**Key learning points:**

- septicæmia often starts with subtle signs and symptoms
- septicæmia can progress rapidly to a life-threatening condition.
- the patient's setting can give useful clues to the type of septicæmia.
- early microbiological investigations can help define the correct choice of therapy.
- early presumptive therapy is needed to halt the progression of septicæmia and reduce the risk of adverse outcomes.

---

**Key words:**

Septicæmia: a potentially life-threatening infection in which microbes or their products are present in the bloodstream, with alteration of organ perfusion and other systemic responses to infection

Bacteræmia: the presence of bacteria in the bloodstream with OR without clinical features. Transient bacteræmia is common and usually has no serious clinical outcome. Clinically significant bacteræmia can be intermittent or continuous; low or high density.

Sepsis: is a colloquial term often used in clinical practice to describe an infection accompanied by alteration of body temperature (raised or lowered), a change in vital signs (raised pulse and respiratory rate) and a change in the white cell count.

Fever: a rise in recordable body temperature brought about by a change in the body's temperature set point and often accompanied by physiological responses such as sweating and chills.

SIRS: the systemic inflammatory response syndrome is a combination of altered body temperature (<36'C or >38'C ), a rise in pulse ( >90/min ), a rise in respiratory rate ( > 20/min ) and a change in white cell count < 4 e9/L or > 12e9/L ). It is not necessarily caused by infection.

**Microbiology**

While viruses, fungi and parasites can cause septicæmia, the majority of cases are caused by bacteria. Many, many bacterial species can cause much the same pattern of clinical disease, particularly in the early stages of septicæmia, but the commonest 10 species account for the majority of community-acquired infections. Staphylococci (CNS and *S. aureus*) are the commonest Gram positive bacteria, and *E. coli* is the commonest Gram negative species isolated from blood cultures. This is a breakdown of the results from the SCGH clinical microbiology laboratory in 2005-2006:

| **Gram positive bacteria** | | **Gram negative bacteria (GNB)** | |
|---|---|---|---|
| coagulase negative staphylococci | 119 | *E. coli* | 66 |
| CNS + *Bacillus* sp. | 2 | *K. pneumoniae* | 30 |
| *S. aureus* | 44 | *P. aeruginosa* | 13 |
| MRSA | 7 | *P. mirabilis* | 6 |
| *S. aureus*, mixed | 9 | *S. marcescens* | 4 |
| *E. faecalis* | 17 | Enterobacter | 3 |
| *P. acnes* | 16 | *Citrobacter* sp. | 3 |
| *S. pneumoniae* | 16 | *S. maltophilia* | 2 |
| Corynebacteria | 8 | Acinetobacter | 2 |
| viridans streptococci | 7 | Mixed GNB | 12 |
| *Bacillus* sp. | 7 | | |
| *E. faecium* | 6 | **Yeasts** | |
| *S. anginosus-constellatus* | 3 | *Candida* | 5 |

**Pathogenesis**

The common clinical presentation of the early stages of septicæmia despite the great diversity of microorganisms that can cause it suggests a condition dominated by features of the host response in a final common pathway. This is complex and not fully understood. A cumulative process in which multiplying bacteria contribute to an increasingly disorganized host response has been proposed, and could be seen as an example of cumulative dissonance (reference 4). There is thus an increasingly damaging cycle of vasodilation, shock and ischaemia which is multifactorial. Major aspects of this pathophysiological process are systemic vasodilation, reduced cardiac output and tissue injury. Blood vessels become resistant to natural vasoconstrictors such as catecholamines. Organ systems will fail due to circulatory failure. Adrenal responses are inadequate, and mediators from the monocyte/macrophage system exacerbate the downward spiral.

**Clinical features**

The early features may be subtle and include fever, hypothermia, sweats, shaking chills (rigors), and progress to a change in mental state (e.g. confusion), organ system failure, and coma. Other features of septicæmia include increased respiratory rate, restlessness, lethargy, malaise, oliguria, postural hypotension and rash. None of these are specific to septicæmia. Foremost among these; fever, can be caused by non-infectious diseases, and can also be absent in established septicæmia. Elderly people and patients on steroid medication can have a blunted fever response. The physiological stress of septicæmia may present with early failure in any organ system that already has an established underlying disorder.

Australian authorities (reference 2, abridged version) recommend addressing a series of key questions when approaching the patient with suspected septicæmia:

1 is it septicæmia?
2 How close to organ system failure is this patient?
3 What is the clinical context & does it help direct management?
4 Are there any aetiological clues or illness patterns?
5 What are the crucial investigations?
6 Is there a removable focus of infection?
7 Is expert advice needed now?

**Laboratory diagnosis**

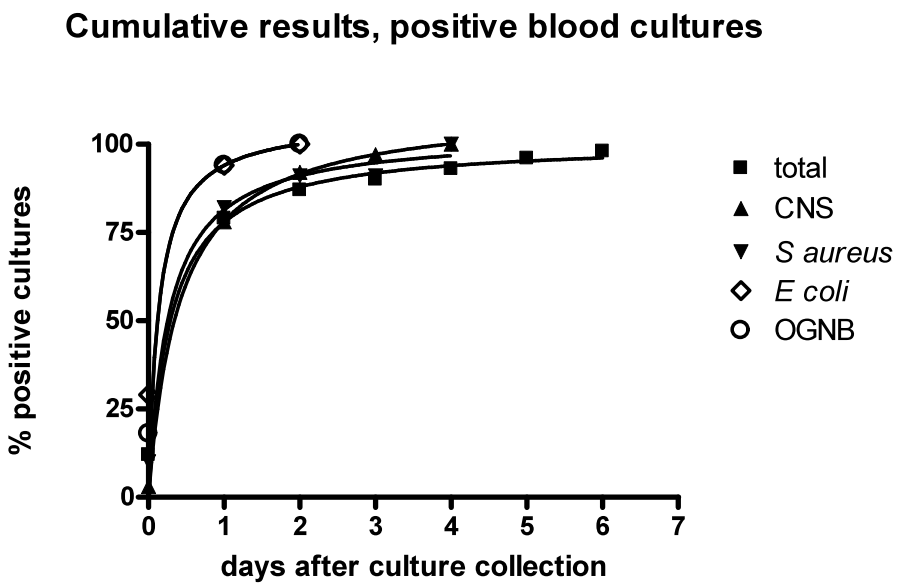
Baseline investigations include blood culture, microbiological samples from any localized infection suggested by the history and examination, full blood count, C-reactive protein, liver and renal function tests and a chest X-ray. Understanding the role of blood culture (BC) is essential. Definitive BC results can take two or more days to reach the requesting physician, but preliminary results can be ready in a few hours. Early blood culture shortly after a patient's admission to hospital with community-acquired septicæmia has been shown to act as a marker for reduced attributable mortality (reference 3). Delayed blood culture is a marker for significantly increased mortality.

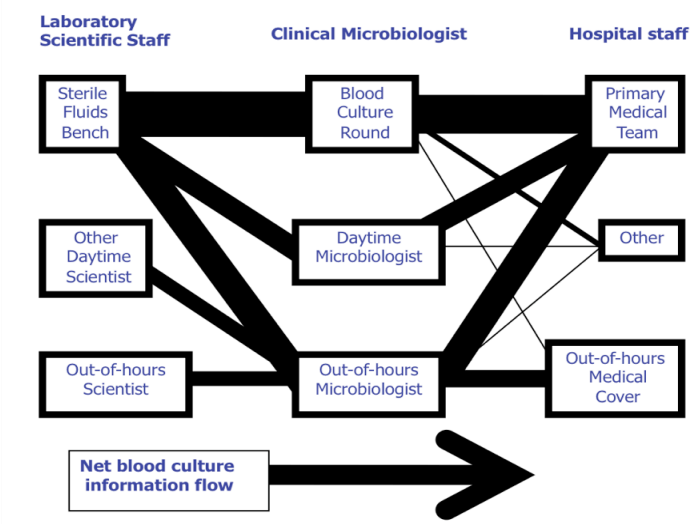
Bottles come in pairs for adult patients; aerobic (blue top) and anaerobic (purple top). They both require 8-10mL blood for optimum results. Too little and you risk getting a false negative. Too much and you dilute the anticoagulants and also risk .. getting a false negative result. More isn't always better. A tiny amount ( < 2.5mL) isn't worth the effort in either type of bottle. If you have only a small amount of blood ( < 8mL) from a patient with shock, put it in the aerobic (blue top) bottle by preference. Use no-touch technique and a Vacutainer or butterfly and connector assembly to minimize the risk of contaminating the culture with bacteria from your skin or from the patient.

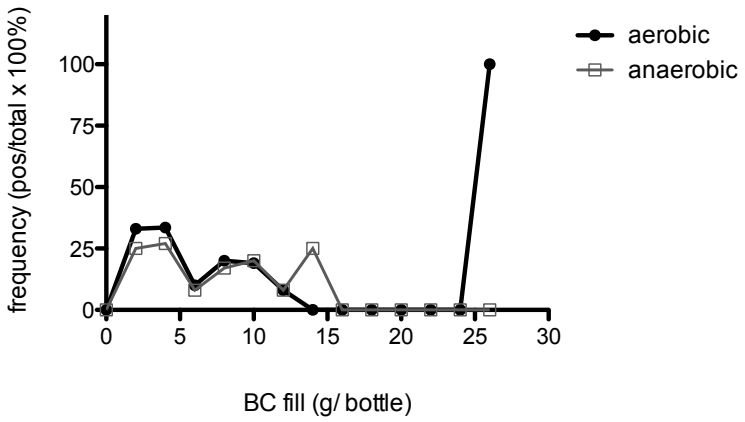
If fever is intermittent, repeat the cultures at least once when fever peaks again. Do not collect three or more cultures per infective episode unless you suspect bacterial endocarditis or have been instructed to do so by an ID physician or clinical microbiologist.

Take great care when filling the BC bottle that it does not over fill. The vacuum it contains can draw over 20mL blood into the bottle, reducing the ability to detect bacterial growth. Dispense 8-10mL per high fill bottle carefully. Pædiatric bottles are smaller and do not come in pairs. Special BC bottles are available for detection of Mycobacteria in HIV/AIDS and other immunocompromised patients.

The bottles should be labeled carefully, including the time taken. This helps the lab staff work out how quickly the bacteria grow and thus give a rough measure of how many bacteria were there to start with. Fast growth often equates to high level bacteræmia. These bottles are put in a special incubator in most diagnostic labs that can detect an early positive. Lab staff will perform a Gram stain on the BC bottle contents as soon as an alarm has been triggered and the local practice is to call the Gram stain result through to the clinical team managing the patient. The precise details of the information flow are complex and vary with the time of day, staffing arrangements in the clinical lab and hospital, and the availability of other lab results. Here are some more results from studies at SCGH:






Distibution of blood culture positives by amount of blood inoculated

**Medical management**

The success of septicæmia management depends on early and aggressive treatment of infection. There are three key components: removal of any identifiable focal source of infection, reversal of physiological abnormalities and correct use of appropriate antibiotics. Abscesses should be drained. Infected cannulas removed and replaced. Tissue perfusion and oxygenation should be maintained, if necessary by ICU admission. Antibiotic choice should be governed by the likely aetiology of the infection if there are any clues from the clinical history and examination, knowledge of patterns of local antibiotic resistance and the patient's ability to tolerate the antibiotics in question. Antibiotic therapy should not be delayed pending the results of culture. There is no single, catch-all antibiotic for all possible causes of septicæmia. The best we can do is to start with a presumptive choice made with information available at the time. Specific clinical scenarios are considered below with reference to Perth, WA. The Antibiotic Guidelines (Therapeutic Guidelines) give good general advice. Your Infectious Diseases, Clinical Microbiology or antibiotic stewardship service is an important additional source of locally accurate advice.

**Specific issues**

*S. aureus*. This is one of the commonest causes of skin and soft tissue infection, and in a proportion of cases will be resistant to the first-line antistaphylococcal antibiotics, Flucloxacillin and Cloxacillin. For this reason, most cases of community-acquired septicaemia with skin lesions will include antistaphylococcal therapy: Flucloxacillin and Vancomycin. *S. aureus* bacteræmia in Perth has a crude mortality rate of around 20-25% and is prone to relapse unless therapy is continued for several weeks.

*E. coli* is the commonest Gram negative cause of septicæmia and is often the result of a prior urinary tract infection. Uncomplicated urosepsis can be treated with an oral quinolone by itself or with a single intravenous dose of the aminoglycoside gentamicin. Upper UTI, or otherwise complicated urosepsis will require a more aggressive antimicrobial approach for longer periods. Amoxycillin resistance is so common in *E. coli* isolates locally that this antibiotic should not be relied upon as a sole anti-infective agent in Gram negative septicaemia.

*Streptococcus pneumoniae* septicæmia can occur without clear evidence of pneumonia and may be a feature of pneumococcal meningitis. It can cause a purpuric rash similar to meningococcal septicæmia, and is commonest during the winter respiratory infection season, often accompanying the peak influenza case load. High dose penicillin or ceftriaxone are suitable antibiotics if the identity of the infective agent is already known.

Febrile neutropænic patients are at increased risk of bacterial and yeast infections in approximate proportion to the severity of their neutropænia. They develop opportunist infections with bacteria

and yeasts from their own microbial flora and organisms present in their immediate environment. Antibiotic treatment needs to take into account a wider than normal range of infective species, a higher probability of antibiotic resistance, and a more rapid deterioration. Usually two antibiotic agents are given to provide a wide range of antibiotic action e.g. Gentamicin and Timentin. If a central line infection is suspected, Vancomycin may well be used at the start of presumptive therapy. Failure to respond to antibacterial therapy in 24-48hr will often result in presumptive antifungal therapy e.g. with Amphotericin.

**Emerging issues**

There are several important emerging themes in septicæmia.

1 point-of-care diagnostic tests to aid physician decision-making in the early stages of septicæmia are under development to get round the delays in arriving at a definitive ætiological diagnosis. These include rapid non-specific tests such as pro-calcitonin and molecular diagnostic tools (usually based on multiplex PCR systems). The difficulty with these is the validation and quality control of tests run outside a carefully regulated clinical laboratory.

2 treatment pathways have been developed in many centres to streamline the management of septicæmia in well-defined patients such as febrile neutropænia. These pathways are usually based on clinical studies, trials or audits and aim to establish standard procedures to make sure the patients get the right treatment at the right time for the right reason.

3 little recent progress has been made in the primary prevention of community-acquired septicæmia, however better programmes for surveillance, monitoring and management of intravenous cannulas have been shown to reduce i.v. device – related infections.

**Reading**


1 Inglis TJJ. Orphan Infections, in: Microbiology & Infection. Master Medicine, 3rd edition, Elsevier, 2007

2 Iredell J et al. Septicaemia. In: Infectious Diseases, A Clinical Approach. IP Communications, Melbourne 2005.

3 Inglis TJJ, Hodge M, Ketharanathan S. A hospital-wide study of the impact of introducing a personal data assistant-augmented blood culture round. J Med Microbiol. 2008; 57: 43-9.

4 Inglis TJJ. *Principia Aetiologica*: taking causality beyond Koch's postulates. J Med Microbiol. 2007; 56: 1419-22.