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 and evidence shows that it can be significantly 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. The red flag features of sepsis by NICE is a recommended screening tool. Current biomarkers do not reliably differentiate beween 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.
(143 of 150 words)

Key words

- Sepsis
- Septic shock
- Organ dysfunction
- pSOFA
- Infection
- Biomarker
- Procalcitonin

'Early diagnosis of severe infection'

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.

Defining the terminology used in sepsis

Infection is common, especially in childhood due to the developing immune system, and can be due to viral, bacterial, fungal or parasitic microorganisms. Frequently, it is localised, causes no or few systemic symptoms and resolves rapidly, which is in contrast to sepsis, a systemic and overwhelming infection, which can be catastrophic. Definitions have recently changed. Previously, for over 20 years, systemic inflammatory response syndrome SIRS) (if 2 or more of 4 criteria were met: heart rate, respiratory rate, temperature and white cell count) alongside a presumed or confirmed source of infection, were adequate to diagnose sepsis. 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 >4 mmol/L or systolic blood pressure <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 have a greater understanding 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. Therefore, clinicians should be cognisant of certain groups who may be predisposed to sepsis, for example neonates or oncology patients (see box 1), whilst displaying less profound features such as normothermia and diminished physiological responses e.g. tachycardia. During sepsis, protracted upregulation of genes involved in innate immunity and reduced expression of genes that control the adaptive immune response have been identified. 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 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 5.8-32%, 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. This has been shown to reduce mortality in paediatric sepsis and is supported by national guidelines for treatment to commence within an hour. Risk of mortality increases with each hour delay from sepsis recognition to antimicrobial therapy greater than 3 hours, regardless of initial severity of illness. Prompt antimicrobial administration also reduces organ failure days.

Screening

In view of the above, a sepsis screening bundle is recommended by the Surviving Sepsis campaign since early diagnosis and intervention improves outcomes. National institute of health and care excellence (NICE) guidelines have graded clinical parameters for those at high and moderate risk of sepsis, see Table 1. This 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

Infection is the first component required to make a diagnosis of sepsis. This is largely elucidated from the history and examination. Features may be non-specific in newborns such as irritability and poor feeding but in older children for example, increased work of breathing and productive cough and chest signs are suggestive of pulmonary infection. Localising symptoms can also be seen in meningitis, encephalitis, urinary tract infection, peritonitis or cellulitis. Certain features of infection can be relatively non-specific such as vomiting and exanthem. However, sources of infection that are more commonly overlooked include infective endocarditis and osteomyelitis.

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 evidence of infection: examples are found in Box 1. Specific guidelines should be followed for those at risk of early neonatal sepsis and also for neutropenic sepsis.

Finally, the infection must cause organ dysfunction and there are a number of tools to assess this. Paediatric Logistic Organ Dysfunction (PELOD) or paediatric Sequential Organ Failure Assessment (pSOFA- see Table 2) are both highly validated prognostic scores, with pSOFA being more widely used and supported in the Sepsis-3 guidelines. SOFA scores are adjusted for age appropriate cardiovascular and renal values and alternative SpO_2: FiO_2 ratios are added to respiratory parameters. pSOFA scores show excellent discrimination for in-hospital mortality on admission or sequentially during admission. A single centre retrospective study identified that a score above 8 was the optimal cut-off to discriminate mortality, which is identical to the cut off score in adults. Nevertheless, both require detailed results that are not available on initial presentation or in most clinical treatment settings except intensive care.

Septic shock, is evidence of profound organ dysfunction but in children development of arterial hypotension occurs at a later stage than in adults. Previous consensus definitions are hyperlactataemia (varies between >2 mmol/L to >8 mmol/L), vaso-inotrope dependency or myocardial dysfunction and have not been updated with the publication of Sepsis-3 guidelines. It should be managed within intensive care facilities as it carries an excess mortality risk of 49.7%.

Investigations

When severe infection is suspected, appropriate investigations should be taken to identify the pathogen, its sensitivities if applicable, and source. NICE guideline NG51, Sepsis: recognition, diagnosis and early management, recommends in children that investigations should be tailored based upon history and clinical examination. A sterile urine sample should be collected for a urine dipstick test in all children over 3 months old and sent for microscopy, culture and sensitivity if positive, or if the child is under 3 months, then microscopy, culture and sensitivities should be sent in all cases. Blood cultures are recommended in children with 1 red flag symptom, alongside haematology, biochemistry and coagulation, unless if after senior review an alternative diagnosis is found. If the child has coryzal symptoms, nasopharyngeal aspirate is recommended . If there are suggestive chest signs, a chest radiograph may be useful in evaluating pneumonia and its sequelae. Stool cultures should be obtained if diarrhoea is present. Lumbar puncture is recommended, provided there are no contraindications in suspected meningitis or encephalitis, in all infants presenting under 1 month and in those 1-3 months old with white cell count <5 or >15 $x10^9$/L or who appear unwell. Imagining of the abdomen and pelvis is recommended if no source is found on examination and after initial test results.

Sepsis can be a consequence of bacterial, viral, or fungal infections, therefore, diagnosis depends upon the underlying aetiology. Surviving Sepsis campaign recommends galactomannan and beta-D-glucan measurements as aspergillus and invasive fungal biomarkers. However, there are no other recommended gold standard investigations. White cell count may be raised or inappropriately suppressed in sepsis, and neutrophilia rather than lymphocytosis may suggest a bacterial cause as opposed to a viral source, but this is not very reliable. Equally, minimal increases in C reactive protein (CRP) are more typical of viral infection, compared to higher values in bacterial infection but CRP shows a delayed response (12-24 hours) to bacterial infection, so may be falesly low in rapid onset life-threatening sepsis. Lactate is a sensitive biomarker of cellular dysfunction- typically tissue hypoperfusion and impaired aerobic respiration. However, it is not specific to sepsis or its aetiology, although as discussed earlier it is an important marker of septic shock.

New advancements for the diagnosis of sepsis

Although not currently used in regular clinical practice within the UK, there is a variety of biomarkers for bacterial and viral causes of sepsis. Additionally, they are being developed as point of care rapid tests that can influence real time, refined clinical decision making. This will also reduce unnecessary antimicrobial prescribing and in so, decreasing adverse drug reactions and antimicrobial resistance. Procalcitonin is a biomarker of bacterial infection, which in contrast to CRP, PCT rises early (within 6-12 hours) and peaks early, falling rapidly in response to effective antimicrobial therapy. A multicentre randomized controlled trial in neonates found it was safe and effective to reduce the duration of antibiotic treatment in early onset sepsis using procalcitonin to guide clinical decisions to stop antibiotics, without increasing re-infection or death. There is additional supporting data available for adults but no publications for procalcitonin guided paediatric antimicrobial prescribing and duration. Procalcitonin can also discriminate between mycobacterial tuberculosis pneumonia and other bacterial causes of pulmonary infiltrates, infection versus disease flare in autoimmune conditions and invasive fungal infections. Pro-adrenomedullin (pro-ADM) concentration in neonatal sepsis are significantly higher at baseline compared to CRP or IL-6. However, in a larger study involving children under 36 months with fever, pro-ADM was less sensitive and specific than CRP or procalcitonin in diagnosing invasive bacterial infections. Viral biomarkers include tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and interferon γ-induced protein-10 (IP-10) which are induced by viral infections. Other potential biomarkers include soluble receptors and cytokines. Increasingly, biomarker panels, such as ImmunoXpert assay for TRAIL, IP-10 and CRP are being show to have high sensitivity and specificity for identifying bacterial or viral pathogens in sepsis.

Microbiology offers more promise in confirming diagnosis, but techniques are often slow. Viral pathogens may be identified from PCR of nasopharyngeal aspirates or cerebrospinal fluid (CSF) in 24 hours. Sputum samples are difficult to obtain in children, and although cultures from bronchoscopy have high yields this is an invasive procedure. In paediatrics, urine and venous blood samples can be very difficult to obtain practically. Blood cultures take 24 hours for initial results but 72 hours for definitive results. Additionally, we do not have robust culture methods for certain bacteria like *Chlamydia* or *Borellia* spp and yield remains low with only 30-40% of total cases being 'culture positive' once all microbiological tests are completed. Molecular microbiology allows polymerase chain reaction (PCR) of

blood or CSF to diagnose the microbe more rapidly than culture techniques . The FilmArray system from Biofire has respiratory, meningitis/encephalitis and blood culture panels. Novel advancements within spectroscopy are showing promise in this area. With further validation, molecular signatures from transcriptomic, metabolomic or proteomic analysis will likely lead to faster diagnosis and better characterization of specific population subsets for targeted therapies.

Differential diagnoses

The features of sepsis overlap with many other conditions. Some of the most common differentials include post immunisation reactions (particularly Men B vaccine), autoimmune conditions e.g. SLE or Still's disease, neoplastic e.g. ALL, vasculitides e.g. Kawasaki's disease, pancreatitis and burns or trauma inflammatory responses.

Conclusion

Sepsis carries a high morbidity and mortality rate and public awareness and healthcare bundles have improved in recent years. Careful history taking and examination, alongside refined definitions and NICE sepsis red flag symptoms can guide clinicians to diagnose sepsis earlier, although this remains a challenge without a gold standard test. Revised definitions of sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection, allows more accurate diagnoses with greater specificity. Without a definitive test for sepsis, clinicians must satisfy each of the above components but current areas of research are showing promise in development of tests. Early diagnosis allows for early instatement of antimicrobials, fluids, oxygen and if appropriate, referral to other specialties. Sepsis biomarkers with high diagnostic accuracy and predictive value, and which can be measured at the bedside should reduce the risks of failing to identify potentially life-threatening sepsis.

Practice Points

- Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.
- NICE sepsis criteria of high and moderate risk parameters should be used in screening to guide referral and investigations.
- Careful clinical examination can identify the source of infection and pSOFA score identifies organ dysfunction.
- No gold standard test exists to diagnose sepsis but appropriate microbiological investigations may yield a diagnosis.
- Areas of rapid diagnostic development include biomarker panels for procalcitonin , CRP , IP-10 and TRAIL

3329 words (3 tables ~450 words equivalent according to guidance- max 4000 words)

Conflict of Interest

Both authors have no financial or personal conflicts of interest.

Further reading

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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 >3s
Mottling or ashen appearance	Cold extremities
Temperature <36˚C in under 5s	Temperature <36˚C in over 5s
Less than 3 months old and >38˚C	Reduced urine output

Table 1 : NICE guidelines for features to evaluate of the level of risk of sepsis in children.

• 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: Groups of patients who may be at increased risk of sepsis

System	0		1	2	3	4
Respiratory PaO_2: FiO_2 (mmHg)	≥53.3		<53.3	<40	<26.7 with respiratory support	< with respiratory support
SpO_2:FiO_2 *	≥292		264-291	221-264	148-220 with respiratory support	<148 with respiratory support
Circulatory MAP (mmHg) or vasoactive infusion (µg/kg/min)	<1 month	≥46	<46	Dopamine ≤5 or dobutamine	Dopamine 5.1-15, noradrenaline/ adrenaline ≤0.1	Dopamine >15, noradrenaline/ adrenaline >0.1
	1-11months	≥55	<55			
	12-23 months	≥60	<60			
	24-59 months	≥62	<62			
	60-143m	≥65	<65			
	144-216m	≥67	<67			
	>216m	≥70	<70			
Coagulation platelets ($x10^9$/L)	≥150		100-149	50-99	20-49	<20
Liver bilirubin (µmol/L)	<20		20-32	33-101	102-204	>204
CNS Paediatric Glasgow Coma score	15		13-14	10-12	6-9	<6
Renal creatinine (µmol/L)	<110		110-170	171-299	300-440	>440
urine output (mL/d)	-		-	-	<500	<200

Abbreviations: PaO_2 arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; SpO_2 peripheral oxygen saturation; MAP, mean arterial pressure; m, months old. *Only SpO2 measurements of ≤97% were used in the calculation

Table 2: Paediatric Sequential Organ Failure Assessment parameters to score organ dysfunction severity.