Mechanisms and detection of bacteraemia

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Bacteraemia refers to the presence of viable bacteria in the bloodstream. This may be transient and of little clinical significance; for example, we all experience transient bacteraemia when brushing our teeth. The consequences of bacteraemia may, however, be severe, leading to focal infection (osteomyelitis, endocarditis) or systemic illness (severe sepsis, shock and death). Thus, an appreciation of the mechanisms underlying bacteraemia is critical in understanding the pathogenesis of many infections.

Mechanisms underlying bacteraemia

To cause sustained bacteraemia, an organism must be able to penetrate host defences and then avoid the immune response, particularly complement-mediated killing and opsonophagocytosis.

Penetration of mucosal surfaces

Cutaneous and mucosal surfaces protect against continual exposure to environmental organisms. Bacteria that colonise or invade these sites may in certain circumstances lead to significant local disease and/or bacteraemia (Fig 1). In order to cause disease in a host with intact mucosal barriers an organism must possess both specific surface adhesion molecules to allow adherence to the epithelial surface and a mechanism for penetration. Many strains of Escherichia coli are unable to adhere to urinary epithelium. E. coli cultured from patients with urinary tract infection, however, have surface pili with receptors that bind to uroepithelium. This general principle applies to many other pathogens, including parasites, fungi and viruses: for example, rhinoviruses that cause the common cold have a surface protein that binds to intercellular adhesion molecule (ICAM)-1 on nasal epithelium.

Once adherent to an epithelial surface, many bacteria remain as colonising organisms and do not invade. Some pathogens have the ability to penetrate between epithelial cells or may be phagocytosed and cross directly through epithelia. This process may be facilitated by epithelial damage permitting traffic of colonising bacteria and subsequent invasion and possible bacteræmia. Damage to the epithelium may be direct, such as trauma or toxins, or it may be caused by another organism. This combination of factors is well

Key Points

- Bacteraemia is the result of bacterial invasion through host epithelia
- Epithelial damage increases the risk of bacteraemia
- Host defences destroy or clear most bacteria from the bloodstream
- Pathogenic bacteria have cell surface features that avoid serum killing and opsonophagocytosis
- Blood cultures need to be taken correctly to optimise yield
- Rapid diagnostic techniques have the potential to improve empirical antibiotic therapy and clinical outcome
illustrated in respiratory tract infections. Lung damage, such as that related to cigarette smoking, increases bacterial colonisation of the respiratory epithelium. A respiratory virus infection leads to inflammation and further reduction in epithelial function, allowing bacterial invasion. If the invading organism can evade host defences, bacteraemia, septis and death may result. This explains the recent observation that pneumococcal bacteraemia is four times more likely in smokers than in non-smokers, even in the absence of overt lung disease.

Direct entry of bacteria into the bloodstream

In addition, bacteria may be inoculated directly into the bloodstream by trauma or, more significantly, through medical interventions. These bacteria often have a low potential for pathogenicity and are unlikely to cause disease in normal hosts. Thus, the daily bacteraemia associated with tooth brushing is innocuous unless there is an endothelial abnormality predisposing to infective endocarditis. In the hospitalised patient, bacteraemia is often the result of bacterial entry through intravascular devices including peripheral and central venous catheters or arterial lines. The severity of these line-related infections will depend on the pathogenic potential of the organism and other diseases in the patient.

Bacterial translocation from the gut

The gastrointestinal tract is colonised with numerous different aerobic and anaerobic bacteria. In normal circumstances, some bacteria cross into the splanchnic circulation and are carried to the liver where they are cleared by Kupffer cells. Entry into the systemic circulation may occur when portal blood bypasses the liver, as in cirrhosis. Furthermore, cirrhotic patients are immunosuppressed and less well equipped to handle bacteria in the blood. Both these factors contribute to increased frequency and severity of bacteraemia in liver disease.

Bacterial translocation is increased if gut mucosal integrity is compromised. For example, the high rate of 'spontaneous' bacteraemia following cytotoxic chemotherapy is in part due to damage to the gastrointestinal mucosa. Increased bacterial translocation has also been implicated in the high frequency of sepsis in the intensive care setting where gut ischaemia may occur for many different reasons. Indeed, in some studies antimicrobial decontamination of the gastrointestinal tract has reduced subsequent episodes of bacteraemia.

Evasion of host responses

Following entry into the bloodstream, bacteria are attacked by a wide array of innate, humoral and cellular defence mechanisms (Fig 2). Innate immunity is conferred by a number of different plasma proteins. Lysozyme and the
complement cascade can directly lyse susceptible bacteria. Complement, C-reactive protein and mannose-binding protein act as opsonins and bind to bacteria, facilitating clearance through the reticuloendothelial system. If there has been previous exposure to the organism, antibody may also mediate bacterial clearance. Phagocytes are important in the initial defences against bacterial Invasion, particularly within tissues. Thus, in neutropenia bacterial infection cannot be localised, and both the frequency and severity of bacteraemia are increased.

Pathogenic bacteria possess a number of different mechanisms to avoid killing or clearance from the blood. Strains of Neisseria gonorrhoeae isolated from patients with localised genital disease are usually rapidly killed by complement in normal human serum. Strains of gonococcus from patients with disseminated disease are serum resistant due to the acquisition of surface sugar residues from the host (sialylation) that protect against complement.

Failure in any of these specific host responses, for example a reduced ability to clear bacteria following splenectomy, will increase both the frequency and severity of bacteraemia.

Detection of bacteraemia

The entry of bacteria into the bloodstream is a pivotal event in the development of septicaemia. Early administration of the correct antibiotic is linked to successful outcome. Thus, the rapid and accurate detection and sensitivity testing of bloodstream infection is a key factor in successful management. Despite the advent of new technologies, blood culture remains the gold standard for the isolation and identification of bacteria in blood. In general, a single set consists of one aerobic and one anaerobic culture bottle. Special media have been developed to maximise the yield of mycobacteria or fungi, and these may be used in selected cases. The ability to detect bacteria in the blood is affected by many factors (Table 1). The yield and time to positivity from standard blood culture techniques are closely related to the intensity of bacteraemia and the amount of blood being cultured. In transient bacteraemia as few as 1–100 bacteria/ml may be present, whereas in acute infection the number may be as high as 10^3–10^4 bacteria/ml. Levels of bacteraemia are generally higher in children, which explains why quite small volumes of blood will often suffice.

Method for taking blood cultures

Although the precise method used to take blood cultures will vary depending on the system used, the basic procedure is shown in Table 2. Blood cultures are frequently taken poorly, decreasing the yield and increasing the contamination rate. This is important because a contaminated blood culture may lead to inappropriate therapy, prolonged hospitalisation and considerable cost. The most common causes of a low yield are:

- an inadequate blood volume is taken
- failure to incubate the bottles promptly
- antibiotic use

Which sites should be used?

Repeat blood culture sets should be taken from different venepuncture sites to allow for easier detection of contamination. In general, venous blood samples are used, although there is little difference in yield between arterial and venous samples. Central line samples are easily contaminated because central venous line hubs are often colonised with bacteria. A recent study comparing simultaneous centrally and peripherally taken blood cultures revealed that in only 30% of positive central line cultures were the peripheral cultures also positive. In this study, a negative central line culture had quite a good negative predictive value. Thus, wherever possible, at least one peripheral blood sample should be taken at the same time as a central venous sample.

Table 1. Factors determining blood culture positivity.

| Factor                     | Influence                                      |
|----------------------------|-----------------------------------------------|
| Volume of blood            | Inadequate volume reduces yield               |
|                            | Optimum for most circumstances: 20–30 ml      |
| Intensity of bacteraemia   | Low level bacteraemia (eg endocarditis) is more difficult to detect and may take longer to become positive |
| Timing of bacteraemia      | Intermittent bacteraemia can be missed        |
|                            | Try to take the blood when there is a fever spike |
| Antibiotic use             | Reduce yield if given before cultures taken   |
| Slow growing organism      | Standard blood cultures are discarded after 5–7 days. |
|                            | If a slow growing organism is suspected (eg brucellosis), request prolonged incubation |
| Delay to incubation        | May reduce yield                              |

Table 2. Basic procedure for taking blood samples.

- Clean the top of each bottle with alcohol
- Venepuncture site should be free from visible contamination or infection
- Swab the site with alcohol or iodine and allow to dry
- Use a 'no touch' technique to draw the blood sample
- Fill the bottles to their capacity
- Inoculate into the prepared blood culture bottles without delay
- Do not change needles between blood culture bottles; this does not reduce contamination but increases the risk of needle-stick injury
- Ensure the bottles are incubated at 37°C as soon as possible
How many sets should be taken?

The number of blood cultures required will vary depending on the clinical situation. In low-level bacteraemia, such as infective endocarditis, five or six sets taken over time may be required in order to maximise the yield. In acute bacteraemic infections, the yield tends to plateau at 20–30 ml total blood volume, which means that two or three blood culture sets are needed\(^{16,17}\).

Positive cultures

When a culture is identified as positive an aliquot of medium is removed, a Gram-stain performed and cultures set up on solid media. The Gram-stain provides an immediate clue as to the diagnosis (Fig 3. Table 3) and is invaluable in aiding empirical therapy. Definitive identification and sensitivity tests will take a further 24–48 hours in most cases.

Recent developments

Automation of blood culture systems has greatly improved the processing and identification of positive specimens. The use of these systems has decreased the length of time between taking the blood and obtaining a positive result. Bacterial proteins, for example pneumococcal or meningococcal antigens, may be detected with rapid techniques from the positive blood culture. This has the potential to speed up the identification process, but is not available in all centres. Polymerase chain reaction (PCR)-based technology has great promise, but has yet to enter widespread clinical use. PCR can rapidly detect and identify organisms and may recognise resistance genes. PCR for \(N.\, meningitidis\) on peripheral blood samples is now available from the meningococcal reference laboratory, but is currently of most value in confirming disease in patients with negative cultures rather than in rapid diagnosis\(^{18}\).

Conclusion

Bacteraemia is a serious condition with potentially fatal consequences. Recognition and prompt therapy of significant bacteraemia will reduce the risk of severe sepsis or metastatic infection. To identify cases accurately and direct therapy it is essential that blood cultures are taken correctly to optimise yield and avoid contamination. The development of new technologies should improve the detection and identification of bacteraemia in the future.

References

1 Bone RC, Balk RA, Cerra FB, Dellinger RP, \textit{et al.} Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. \textit{Chest} 1992; \textit{101}:1644–55.

2 Lucas V, Roberts GJ. Odontogenic bacteraemia following tooth cleaning procedures in children. \textit{Pediatr Dent} 2000;\textit{22}: 96–100.

3 Green J, Lynn WA. Presentation and clinical features of severe sepsis. \textit{J R Coll Physicians Lond} 2000;\textit{34}:418–23.

4 Kok M, Pechere JC. Nature and pathogenicity of microorganisms. In: Armstrong D and Cohen J (eds). \textit{Infectious diseases}. London: Mosby, 1999:1.1–1.25.

5 Mulvey MA, Schilling JD, Martinez JJ, Hultgren SJ. From the cover: bad bugs and beleaguered bladders: interplay between uropathogenic \textit{Escherichia coli} and innate host defenses. \textit{Proc Natl Acad Sci USA} 2000;\textit{97}:8829–35.

6 Bella J, Rossmann MG. Rhinoviruses and their ICAM receptors. \textit{Review J Struct Biol} 1999;\textit{128}:69–74.

7 Talbot UM, Paton AW, Paton JC. Uptake
of *Streptococcus pneumoniae* by respiratory epithelial cells. *Infect Immun* 1996; 64:3772–7.

8 Feltis BA, Kim AS, Kinneberg KM, Lyerly DL, et al. *Clostridium difficile* toxins may augment bacterial penetration of intestinal epithelium. *Arch Surg* 1999; 134: 1235–41; discussion: 1241–2.

9 Nuorti JP, Butler JC, Farley MM, Harrison LH, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. *N Engl J Med* 2000; 342:681–9.

10 Moore FA. The role of the gastrointestinal tract in postinjury multiple organ failure. *Am J Surg* 1999; 178:449–53.

11 McQuillen DP, Gulati S, Ram S, Turner AK, et al. Complement processing and immunoglobulin binding to *Neisseria gonorrhoea* determined in vitro simulates in vivo effects. *J Infect Dis* 1999; 179:124–35.

12 McCabe WR, Jackson GG. Gram-negative bacteremia II. Clinical, laboratory, and therapeutic observations. *Arch Intern Med* 1962; 110:856–64.

13 Ibrahim EH, Sherman G, Ward S, Fraser VJ, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Crit Care* 2000; 118:146–55.

14 Merrel LA, Maki DG. Detection of bacteremia in adults: consequences of culturing an inadequate volume of blood. *Ann Intern Med* 1993; 119:270–2.

15 Boyce TG. Utility of peripheral venous blood cultures in patients with central venous catheters (letter). *Pediatr Infect Dis J* 2000; 19:491–2.

16 Washington J. Blood cultures: principles and techniques. *Mayo Clin Proc* 1975; 50: 91–7.

17 Washington J, Illstrup D. Blood cultures: issues and controversies. *Rev Infect Dis* 1986; 8:792–802.

18 Kaczmarski EB, Ragunathan PL, Marsh J, Gray SJ, et al. Creating a national service for the diagnosis of meningococcal disease by polymerase chain reaction. *Commun Dis Public Health* 1998; 1:54–6.

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**Q1** Common laboratory abnormalities in severe sepsis include:

a) Increased plasma lactate  
b) Abnormal liver function tests  
c) Hypoglycaemia  
d) Thrombocytopenia  
e) Hypocalcaemia

**Q2** The following are true regarding the aetiology of sepsis:

a) Gram-negative bacteria are the most common bacteria isolated from patients with sepsis  
b) Fungi are an increasing cause of community-acquired sepsis  
c) Severe sepsis can be the result of protozoal infection  
d) Severe sepsis is more common in hospitalised patients  
e) Rates of severe sepsis can be reduced by staff handwashing

*continued over*