Early diagnosis of severe infection

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Abstract

Sepsis is recognised as a global health concern and has a high morbidity and mortality. Evidence shows that mortality rates can be reduced by up to 50% through early recognition and treatment. However, indiscriminate antibiotic use can lead to resistant microbial strains, and increased cost. Sepsis is newly redefined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Screening tools exist and the UK National Institute for Health and Care Excellence (NICE) provide a recommended screening tool which identifies most children at risk from sepsis. Current biomarkers do not reliably differentiate between sepsis and inflammation, and show a delayed response (12–24 hours) to bacterial infection. Evolving research shows procalcitonin is a biomarker released in response to inflammatory stimuli during bacterial infections, with very high levels produced in sepsis and enables real-time monitoring. This review discusses the new definitions of sepsis, importance of making an early diagnosis with appropriate investigations and future diagnostic advancements.

Keywords biomarker; infection; organ dysfunction; procalcitonin; pSOFA; sepsis; septic shock

The scale of the problem

The Surviving Sepsis campaign has increased clinician and public awareness of sepsis and the need for early recognition of this medical emergency. In May 2017, the World Health Organisation passed a resolution to improve the prevention, diagnosis and treatment of sepsis. Sepsis remains a prevalent and problematic global health concern with 30 million people affected per year which results in 6–9 million deaths a year and long-term morbidity. Data from the United States of America reflects a worldwide trend that the incidence is rising by 8% annually. Within the UK, the estimated incidence of sepsis is 147,000 cases per year, and the estimated costs of sepsis are £7.76 billion per year, including approximately £830 million of direct costs.

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Defining the terminology used in sepsis

Infection is common in childhood due to the developing immune system, and can be due to viral, bacterial, fungal or parasitic microorganisms. Frequently, it is localised, causes few systemic symptoms and resolves rapidly. This is in contrast to sepsis, a systemic and overwhelming infection, which can be catastrophic. Definitions have recently changed. Until recently and for over 20 years, sepsis was defined as the coexistence of a presumed or confirmed source of infection with systemic inflammatory response syndrome (SIRS) (≥2 following abnormal: heart rate, respiratory rate, temperature and white cell count). Severe sepsis was defined as the above accompanied by organ dysfunction; and septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation.

These definitions are no longer used, due to a lack of specificity, overemphasis upon inflammation and an improved understanding of the pathophysiology of sepsis. Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. This can result in septic shock', which is cardiovascular dysfunction despite fluid resuscitation. In adults, it is defined by lactate more than 4 mmol/Litre or systolic blood pressure less than 90 mmHg unresponsive to fluid challenge. Although these definitions were devised in adults, there is no physiological justification to suggest that there is need for alternative definitions in children. However, age specific criteria are required to identify the above processes.

Despite its prevalence, sepsis is difficult to diagnose as there is no gold standard test available and there is significant biological and clinical heterogeneity in individual patients. Therefore, a diagnosis should require all 3 components of i) infection ii) dysregulated host response iii) organ dysfunction.

In this review, we will first consider the natural history of sepsis and pathobiology, screening for sepsis, examine the individual components required to make a diagnosis, appropriate investigations and finally address future advancements within the field.

Pathophysiology

Although the pathophysiology of sepsis is not fully elucidated, we understand that early in sepsis there is activation of both pro-inflammatory and anti-inflammatory responses, with a net early inflammatory response comprising fever, increased metabolism and shock.

However, the extent of such features depends upon pathogen load and virulence, nutritional status and co-morbidities. Clinicians should be aware of certain groups who may be predisposed to sepsis, for example neonates or oncology patients (see Box 1), who display less profound features. These individuals may maintain normothermia and also have diminished physiological responses e.g. less tachycardia.

During sepsis there is protracted upregulation of genes involved in innate immunity and reduced expression of genes that control the adaptive immune response. Nonetheless, studies from patients who died of sepsis have shown a profound anti-inflammatory response due to downregulation of activation receptors (CD28, MHC), increased proportions of T regulatory cells and poverty of pro- and anti-inflammatory cytokine gene expression. Therefore, in untreated sepsis, it is unclear whether

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Groups of patients who may be at increased risk of sepsis

- Children under 1 year of age
- Patients undergoing chemotherapy (or within past 6 months)
- Patients undergoing surgery/invasive procedures within the past 6 weeks
- Patients with congenital/acquired immunodeficiency (CVID, HIV, diabetes)
- Patients on disease modifying agents (IBD, JIA)
- Patients on long term steroids (asthma)
- Patients with (functional) asplenia (sickle cell, SLE, splenectomy)
- Patients with indwelling lines or catheters
- Patients who use intravenous drugs
- Patients with a breach to skin barrier function (burns)
- Neonates: particularly if any of the following:
  - Invasive group B streptococcal infection in a previous baby
  - Maternal group B streptococcal colonisation, bacteriuria, or infection in the current pregnancy
  - Prelabour rupture of membranes
  - Preterm birth after spontaneous labour (before 37 weeks' gestation)
  - Suspected or confirmed rupture of membranes for >18 hours in a preterm birth
  - Maternal intrapartum fever >38 °C, or confirmed or suspected chorioamnionitis

Box 1

NICE guidelines for features to evaluate of the level of risk of sepsis in children

High risk	Moderate risk
Abnormal behaviour: - no response to social cues - does not wake, or if roused does not stay awake - weak, high-pitched or continuous cry	Unusual behaviour: - not responding normally to social cues - no smile - wakes only with prolonged stimulation - decreased activity
Appears ill to a healthcare professional	Parent or carer concerned that the child is behaving differently from usual
Severe tachycardia according to age	Moderate tachycardia according to age
Severe tachypnoea according to age	Moderate tachypnoea according to age
Grunting, apnoea	Nasal flaring
$SpO_2 < 90\%$	$SpO_2 < 92\%$
Cyanosis	Pallor
Non blanching rash	Capillary refill time > 3 seconds
Mottling or ashen appearance	Cold extremities
Temperature <36 °C in under 5 seconds	Temperature <36 °C in over 5 seconds
Less than 3 months old and >38 °C	Reduced urine output

Table 1

deaths result from intractable inflammation-induced organ dysfunction or due to overwhelming pathogen-driven damage, facilitated by immunosuppression.

Even with gold standard care, mortality from sepsis in paediatric ICU populations ranges from 5.8 to 32%, but if left untreated can rapidly lead to death in virtually 100% of cases.

Importance of early diagnosis

Sepsis is a medical emergency and prompt recognition of its features allows timely antimicrobial administration and supportive measures. Prompt treatment has been shown to reduce mortality in paediatric sepsis and is supported by national guidelines highlighting the need for treatment to commence within an hour. Risk of mortality increases with each hour's delay from sepsis recognition to antimicrobial therapy regardless of initial severity of illness. Prompt antimicrobial administration also reduces associated morbidity e.g. organ failure days.

Screening

To minimize diagnostic delay a sepsis screening bundle is recommended by the Surviving Sepsis campaign. The UK National Institute for Health and Care Excellence (NICE) guidelines have graded clinical parameters for those at high and moderate risk of sepsis, see Table 1. This screening tool is useful in community and triage settings to identify red flag signs of sepsis for further, urgent referral and management. Within UK hospitals, these parameters are being coupled with early warning scores and trigger instigation of a comprehensive sepsis bundle based on NICE guidance.

Diagnosis requires infection with dysregulated host responses and organ dysfunction

Infection is the first component required to make a diagnosis of sepsis. This is largely elucidated from the history and examination. Elevated core temperature is a common but not invariable feature. Other features may be non-specific in newborns such as irritability and poor feeding but in older children localizing features are usually present. Respiratory infections are common. Upper respiratory tract infection can be determined by clinical examination and typically results in coryza with or without signs of otitis media and pharyngeal or tonsillar erythema and swelling. Lower respiratory tract infection usually results in increased work of breathing and productive cough. It may be accompanied by other more specific signs suggestive of pulmonary infection including crackles, crepitations or wheeze. Localising symptoms can also be seen in meningitis (neck stiffness and photophobia), encephalitis (headache and encephalopathy), urinary tract infection (dysuria), peritonitis (abdominal tenderness) or cellulitis (swelling and erythema of the affected area). Certain features of infection can be relatively non-specific such as vomiting and exanthema (widespread rash). However, sources of infection that are more commonly overlooked include infective endocarditis (a difficult diagnosis in children) and osteomyelitis or septic arthritis.

There are no clinical tests currently available for dysregulated host response. However, certain groups of patients are more susceptible to infection and may have more non-specific or subtle

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