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Sepsis in children

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BMJ Best Practice

This is an edited version of the clinical review. The full version is on thebmj.com

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]

The aim of this review is to provide an overview of the causes, diagnosis, and current management of sepsis in children.

SOURCES AND SELECTION CRITERIA

We searched Medline and Embase from October 2008 to October 2013 and the Cochrane Library to issue September 2013 (online) for systematic reviews and randomised controlled trials (any size) on treatment, prevention, and diagnosis and searched specified websites for guidelines using the terms *sepsis*, *severe sepsis*, *septic shock*, *paediatric*, *children*. Our search was updated in January 2015. Additional data sources came from authors' institutional guildelines and policies.

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.[7 8] These studies show a rising annual incidence of severe sepsis (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]

What causes sepsis?

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]

Sepsis occurs when the normal, pro-inflammatory host response to infection exceeds its usual homeostatic 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.

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 are 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

Can sepsis be prevented?

Primary prevention

The principal method of primary prevention is immunisation. 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]

Primary prevention is also relevant with 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).

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.

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).

How is sepsis diagnosed?

Sepsis should be considered as a time critical emergency, as

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*)
- *Staphylococcus aureus* and coagulase negative staphylococci, *Haemophilus influenzae*, and enterococci
- *Listeria monocytogenes* (rare)

Late onset neonatal sepsis
Defined as neonatal sepsis occurring after the first 72 hours to one month of life[18]
- Coagulase negative staphylococci (common cause 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*
- *Neisseria meningitidis* (occurs in a bimodal age distribution, affecting young children and adolescents)
- *S aureus* and group A streptococci
- *Haemophilus influenzae* type b (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)
- In resource poor settings 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)
- 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)

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]

the disease may progress rapidly to organ failure, shock, and death. Prompt and early recognition of the condition is therefore imperative. 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.

When sepsis is suspected 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]

In practice, the clinician should consider sepsis or septic shock if a child has a suspected or proved 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]

In neutropenic patients sepsis should be considered if the core temperature is >38°C (>100°F).

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 see thebmj.com). In both shock states, the patient will show clinical signs of shock outside the cardiovascular system, the most important of which is impaired neurological function. This may manifest as irritability, apnoeas and drowsiness, obtundation, or delirium.

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

Purpura fulminans is a widespread non-blanching purpuric rash classically seen in meningococcaemia.

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.

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).

How is sepsis managed?

Management of sepsis in children first requires prompt recognition. A standard ABC (airway, breathing, circulation) approach with particular emphasis on early administration of antibiotics and fluid resuscitation is key in children with sepsis and septic shock.

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

Compliance with guidelines or care bundles is associated with improved outcomes.[43]

One study in the tertiary accident and emergency department at Boston Children's Hospital looked at delivery of care. Those who received the care bundle recommended by the American College of Critical Care Medicine[44] guidelines (early recognition of severe sepsis, vascular access, antibiotic administration, administering intravenous fluids, and vasopressors for fluid refractory shock) 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).

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%.[46] Reasons for poor

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

*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

compliance are multifactorial.[47] The same team at Boston Children's Hospital subsequently reported improvement in compliance 19% to 100% using process focused quality improvement methodology. They observed a reduction in mortality from 4.8% to 1.7%.[48]

The Surviving Sepsis Campaign (SSC) (www.survivingsepsis.org/Pages/default.aspx) suggests making systems change within institutions through incremental steps. The SSC bundles are available here. (www.survivingsepsis.org/Bundles/Pages/default.aspx).

Paediatric Sepsis Six initiative

Developed by the UK Sepsis Trust Paediatric Group, the Paediatric Sepsis Six is modelled on the adult Sepsis Six programme that has been shown to improve adherence to resuscitation bundles and early goal directed therapy guidelines, and is associated with reduced mortality.[31]

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 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 blood gases. Full blood count, serum lactate, and C reactive protein should also be ordered
- Intravenous or intraosseous antibiotics should be given with broad spectrum cover as according to 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 in advanced life support and resuscitation algorithms.

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.

Intubation is recommended if respiratory support is required or for patients with a reduced level of consciousness. The clinician should be prepared for cardiovascular collapse or cardiac arrest on induction of anaesthesia for intubation.

Initial fluid resuscitation

Profound fluid loss from the intravascular space occurs owing to capillary leak and may persist for several days.

The key is rapid early infusion, aiming to restore normal physiological parameters of heart rate and blood pressure.[44] The choice of fluid 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]

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.

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.[53] 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 signifi-

Box 4 | Diagnostic tests for sepsis (for full explanation see box online)

First tests to order

Full blood count with differential

Serum glucose

Blood culture

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.

Serum lactate—Lactate is most reliably assessed using an arterial sample; venous and capillary lactate should be interpreted with caution.

Serum electrolytes—Should be measured at baseline and regularly until patients improve.

Serum creatinine—Increased serum creatinine 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 are indicative of disseminated intravascular dissemination.[3 36]

C reactive protein—May be useful for the diagnosis and monitoring of sepsis and septic shock. Current practice varies regarding the use of C reactive protein, and clinicians should continue to use clinical judgment.

Chest radiography—Infants and small children with respiratory distress in the context of suspected sepsis should undergo chest radiography to assess for pneumonic changes.

Tests to consider

Lumbar puncture—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.

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—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.

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.

cantly shorter.[54] 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).[55]

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. This can 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.

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.

Antifungal and antiviral therapy

The practice of providing antifungal prophylaxis while giving antibiotic therapy varies between institutions.

Blood transfusion

It is suggested a haemoglobin concentration of >10 g/dL (approximate packed cell volume of 0.3) should be maintained. Once shock has resolved, a lower transfusion threshold may be appropriate.

Corticosteroids

Evidence for the use of corticosteroids in severe sepsis and septic shock has often been conflicting.[61] 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 proved absolute adrenal insufficiency.[59 62]

Special considerations for newborn septic shock

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 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.

What is the prognosis?

Without treatment, severe sepsis carries a mortality rate in excess of 80%.[68] With treatment, overall mortality is approximately 10% in children up to the age of 19 years.[69] There is 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.[70]

Persistent shock on admission to an intensive care unit is associated with an increased odds ratio for death of 3.8.[45] The complications of sepsis, their management and follow-up are discussed in more detail online.

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