienced senior clinicians or specialists should be involved and consulted early
- Vasoactive-inotropic support should be considered early if normal physiological parameters are not restored after giving ≥40 mL/kg of fluids. Adrenaline (epinephrine) or dopamine may be given via peripheral intravenous or intraosseous access.

Airway and respiratory support

The airway and breathing should be managed as per advanced life support and resuscitation algorithms.

Supplemental oxygen should be provided, initially at high flow and high concentration during cardiovascular instability or shock. It should be delivered, preferably, via a mask with reservoir bag or headbox in neonates. Oxygen should be titrated according to pulse oximetry, aiming for an oxygen saturation of >94% once the patient is haemodynamically stable. Caution should be exercised in premature neonates or neonates suspected of having congenital heart disease.

The patient's airway should be maintained. Intubation is recommended if respiratory support is required or for patients with a reduced level of consciousness. Mechanical ventilation reduces the cardiac workload in the cardiovascularly compromised patient by reducing the effort of breathing and positive effects on left ventricular function.[48] The clinician should be prepared for cardiovascular collapse or cardiac arrest on induction of anaesthesia for intubation.

The clinician should consider concomitant fluid resuscitation and inotrope use during induction. Anaesthetic agents with a relatively stable cardiovascular profile are recommended (such as ketamine and rocuronium). Etomidate is not currently recommended for anaesthesia in children with septic shock because of concerns regarding adrenal suppression.

Initial fluid resuscitation

Profound fluid loss from the intravascular space occurs due to capillary leak and may persist for several days. Fluid resuscitation is aimed at restoring normal heart rate, blood pressure, and capillary refill time.

The key is rapid early infusion, aiming to restore normal physiological parameters of heart rate and blood pressure.[43] The choice of fluid, though a topic of debate, is less important provided it is isotonic. Crystalloids such as sodium chloride (0.9%) and compound sodium lactate (Hartmann's solution or lactated Ringer's solution) are commonly used and are appropriate; albumin (4.5%) may also be used. There could be theoretical advantages in using colloids for resuscitation in children with sepsis, but colloids are not favoured in adult resuscitation,[49] and there is insufficient evidence to make a

recommendation for or against colloids in children.[50 51] Vasoactive-inotropic support should be considered early in fluid-refractory shock.

Fluids should be given as a rapid bolus at 20 mL/kg and repeated as necessary. Fluids should be administered only in the absence of signs of fluid overload (that is, increased work of breathing, pulmonary crepitations, hepatomegaly, gallop rhythm). It would not be unusual for a child in septic shock to receive >100 mL/kg of fluid resuscitation within the first 24 hours of admission, due to fluid maldistribution, but vasoactive-inotropic support should also be considered early in fluid refractory shock.

Maintenance fluid requirements vary depending on the clinical condition and should be assessed and tailored according to each child's needs. The following equation is used to calculate fluid requirements:

(4 mL/kg for the first 10 kg)+(2 mL/kg for each kg between 11-20)+(1 mL/kg for every kg >20)=hourly rate.

Fluid requirements assessed using this equation are often overestimated. The usual advice is to restrict fluid to 60-80% of the estimated value based on the equation, as children with sepsis often have water retention due to the presence of syndrome of inappropriate antidiuretic hormone. In contrast, insensible losses of water may be increased if the child has significant fever.

It is important to review fluids alongside regular formal review of renal function and serum electrolyte levels. Further guidance on intravenous fluid administration from NICE are currently under consultation and will become available in due course.

Further fluid balance maintenance

Diuresis may be indicated for patients who cannot maintain an even fluid balance naturally after adequate fluid resuscitation. Options include diuretics, peritoneal dialysis, continuous veno-venous haemofiltration, or renal replacement therapy. Data from cohort studies show that critically ill children with fluid overload (>20%) before initiation of renal replacement therapy have higher mortality.[52 53]

Fluid overload is common in critically ill children with haemodynamic instability and acute kidney injury, and it is important to monitor for clinical signs. Indicators of fluid overload include pulmonary crepitations on auscultation, hepatomegaly, and a >10% weight increase from baseline.

Antibiotic therapy

Early administration of antibiotics saves lives. In adults, a study has shown that for every hour of delay in starting antibiotics in septic shock, there is an associated 7.6% increase in mortality.[54] There are only a few similar studies in children, but there is compelling evidence that early antibiotic administration saves lives in children as well. In a retrospective study of 80 children, those who received antibiotics within 1 hour of admission were observed to have significantly lower levels of serum lactate and C reactive protein within the first 24 hours of admission. Although the study was underpowered to detect a change in mortality, the time to reversal of shock in children who received antibiotics within an hour was significantly shorter.[55] Another retrospective study of 130 children with sepsis or septic shock reported an increase in the odds ratio (3.92) for mortality in a paediatric intensive care unit in children who received antibiotics more than 3 hours from recognition of sepsis (odds ratio 4.84 after adjusting for severity of illness).[56]

The choice of antibiotic is complex and should be based on the clinical syndrome, underlying disease, drug intolerances, and local pathogen susceptibility. Treatment should be initiated with broad spectrum antibiotic cover appropriate for the prevalent organisms for each age group and geographical area. This should be changed to an appropriate narrow spectrum antibiotic regimen once a causative pathogen is identified.

It is good practice to review antibiotic therapy on a daily basis for clinical effect and de-escalate when appropriate. A 5-7 day course of intravenous antibiotics would suffice in most uncomplicated infections. In deep seated or disseminated infections, or infections in immunocompromised patients, prolonged courses of antimicrobials may be required.

An infectious disease specialist should be consulted if there are any unusual features to the case, or for advice on appropriate antimicrobial choice and length of treatment if the clinical condition is not improving.

Box 6 provides a general guide to antibiotic therapy in neonates with sepsis.

For infants and young children, empirical antibiotic regimens should include cover for the most common prevailing organisms (such as *Staphylococcus*, *Streptococcus*, *Neisseria meningitides*, and *Haemophilus influenzae*). For community acquired infection, a third generation cephalosporin (such as cefotaxime or ceftriaxone) is a suitable first line option. For hospital acquired infection, an extended spectrum penicillin (such as piperacillin with tazobactam) or a carbapenem (such as meropenem) may be used. Additional broadening of this cover may be considered depending on case-specific factors (for example, gentamicin, ciprofloxacin, or vancomycin.[58]

Meropenem provides broad spectrum cover against both Gram positive and Gram negative bacteria, including *Pseudomonas*. Ciprofloxacin and piperacillin with tazobactam also cover Gram negative bacteria.[58] Vancomycin is recommended to cover vascular catheter associated coagulase negative staphylococci and MRSA. It is also recommended in patients with neutropenia to treat line sepsis, although this is not usually indicated as first line therapy unless there are signs of line related sepsis.[59] Teicoplanin may also be used for this indication. Clindamycin should be used for toxin induced toxic shock syndromes with refractory hypotension.[60]

In neutropenic patients, piperacillin with tazobactam or meropenem are considered first line agents. NICE supports the use of piperacillin with tazobactam as a first line agent, with escalation to a carbapenem (such as meropenem) if there is clinical deterioration (such as shock).[59]

Antifungal and antiviral therapy

The practice of providing antifungal prophylaxis while giving antibiotic therapy varies between institutions. Neonates may be given oral nystatin to help prevent candidiasis.

Very low birth weight infants (<1500 g) and immunocompromised children of any age are at particular risk of primary invasive fungal infections or secondary fungal infections, as a result of altered surface colonising flora during antibiotic treatment. Patients may require prolonged treatment with intravenous fluconazole or liposomal amphotericin-B if invasive fungal infection is suspected or confirmed. Antifungal treatment should be given in addition to empirical antibiotics in very low birth weight infants and immunocompromised patients with suspected sepsis.

Cover for herpes simplex virus (such as aciclovir) should be considered in severe sepsis or if indicated from the patient history or investigative tests. Herpes simplex virus type 1 (HSV-1) infection may be acquired at birth from mothers with

Box 6: Antibiotics for neonatal sepsis

Antibiotics for early onset neonatal sepsis

Early onset neonatal sepsis is defined as neonatal sepsis occurring in the first 72 hours of life.[15]

The antibiotic regimen should cover group B streptococci and Gram negative bacilli. An example of a suitable empirical antibiotic regimen recommended by NICE is benzylpenicillin plus gentamicin.[57] Ampicillin plus gentamicin or cefotaxime is another example.

Antibiotics for late onset neonatal sepsis

Late onset neonatal sepsis is defined as neonatal sepsis occurring after the first 72 hours to 1 month of life.[18]

Causative organisms differ from early onset neonatal sepsis and vary widely among units. In developed countries, coagulase-negative staphylococci are the leading cause, followed by group B streptococci and Gram negative bacteria.

Treatment options for causative organisms include:

- Coagulase negative staphylococci: vancomycin
- Group B streptococci, *Escherichia coli*, enterococci: cefotaxime or piperacillin with tazobactam
- Gram negative bacteria (such as *Klebsiella*): gentamicin
- *Pseudomonas*: ceftazidime or piperacillin with tazobactam
- Listeria monocytogenes: ampicillin
- Anaerobic bacteria (such as in necrotising enterocolitis): metronidazole or clindamycin

Examples of suitable empirical antibiotic regimens include ampicillin plus gentamicin or cefotaxime, or vancomycin plus gentamicin or cefotaxime. Ceftazidime or piperacillin with tazobactam may be added to the empirical regimen if *Pseudomonas* is suspected. Metronidazole or clindamycin may be added to the empirical regimen to cover for anaerobes or necrotising enterocolitis.

an active infection. Congenital HSV-1 infection can be severe and devastating; therefore, treatment should be started before tests results are available in patients with early onset neonatal sepsis.

Blood transfusion

Haemoglobin is essential for tissue oxygen delivery and important in the overall management of the septic child who is haemodynamically unstable (poor cardiac output, low mean arterial pressure) with impaired oxygen delivery. It is suggested a haemoglobin concentration of >10 g/dL (approximate packed cell volume of 0.3) should be maintained in these patients

Once shock has resolved, a lower transfusion threshold may be appropriate. In an intensive care unit trial of transfusion thresholds, subgroup analysis of children with haemodynamically stable sepsis showed no significant differences in mortality, length of stay, or progressive organ failure between restrictive and liberal transfusion thresholds (haemoglobin <7 g/dL *v* <9.5 g/dL, respectively).[61]

Corticosteroids

Evidence for the use of corticosteroids in severe sepsis and septic shock has often been conflicting.[62] The Surviving Sepsis Campaign guidelines do not recommend routine use of hydrocortisone in adult severe sepsis but recommend it as an option in the context of fluid refractory and inotrope resistant septic shock. In children, there is limited evidence for the use of hydrocortisone in fluid refractory and inotrope resistant shock with suspected or proven absolute adrenal insufficiency.[60 63]

Special considerations for newborn septic shock

Septic shock is difficult to differentiate from other forms shock in the premature neonate and newborn infants. Any newborn presenting with signs of cardiogenic shock (such as poor perfusion, cyanosis, heart murmur, hepatomegaly, differential pulse volume, and limb pressure between upper and lower limbs) should be started on a prostaglandin infusion (that is, alprostadil or dinoprostone) under expert guidance until a duct dependent cardiac lesion can be ruled out.

Temperature control

Normothermia (36.5°C to 37.5°C (97.5°F to 99.5°F)) should be maintained. External sources of heat may be required. Conversely, hyperthermia increases metabolic demand at any age, and should be avoided.

Follow up

Children who have specific premorbid conditions that put them at high risk of sepsis and its sequelae will require different monitoring from other patients. Follow-up often depends on the underlying condition (for example, respiratory follow-up for a child who has had pneumonia). Some children may need follow-up with a team of clinicians such as a specialist, a community pharmacist, and a community paediatrician.

Children who present with recurrent sepsis or who have a family history compatible with primary immunodeficiency (such as complement disorders) should be referred for formal immunological follow-up. Where recurrent infection is a feature, the need for prophylactic antibiotics should be discussed with a paediatric immunologist.

Long term monitoring of development is a further important consideration after recovery from severe sepsis or critical illness.

What are the complications of sepsis?

Renal dysfunction

Reduced cardiac output commonly causes transient oliguria; however, anuria is rare.[64] Although acute renal dysfunction is relatively common, it is rarely associated with histological changes or with a need for long term renal replacement therapy. Reversal of oliguria can usually be achieved by the correction of volume depletion and hypotension.[64]

Myocardial dysfunction

Myocardial dysfunction is usually transient and not severe. It rarely results in death.[65] Circulating myocardial depressant factors are thought to be the cause. After adequate fluid resuscitation, vasoactive inotropic agents should be considered. Early use of vasoactive inotropes in fluid refractory shock has been shown to improve outcomes.[43 66]

Disseminated intravascular coagulation

Patients with coagulopathy and disseminated intravascular coagulation require maintenance of a normal platelet count and international normalised ratio.

No trials have been done on transfusion of platelets and clotting components in children for disseminated intravascular coagulation and coagulopathy in sepsis. It is prudent to treat patients symptomatically to avoid bleeding. Platelet concentrate should be transfused to maintain platelet count >50 000/μL to reduce the risk of intracranial bleeding. Fresh frozen plasma should be given for normalisation of coagulation profile to aim for a normal international normalised ratio. Cryoprecipitate has a higher concentration of factor VIII and fibrinogen and can be used to treat hypofibrinogenaemia.

Hypoglycaemia

Moderate hypoglycaemia is defined as a blood glucose level of 2.0-3.0 mmol/L. Severe hypoglycaemia is defined as a blood glucose level of <2.0 mmol/L.[33]

In sepsis, glycogen stores can become depleted; therefore, it is important to monitor for and treat hypoglycaemia with a continuous infusion of intravenous dextrose to provide age appropriate glucose delivery (for example, 2 mL/kg of 10% intravenous dextrose, followed by maintenance infusion at standard maintenance fluid requirement).[43]

Hyperglycaemia

Hyperglycaemia is common as part of the stress response to sepsis or as a side effect of corticosteroid treatment. Although hyperglycaemia is known to be associated with adverse outcomes in multiple clinical settings (including paediatric intensive care), a firm recommendation for glycaemic control is yet to emerge from the scientific literature.[33] Current practice regarding management of hyperglycaemia in this setting varies among institutions, but tight control (that is, treatment to target blood glucose of 4.0-7.0 mmol/L did not improve major clinical outcomes while increasing the risk of hypoglycaemia.[33] The authors' practice is to introduce continuous insulin infusion if two consecutive blood glucose levels exceed 12 mmol/L (if the patient is in paediatric intensive care).

Neuromuscular weakness

Sepsis, systemic inflammatory response syndrome, and multiorgan failure are risk factors for acquired neuromuscular weakness.[32] Neuromuscular weakness is related to duration of immobilisation and is associated with use of corticosteroids, sedation, and neuromuscular blockade.

Necrotising enterocolitis

The pathophysiology of necrotising entercolitis is not fully understood. It seems to be a multifactorial and multisystem disease.[67] Risk factors include intestinal immaturity, inappropriate gut microbiota colonisation, hypoxia or ischaemia, feeding with artificial formula, and elective packed red cell transfusion. The mean prevalence among infants with a birth weight of 500-1500 g is 7%. Estimated mortality associated with necrotising entercolitis is 20-30%.[67]

The classic presentation would be a premature infant developing bilious gastric aspirate and emesis, abdominal distention, and blood in stools after an increase in volume of enteral feeding. Abdominal imaging may include pneumatosis intestinalis, gas in the hepatobiliary tree, and pneumoperitoneum.

Management involves conservative medical treatment with combination broad spectrum intravenous antibiotics and bowel rest. Surgical intervention is required in patients with intestinal perforation and may involve laparotomy with resection of diseased or necrotic bowel, and enterostomy with creation of a stoma. Infants may develop small bowel obstruction secondary to bowel stricture during recovery.

Survivors of necrotising entercolitis are at substantially increased risk of long term neurodevelopmental problems. Other complications include requirement for long term parenteral nutrition and short bowel syndrome.

Multiorgan failure

Treatment of multiorgan failure in sepsis is primarily supportive. It includes effective antibiotic treatment, goal directed treatment (to reverse hypotension, anaemia, coagulopathy, bleeding, and shock), and standard supportive care in the intensive care unit. This may include ventilatory support, sedation, and haemofiltration.

Persistent pulmonary hypertension of the newborn

Acidaemia and hypoxia caused by sepsis can lead to pulmonary artery hypertension and persistence of the ductus arteriosus. The increased right ventricular workload can lead to right ventricular failure with hepatic congestion and reduced cardiac output.

Mixing of deoxygenated blood from the pulmonary artery with oxygenated blood in the aorta by way of the ductus arteriosus leads to differential oxygen saturations between the right arm and lower limbs.

Treatment includes inhaled nitric oxide or inotropic support, or both.

Hypocalcaemia

Hypocalcaemia is common in children requiring admission to an intensive care unit for severe sepsis or septic shock.

Consensus international guidelines for the treatment of septic shock in children include a recommendation for the correction of metabolic abnormalities, including hypocalcaemia. This recommendation is not based on specific evidence from randomised controlled trials; however, hypocalcaemia is recognised as a contributor to poor cardiac function.[68] Caution is advised when administering blood transfusions, as the plasma calcium level may be reduced by the citrate used for blood storage. Intravenous calcium gluconate 10% is the recommended treatment.

Abdominal compartment syndrome

Abdominal compartment syndrome is caused by raised intra-abdominal pressure from factors such as bowel oedema and ascites. Abdominal organ perfusion becomes compromised if the mean arterial pressure cannot compensate for rising intra-abdominal pressure.

Thyroid insufficiency

When there is evidence of low cardiac output or cardiac index, thyroid function should be measured and thyroid replacement therapy initiated if there is evidence of thyroid insufficiency (that is, increased serum thyroid stimulating hormone level or free serum thyroxine is low). Patients with sick euthyroid syndrome do not benefit from thyroid replacement therapy.

Neurological sequelae

Focal neurological deficits and hearing loss are known complications of patients with bacterial meningitis. The mortality and morbidity is higher for pneumococcal meningitis than for meningococcal meningitis.

What is the prognosis?

Without treatment, severe sepsis carries a mortality rate in excess of 80%.[69] With treatment, overall mortality is approximately 10% in children up to the age of 19 years.[70] There was no gender difference in children. Patients with pre-existing disease experience a higher mortality rate of 12.8% compared with 7.8% in previously healthy children.[71]

In children with cancer, overall mortality from sepsis was 17%. The rate increased to 30% in children who had undergone haematopoietic stem cell transplants. Fungal sepsis carried a disproportionate mortality rate of 63% in this high risk group.[72]

Persistent shock on admission to intensive care unit is associated with an increased odds ratio for death of 3.8.[45] For every hour of persistent shock, the odds ratio for death was 2.29 (95% confidence interval 1.19 to 4.44).[73]

One US study at Boston Children's Hospital found that with early recognition of sepsis and resuscitation, according to ACCM-PALS guidelines, the mean length of stay in the intensive care unit was 5.5 days and the mean length of stay in hospital was 8 days.[44]

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Additional educational resources

Resources for healthcare professionals

National Institute for Health and Care Excellence. Feverish illness in children: assessment and initial management in children younger than 5 years. (Clinical guideline CG160.) 2013. (www.nice.org.uk/guidance/CG160)—intended for use by healthcare professionals

Scottish Intercollegiate Guidelines Network 2008. Management of invasive meningococcal disease in children and young people (http://sign.ac.uk/guidelines/fulltext/102/index.html)—a national clinical guideline with recommendations on early assessment of meningococcal disease

Surviving Sepsis Campaign. Guidelines (www.survivingsepsis.org/guidelines/Pages/default.aspx)—international guidelines for management of severe sepsis and septic shock. Includes recommendations for the treatment of paediatric patients

Centers for Disease Control and Prevention. Group B strep (GBS). 2014 (www.cdc.gov/groupBstrep/)—provides a range of educational and practical guidance for group B streptococci

National Institute for Health and Care Excellence. Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection. (Clinical guideline CG149) 2012 (www.nice.org.uk/guidance/cg149)—provides antibiotic recommendations for suspected early-onset neonatal infections

National Institute for Health and Care Excellence. Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. (Clinical guideline CG102) 2010 (www.nice.org.uk/guidance/cg102/chapter/guidance)—offers best practice advice on the care of children and young people younger than 16 years with bacterial meningitis and meningococcal septicaemia

Canadian Paediatric Society. Prevention and management of neonatal herpes simplex virus infections. 2014 (www.cps.ca/documents/position/prevention-management-neonatal-herpes-simplex-virus-infections)—this guideline provides a comprehensive overview of the management of neonatal herps simplex virus infections

Brierley J, Carcillo JA, Choong K, 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;37:666-88—emphasises early use of age specific treatments to attain time sensitive goals

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Standardised criteria for organ dysfunction, according to guidelines of the International Consensus on Pediatric Sepsis[3]

Cardiovascular dysfunction

- Hypotension (defined as blood pressure <5th centile for age or systolic blood pressure >2 standard deviations below normal for age), *or*
- Requirement for a vasoactive drug to treat hypotension, *or*
- Any two of the following abnormalities:
  - Metabolic acidosis (base deficit >5 mmol/L)
  - Increased arterial serum lactate concentraion (more than twice the upper normal limit)
  - Oliguria (urine output <0.5 mL/kg/h)
  - Prolonged capillary refill (>5 seconds)
  - Raised core to peripheral temperature gap (>3°C)
- These abnormalities must be persistent after administration of a 40 mL/kg fluid bolus in one hour

Respiratory dysfunction

Arterial blood gas abnormalities:

- P/F ratio (arterial oxygen pressure/fractional inspired oxygen) <300 (in the absence of cyanotic heart disease or known pre-existing pulmonary disease), *or*
- Arterial carbon dioxide pressure >65 mm Hg, or 20 mm Hg above the baseline level, *or*
- Requirement for fractional inspired oxyten >0.5 to maintain pulse oximeter saturations >92%, *or*
- Requirement for mechanical ventilation (invasive or non-invasive)

Neurological dysfunction

- Glasgow coma score <12, *or*
- Acute decrease in Glasgow coma score of >3 points from an abnormal baseline

Haematological dysfunction

- Platelet count <80 000/µL, *or*
- Platelet count decrease of 50% from highest value in past three days, *or*
- International normalised ratio >2

Renal dysfunction

- Serum creatinine >2 times upper limit of normal, *or*
- Increase in serum creatinine >2 times baseline level

Hepatic dysfunction

- Total bilirubin >68 µmol/L (outside neonatal age range), *or*
- ALT >2 times upper normal limit