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CLINICAL REVIEW

Sepsis: definition, epidemiology, and diagnosis

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On 29 March 2005 a 41 year old journalist died of sepsis six days after a minor surgical procedure; she had consulted eight doctors over the intervening Easter bank holiday weekend. Whereas the national press focused on the political question relating to the provision of out of hours medical services in the United Kingdom, the coroner pointed out that "non-recognition of the seriousness of her condition contributed [to her death]." With an estimated annual mortality of between 30 and 50 deaths per 100 000 population,[1 2] this condition ranks in the top 10 causes of death,[3] affects all ages, and occurs in the community, in long term care facilities, and among patients admitted to hospital under the care of any, and every, medical specialty.

What is sepsis?

Systemic illness caused by microbial invasion of normally sterile parts of the body is referred to as "sepsis. This is a term that specifically serves to differentiate an illness of microbial origin from an identical clinical syndrome that can arise in several non-microbial conditions, of which pancreatitis is the archetype. The similarity in clinical picture is explained by the pathophysiological role of cytokines, host derived peptides released in response to a wide variety of stimuli, which are common to both. The current terminology was defined in the early 1990s and despite recent review remains largely unchanged.[4 5] This defines sepsis as the association of a panoply of non-specific inflammatory responses (fig 1) with evidence, or suspicion, of a microbial origin. When accompanied by evidence of hypoperfusion or dysfunction of at least one organ system, this becomes "severe sepsis." Finally, where severe sepsis is accompanied by hypotension or need for vasopressors, despite adequate fluid resuscitation, the term "septic shock" applies.

Increasing severity correlates with increasing mortality, which rises from 25-30% for severe sepsis up to 40-70% for septic shock. Within this terminology, the archaic term "septicaemia," which persists in the language of the non-specialist and layman, straddles the definitions of sepsis, severe sepsis, and septic shock. The molecular background to the response to sepsis (fig 2) has been well reviewed elsewhere.[6 7]

How common is sepsis and who gets it?

Very large epidemiological studies of up to 6 million people give an incidence of 3 per 1000 population per year or about 750 000 cases a year in the United States.[8] Very few pathogens, other than parasites such as malaria, multiply preferentially in the bloodstream. Sepsis thus originates from a breach of integrity of the host barrier, either physical or immunological, and direct penetration of the pathogen into the bloodstream, creating the septic state.

The physical barriers to host invasion are formed externally by the skin and contiguous with it internally the mucous membranes lining the gastrointestinal, genitourinary, and respiratory systems, as well as the mucous membrane of the eye. Loss of integrity of the external barrier is usually obvious, although unwary observers might overlook more subtle breaches constituted by indwelling urinary catheters, intravenous cannulas, or an endotracheal tube. Occasionally, sepsis can arise from apparently trivial incursions, such as insect bites, thorn pricks, or minor skin abrasions. Loss of integrity of the internal barrier commonly occurs in the gastrointestinal tract, which stretches from mouth to anus and includes the hepatobiliary system.

The diagnosis is simplified when the pathology results in pronounced peritoneal inflammation, which usually generates signs (guarding, rebound, silent abdomen) and symptoms (pain, vomiting) that are hard to overlook. Difficulties may arise in pinpointing the source or severity of an intra-abdominal

SOURCES AND SELECTION CRITERIA

We searched Medline with the search phrase "((sepsis [title] OR septic*[title]) NOT (infant* OR neonat* OR child*))" and restricted the search to articles published in English in the previous three years. We individually reviewed the titles of the 2620 articles retrieved to identify major themes. Where necessary, we made additional searches based on key words or concepts that had been identified in the initial search. We also searched the Cochrane Library and Clinical Evidence. We then each used this information, supplemented by knowledge and experience from our own fields, to prepare a brief review of the sections with which we were most familiar

problem if this is not associated with much peritoneal inflammation, as might be the case with sepsis arising from the genitourinary tract or hepatobiliary system.

Genetic studies seeking genes that confer susceptibility or protection have mostly been underpowered to give anything other than suggestive indications or have yielded contradictory results.[9] No other association is as clear cut as the genetic influence of haemoglobin S in malaria, for example, which in global terms is probably the most common single cause of sepsis. However, data are emerging of susceptibility and protective polymorphisms in invasive pneumococcal disease,[10] and interleukin 1b-511 homozygosity consistently shows an association with mortality from sepsis.[11] Deficiency of mannose binding lectin through mutations in promoter or structural gene sequences leading to functional or quantitative defects is associated with development of sepsis, particularly pneumococcal sepsis.[12] High concentrations of mannose binding lectin may be protective, and this may be relevant with the potential availability of recombinant or plasma derived mannose binding lectin. Some rare primary immunodeficiencies predispose to specific pathogens. For example, deficiency of terminal complement component predisposes to meningococcal sepsis, and agammaglobulinaemia predisposes to pneumococcal and *Haemophilus influenzae* type b sepsis. Phagocytic defects including chronic granulomatous disease, myeloperoxidase deficiency, Chediak-Higashi syndrome, lazy leucocyte syndrome, leucocyte adhesion molecule deficiency, and Job syndrome are also recognised risk factors.

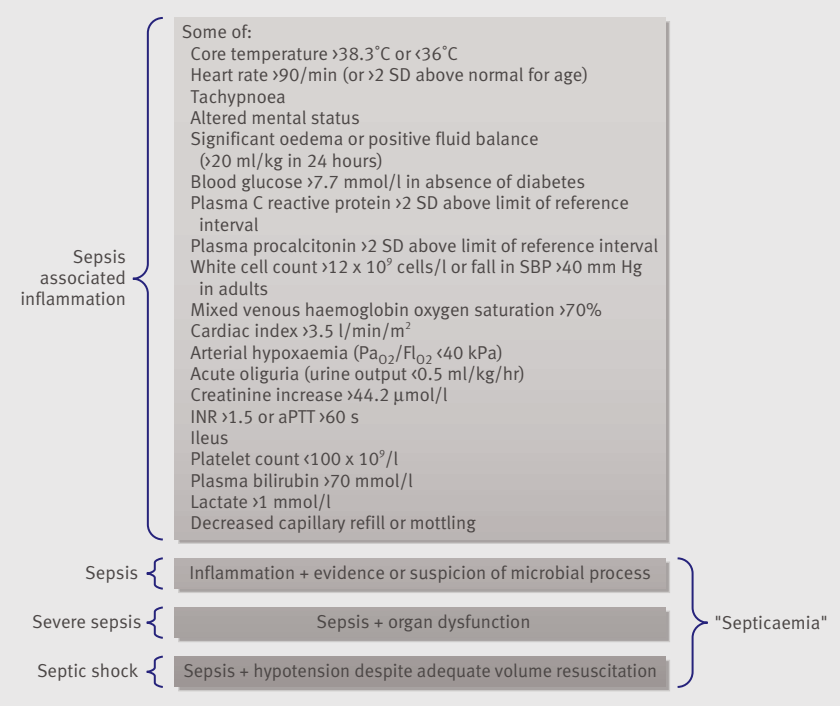

Fig 1 | **Definitions of sepsis, severe sepsis, and septic shock.**
aPTT=activated partial thromboplastin time; INR=international normalised ratio; SBP=systolic blood pressure

Candidate biomarkers for the diagnosis of sepsis

Circulating cells

Cell counts

Total leucocyte count
Neutrophil count
Lymphocyte count
Platelet count

Leucocyte surface markers

Cell differentiation antigen CD11b
Intercellular adhesion molecule (ICAM-1)
CD63
CD64
CD66b

Other properties

Polymorphonuclear leucocyte migration
Leucocyte gene expression profile
Mean platelet volume

Peptides

Monocyte/macrophage

Tumour necrosis factor α (TNF-α)
Interleukin 1α
Interleukin 1β
Interleukin 6
Interleukin 8
Interleukin 10
Interleukin 18
Macrophage migration inhibitory factor (MIF)
Soluble triggering receptor expressed on myeloid cells (sTREM-1)
High mobility group box protein 1 (HMGB-1)

Leucocyte products

Soluble L-selectin (=CD62L)
Soluble P-selectin (=CD62P)

Endothelial cell products

Soluble vascular cell adhesion molecule (sVCAM-1=CD106)
Soluble E-selectin (=CD62E)

Other cell products

Soluble intercellular adhesion molecule (sICAM-1)
Soluble haemoglobin scavenger receptor (sCD163)
Growth arrest specific protein 6 (Gas6)
Soluble urokinase-type plasminogen activator receptor
Soluble tumour necrosis factor receptor 1 (sTNFR-p55)
Soluble tumour necrosis factor receptor 2 (sTNFR-p75)

Acute phase reactants

C reactive protein
Ferritin
Lactoferrin
Neopterin
Procalcitonin
Serum amyloid A

Other

Activated partial thromboplastin time (aPTT) waveform
Fibronectin

Microbial products

Endotoxin

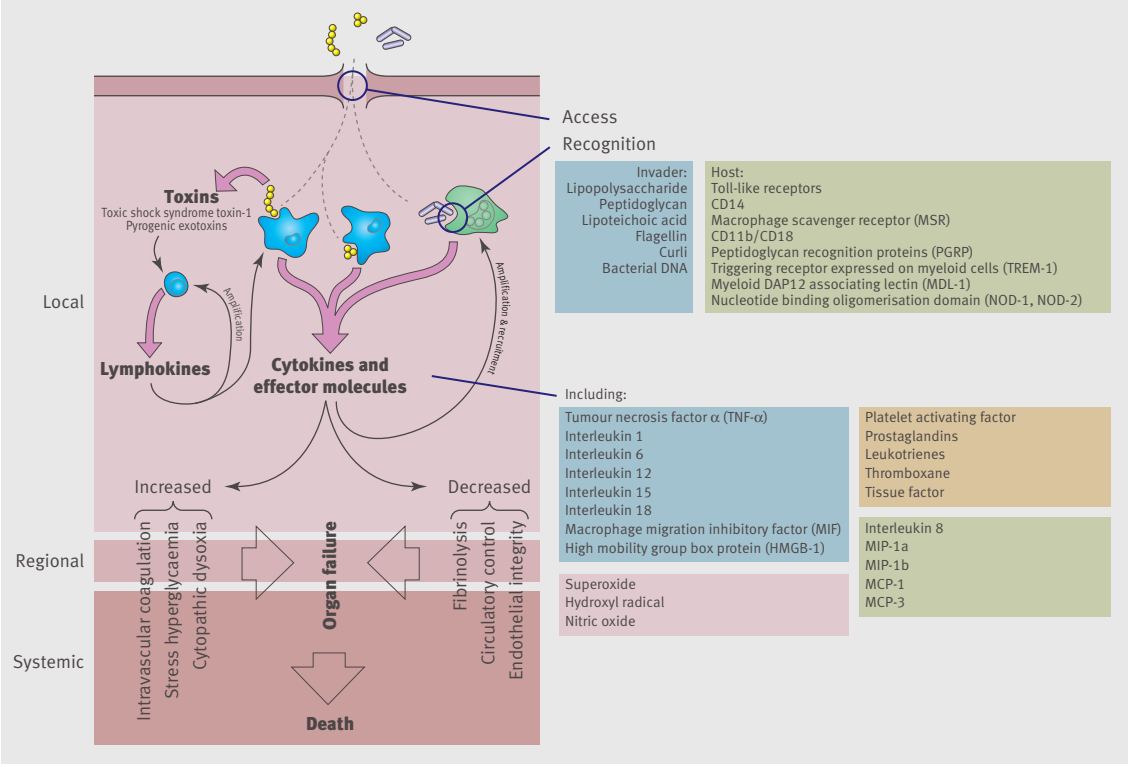

Fig 2 | Pathophysiological pathways of sepsis

Acquired deficiency of the immune system may arise through disease, by deliberate immunosuppression, or by loss of splenic function, surgically or otherwise. Haematological malignancies and several infectious diseases are specifically associated with immune dysfunction. Chief among these are the human immunodeficiency viruses (HIV-1 and HIV-2), but other viral infections also increase susceptibility to bacterial infections—for example, influenza predisposes to staphylococcal pneumonia. Pharmacological immunosuppression may be non-specific, such as immunosuppression from high dose corticosteroids, or may interfere with specific cell types or mediators and may increase susceptibility to certain pathogens (table 1). Splenectomy predisposes to invasion of the bloodstream by capsulated bacteria, particularly pneumococci.

How can sepsis be prevented?

Prevention of sepsis depends on defining the risk group and the availability of appropriate interventions. Invasive pneumococcal disease in agammaglobulinaemic patients has declined since the advent of higher dose intravenous gammaglobulin.[13] Prevention of sepsis by vaccination is validated for certain pathogens,[14 15] and is restricted to specific indications. Pneumococcal, *H influenzae* type b, and meningococcal A and C group vaccines are routine prophylaxis for splenectomy, as in many countries is *H influenzae* type b in the under 5s and meningococcal vaccine in teenagers. Bacteraemia with pneumococci seems to be reduced in the vaccinated population.[16]

Table 1 | Immunomodulatory agents and associated infections

Target	Examples	Infection
Cells	Alemtuzumab, azathioprine, basiliximab, cyclophosphamide, ciclosporin, daclizumab, mycophenolate, rituximab, tacrolimus	Many, including *Pneumocystis jirovecii* pneumonia, *Clostridium perfringens*, *Enterococcus faecium*
Peptide mediators	Adalimumab, etanercept, infliximab, tocilizumab	Staphylococci, streptococci, *Listeria*, *Salmonella*, *Escherichia coli*, malaria, *Candida* spp, mycobacteria, *Nocardia*

How is sepsis diagnosed?

The signs and symptoms (fig 1) of sepsis are highly variable. They are influenced by many factors, including the virulence and bioburden of the pathogen, the portal of entry, host susceptibility, and the temporal evolution of the condition (table 2).

Symptoms are non-specific but contribute to the picture of systemic illness. Localising signs may point to both the underlying problem and the appropriate confirmatory investigations, but they are often absent. As well as the brain being a site of primary infection, in which neurological symptoms are prominent, brain function is often deranged, even in patients with substantial neurological reserve. The presence of clinical evidence of organ dysfunction or shock provides information on severity, usually without contributing to knowledge about causation. Considerable organ hypoperfusion may be present in normally fit adults despite a normal blood pressure. Careful attention should therefore be paid to subtle signs of organ hypoperfusion, such

as confusion, oliguria, lactic acidosis, or a mixed central venous saturation below 70%. In the few septic illnesses that are highly recognisable, such as meningococcal sepsis, microbiological confirmation is useful but not necessary for initial management. In some cases, rapid diagnostic tests will identify the pathogen. In most cases, however, identification occurs after treatment has been started, if at all. Thus, for most septicaemic patients diagnosis begins as a clinical suspicion needing corroboration firstly of an inflammatory process and secondly of a microbial disease.

The published evaluation of diagnostic tests has recently been described as "mediocre at best,"[17] prompting a group of experts (see www.stard-statement.org/) to suggest minimum quality standards for this type of article.[18] In this context, the fact that systematic summaries of the performance of commonly used laboratory tests for diagnosing severe microbial disease in adults have not been done at all (absolute or differential leucocyte counts, measures of granulocyte immaturity), pool studies done in different settings (C reactive protein[19]) or age groups (C reactive protein[19 20]), or include studies with definite spectrum bias (C reactive protein[20]) is not surprising. The most robust systematic review available concerns the plasma procalcitonin concentration assay, which is not yet widely available, used to identify patients with sepsis among critically ill patients in hospital.[21] This study concludes that the test "cannot accurately distinguish sepsis from SIRS [systemic inflammatory response syndrome] in critically ill adult patients." Similar high quality systematic analyses of assays already in widespread use are needed. In future, improved discrimination between microbial and non-microbial inflammation may be provided by novel assays. Of the many candidate biomarkers that have been investigated (see box), analysis of the activated partial thromboplastin time waveform stands out on the grounds that it is already available where the activated partial thromboplastin time is measured with an automated turbidimetric assay.[22]

TIPS FOR NON-SPECIALISTS

- The signs and symptoms of septicaemia are highly variable
- Signs of organ hypoperfusion may be quite subtle in otherwise fit adults
- Fatal sepsis can arise from seemingly trivial wounds
- Early diagnosis and prompt treatment are important
- Clinicians should maintain a high index of suspicion

Confirmation of the microbial nature of a disease relies on either visualisation by microscopy of pathogens in tissue samples or, more commonly, culturing the pathogen from tissue samples, especially blood. Nevertheless, results from cultures usually take at least 24 hours to become available and even then yield positive identification in only about 50% of cases,[3] because of sampling error, previous antimicrobial treatment, or the presence of fastidious or slow growing pathogens. Antimicrobial treatment is thus mostly started empirically; the results of cultures and sensitivity testing serve only to confirm the diagnosis and redirect treatment where necessary. This frustration may be alleviated by new molecular methods that promise the detection, identification, quantification, and determination of the resistance pattern of pathogens from samples within a few hours and without the necessity to culture the organism.[23] These, often automated, techniques use amplification of specific DNA sequences by polymerase

Table 2 | Examples of factors affecting signs and symptoms of sepsis

Factor and organism	Site	Effect
Virulence of pathogen		
Streptococcus pyogenes	Skin	Cellulitis, with fever, localised pain, and redness
Streptococcus pyogenes + SPE-C	Skin	Toxic shock, with hypotension, oliguria, altered mental status, and coagulopathy
Bioburden		
Salmonella typhimurium, 10^3 colony forming units	Gut	Borborygmi and loose stools
Salmonella typhimurium, 10^5 colony forming units	Gut	Haemorrhagic colitis with fever, abdominal discomfort
Portal of entry		
Klebsiella pneumoniae	Renal tract	Pyelonephritis with fever, tachycardia, hypotension, loin pain
Klebsiella pneumoniae	Chest	Lobar pneumonia with high fever, rigors, myalgia, productive cough, tachypnoea, tachycardia, and hypotension
Host susceptibility		
Streptococcus pneumoniae	Chest, fit adult	Pneumonia, with fever, sweats, dyspnoea, and pleuritic chest pain
Streptococcus pneumoniae	Chest, elderly	Obtundation or confusion and "off legs"
Temporal evolution		
Neisseria meningitidis	Blood, early	Fever, malaise, myalgia, arthralgia, headache, but no localising signs
Neisseria meningitidis	Blood, late	Septic shock, with hypotension, oliguria, altered mental status, and widespread purpuric rash

SPE-C=streptococcal pyrogenic exotoxin C.

SUMMARY POINTS

Sepsis encompasses a spectrum of illness that ranges from minor signs and symptoms through to organ dysfunction and shock

Sepsis ranks in the top 10 causes of death

The pathophysiology of sepsis arises largely from the response of the host's innate immune system, under the influence of genetic factors

The signs and symptoms of sepsis are influenced by the virulence of the pathogen, the portal of entry, the susceptibility and response of the host, and the temporal evolution of the condition

Sepsis is a clinical diagnosis; microbiological investigations are commonly negative

Powerful molecular biological techniques are likely to make a substantial contribution to the diagnosis of sepsis in the next five to 10 years

chain reaction. Depending on the target DNA sequence and the detection method used (fluorescent probe, DNA sequencing,[24] DNA microarray[25]) the technique can be used to probe for the presence of single pathogens, members of entire pathogenic species, or even members of entire phylogenetic kingdoms such as the eubacteria by using 16S ribosomal RNA probing. By combining multiple primers into a multiplex polymerase chain reaction, the techniques can also probe for disease specific panels of organisms, such as those associated with a respiratory tract infection or meningitis.[25,26] Problems related to oversensitivity and reference intervals will need to be solved before these techniques become established.

Conclusion

The urgency of treatment and high mortality of sepsis, which will be discussed in the next article, require all clinicians to maintain a high index of clinical suspicion, particularly in circumstances that predispose to sepsis. Robust techniques for differentiating a microbial from a non-microbial cause of systemic inflammation and for rapidly identifying the causative organism(s) remain to be identified.

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Provenance and peer review: Commissioned; externally peer reviewed.

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ADDITIONAL EDUCATIONAL RESOURCES

University of South Carolina. Real time PCR (http://pathmicro.med.sc.edu/pcr/realtime-home.htm)—A tutorial on real time polymerase chain reaction

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