REVIEW ARTICLE

Utility of blood culture in sepsis diagnostics

Mitul Patel

Department of Microbiology, Birmingham Children's Hospital, Birmingham, B46NH, UK

ABSTRACT

Blood culture remains the most important microbiological investigation in the management of sepsis. The conventional definition of sepsis has been challenged recently and likely to increase number of patients screened for sepsis due to the change in the definition. Blood culture contamination still remains a challenge, especially in resource poor settings where educational facilities are limited. Clinical correlation of positive (as well as negative) blood culture is an important aspect of the investigation where a clinical microbiologist can significantly impact on the management of sepsis.

Key words: Blood culture, role of clinical microbiologist, sepsis

SEPSIS IN THE WORLD AND INDIA

Sepsis is a global health problem that carries a high risk of death. In countries where data are available, the number of cases of sepsis is increasing.[1-3] Sepsis is a major contributor to mortality worldwide and where patients survive of morbidity including long-term physical and neurocognitive dysfunction. No reliable population-based studies exist in India on prevalence, management and outcome sepsis. Of note, as per the National Neonatal Perinatal Database (2002–2003), the incidence of neonatal sepsis is 30 per 1000 live births.[4]

BLOOD CULTURE IN INVESTIGATION FOR SEPSIS

Blood culture remains one of the most important investigations in the management of sepsis. It allows identification of the responsible organism(s) for sepsis, appropriate choice of empirical and specific antibiotic(s) and points toward further investigations required to identify the focus of infection.

A blood culture is recommended for all septic patients. Traditionally, sepsis is defined as the presence of systemic inflammatory response syndrome (SIRS) caused by infection. SIRS is the presence of two or more of the following:

- Body temperature <360°C or >38°C
- Heart rate >90 beats/min
- Hyperventilation >20 breaths/min
- White blood cell count >12,000 cells/μL or <4000 cells/μL.

However, this traditional definition has been challenged recently. Much controversy followed and continued following the European Consensus statement on the definition of sepsis.[5] This document defines sepsis as 'life-threatening organ dysfunction caused by a deregulated host response to infection'. Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Although these definitions are correct in a literary sense, it can be argued that they are impractical for a routine clinical use.

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Address for correspondence: Dr. Mitul Patel, E-mail: mitulpatel3@yahoo.co.uk

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It should be noted that there are no separate clinical criteria for indication of blood culture in patients with suspected fungal or other atypical or rare infections. These patients should have clinical criteria as above for their suitability for a blood culture investigation.

One notable exception is blood culture for suspected disseminated tuberculosis using specialised automated liquid culture medium (e.g., BACTEC Myco/F Lytic bottles).[6] These bottles are designed not only to increase the yield of detection of mycobacteria but also to retain the ability to detect conventional organisms.

CONVENTIONAL METHOD AND AUTOMATED SYSTEM

Automation in blood culture system has enabled maximum yield of pathogens in shortest possible time to improve patient management and in turn saving lives. Non-automated or conventional method still has placed in resource-poor settings. However, the method is slow, cumbersome and results in more contamination as a result of daily handling of blood culture bottles in an uncontrolled environment.

Every effort should be made to minimise the time between blood culture collection and loading onto automated or conventional system using local facilities and resources. This may mean access to the machine/incubator 24 h a day and also placing the blood culture machine away from its conventional place (i.e., microbiology laboratory) to other areas of hospital where access is not compromised (e.g., 24 × 7 biochemistry/haematology laboratory or ward areas).

COLLECTION OF BLOOD CULTURE

Blood cultures should only be collected by members of staff (medical, nursing, healthcare assistant, phlebotomist or technician) who has been trained in the collection procedure and whose competence in blood culture collection has been assessed and maintained.

The main reason to have a uniform protocol for blood culture collection is to prevent contamination with skin organisms during collection of blood. A recommended method based on the WHO and Department of Health, UK recommendations, is as below:

- Wash your hands with soap and water or other appropriate disinfectant
- Before collection, make sure you have all you need to collect blood culture specimen including a sharp disposal box
- Apply tourniquet and palpate the skin for suitable vein
- Thoroughly clean the patient's skin before venepuncture. Use soap and water for visibly soiled skin. Use 2% chlorhexidine in 70% isopropyl alcohol/povidone iodine, followed by 70% ethyl alcohol to disinfect the patient's skin. Allow to dry
- Do not touch the skin again as it may cause contamination
- Remove the plastic cover top of the blood culture bottle and clean the rubber bung top with a new 2% chlorhexidine in 70% isopropyl alcohol/70% ethyl alcohol impregnated swab. Allow to dry for 30 s
- Clean your hands again with alcohol rub or soap and water and apply non-sterile gloves
- Collect adequate volume of blood depending on the bottle being inoculated (follow manufacturer's instructions)
- Apply pressure at the puncture site to achieve haemostasis. Remove the tourniquet. Cover the puncture site with appropriate dressing
- Inoculate the bottle(s)
- Do not change needle between sample collection and inoculation. It increases risk of needle stick injury with no major advantage of prevention of contamination
- Discard sharps into sharp disposal box. Wash your hands. Label bottles appropriately.

Literature recommends two blood culture sets, taken from different sites at the same time. The second set increases the yield and also allows recognition of contamination. Blood culture should be collected, if possible, as soon as possible after spike of temperature. In routine practice, a set of blood culture consists of one aerobic and one anaerobic blood culture bottles.

Blood culture collection for infective endocarditis (IE) requires special consideration. Bacteraemia associated with IE tends to be continuous in nature. Three sets of blood cultures, each containing 10 mL of blood, collected at 30 min interval are recommended.[7]

For central venous catheter (CVC) associated bacteraemia, a set of blood culture should be taken simultaneously from periphery and CVC (unless the CVC was recently [<48 h] inserted).[8] Confirmation of CVC-associated bacteraemia is often difficult in the absence of local signs of infection and frequent isolation of normal commensal organisms. Isolation of the same organism from the blood and insertion site or inferior vena cava (IVC) tip may indicate CVC as focus of infection. However, having no organism isolated from either insertion site or IVC tip does not completely exclude CVC as source of infection.

Ideally, blood culture should be collected before antimicrobial treatment. When already receiving antimicrobials, blood

culture should be collected just before the next dose is due to increase the yield of organisms.

Commercially available automated systems will have recommended blood volume stated on blood culture bottles – most allow up to 10 mL of blood per bottle. There is direct relationship between blood volume and yield, with approximately a 3% increase in yield per millilitre of blood cultured.[9]

BLOOD CULTURE CONTAMINATION

Contamination of blood culture can lead to difficulty in interpretation of significance of the blood culture results and unnecessary antibiotic therapy. Literature recommends a contamination target rate of <3%.[10] Prevention of contamination can be achieved through appropriate training of the staff involved in blood culture collection. Collection through a central venous or arterial line is recommended only for diagnosis of central line infection along with a peripheral blood culture. Note that blood cultures collected from central lines are prone to contamination unless meticulously taken.

Once collected, the bottles for automated systems should be put on the machine as soon as possible. Pre-incubation of these bottles should be avoided, and if a delay is unavoidable, then it should be kept at room temperature. In all cases, procedures recommended by the manufacturer should be followed. For conventional cultures, bottles should be put in appropriate incubator as soon as possible.

Table 1: Common source of organisms and recommended antibiotics for the treatment of common Gram positive isolates from blood culture

Organism	Common sources of bacteraemia	Choice of antibiotic (s) for bacteraemia and comments
Coagulase negative staphylococci (*Staphylococcus epidermidis*)	Most common contaminant	High resistance rate for beta-lactams
	Central venous catheter (CVC) associated bacteraemia	Glycopeptides (Vancomycin, Teicoplanin) are most commonly used
	Prosthetic valve endocarditis (PVE)	Linezolid, Daptomycin are also active
Staphylococcus aureus	Skin and soft tissue infections including cellulitis, necrotizing fasciitis, surgical site infection	Flucloxacillin/Cloxacillin
	Endocarditis and cavitatory pneumonia	Cephalosporins with good Gram positive activity (e.g. Cefuroxime/Cephazolin)
	(common in intravenous drug users)	Glycopeptide (less active than beta-lactams, useful in Penicillin- allergic subjects)
	Bone and joint infections (uncommon to have bacteraemia)	For Methicillin-resistant *Staphylococcus aureus* (MRSA): Glycopeptides, Linezolid.
	CVC-associated bacteraemia	Clindamycin and Fusidic acid are used in combination with above agents
Streptococcus pneumoniae	Community-acquired pneumonia (Note that blood culture for pneumonia is no longer recommended)	Benzyl Penicillin or Amoxicillin (Ampicillin)
	Meningitis	Penicillin MIC is important in severe cases.
	Spontaneous peritonitis	Meningitis caused by penicillin-resistant pneumococci (PRP) require combination of third generation cephalosporins , Vancomycin and Rifampicin
	Occult bacteraemia	
Streptococcus pyogenes (Group A streptococci)	Severe cellulitis including necrotizing fasciitis with toxic-shock like syndrome	Benzylpenicillin i.v. is the most preferred agent. Clindamycin is added for its 'anti-toxin' activity.
	(for tonsillitis, blood culture is not indicated unless septic)	Macrolide (Clarithromycin) can be used in Penicillin allergic patients
Streptococcus agalactiae (Group B streptococci)	Neonatal sepsis and meningitis	Benzyl Penicillin i.v. is the most preferred agent. Gentamicin could be added as a synergistic agent
Viridans streptococci	Common cause of transient bacteraemia	For endocarditis, a combination of Benzyl Penicillin and Gentamicin is recommended. If Penicillin resistant, then use glycopeptides in combination with Gentamicin
	Sub-acute bacterial endocarditis	
	Bacteraemia in post-bone marrow transplant patient with mucositis	
Enterococci	Bacteraemia associated with UTI in catheterised patient,	Most resistant to Benzyl Penicillin. Cephalosporins are ineffective. Combination of Amoxicillin or Vancomycin with Gentamicin is recommended for severe infections for synergistic activity.
	Infective endocarditis	
	CVC associated bacteraemia	Prevalence of 'high-level Gentamicin-resistance' is increasing.
		Vancomycin-resistant enterococci (VRE) can be difficult to treat; Linezolid, Chloramphenicol, Daptomycin, Rifampicin, Tigecycline are alternatives
Listeria monocytogenes	Meningitis and bacteraemia in neonates, elderly and pregnant women	Amoxicillin with Gentamycin, Innately resistant to cephalosporins

Table 2: Common sources and recommended antibiotics for the treatment of common Gram negative isolates from blood culture

Organism	Common sources of bacteraemia	Choice of antibiotic (s) for bacteraemia
Escherichia coli, Klebsiella sp., Proteus sp	Gastrointestinal tract (translocation), urinary tract, sepsis and meningitis in neonates, healthcare-associated infections like ventilator-associated pneumonia	Based on local epidemiology and sensitivity patterns. Amoxicillin (not for klebsiella), third-generation cephalosporins and, aminoglycosides can be used depending on the likely source of infection. (Gentamicin has poor penetration in lung tissues but excretes very well into urinary tract) Extended spectrum beta-lactamase (ESBL) producing organisms are resistant to all beta-lactam antibiotics and many of them are resistant to quinolones and aminoglycosides too. Carbapenems (Meropenem, Ertapenem) are the mainstay for treatment. Newer combinations of cephalosporins + beta-lactamase inhibitors are active (Ceftazidime + avibactam) but clinical experience is limited Carbapenemase producing strains; see below.
Citrobacter, enterobacter sp, morganella sp., serratia,	HCAIs like CA-UTI, VAP, SSI, CVC-associated infections etc.	Mostly resistant to Ampicillin/Amoxicillin and co-Amoxiclav. Resistance in initially sensitive strain sometimes emerges on treatment by derepression of class 1 cephalosporinase. Carbapenems, aminoglycosides, Aztreonam and quinolones can be used
Acinetobactor sp.	HCAIs as above	Multidrug- resistance in healthcare-associated strain is common. Can produce ESBL and CPE. Carbapenems, aminoglycosides and quinolones can be effective.
CPE producing bacteria	Usually HCAIs, community associated infections seen especially in developing countries	Treatment is difficult A combination of two or more of the following antibiotics can be used: high-dose Meropenem, Colistin i.v., Fosfomycin i.v. and, Tigecycline. Mortality remains high despite treatment
Pseudomonas aeruginosa	As above, neonatal sepsis, neutropenic sepsis	Cephalosporins active against pseudomoans e.g., Ceftazidime, Cefipime, Piperacillin-tazobactam, aminoglycosides, Meropenem, and Ciprofloxacin are all active. Choice of antibiotic depends on spectrum needed to treat the underlying clinical syndrome
Salmonella enterica serotype Typhi	Typhoid fever (note that blood culture is not indicated for diagnosis of carrier state)	Quinolone resistance is very high for empirical use A combination of Cefotaxime/Ceftriaxone + Azithromycin as empirical therapy. Ciprofloxacin, if sensitive
Neisseria meningitidis	Meningitis, septicaemia	Benzylpenicillin or a third-generation cephalosporin is commonly used Prophylaxis for contacts (single dose Ciprofloxacin) is necessary

Table 3: Antibiotic treatment for candidemia

Organism	Common source	Choice of antibiotic for fungaemia
Candida species	Intra-abdominal sepsis, prolonged exposure to broad-spectrum antibiotics, CVC- associated infection, neonatal infections	*Candida albicans* are usually sensitive to Fluconazole, however, it is unreliable for other species. Liposomal Amphotericin is active against a broad spectrum of candida species but has significant nephrotoxicity Echinocandins (Caspofungin, Micafungin, Anidulafungin) have a broad spectrum of activity but less effective against *C. parapsilosis*. Poor penetration into brain and urinary tract Voriconazole has a broad spectrum of activity and superior tissue penetration but it does not cover mucorales- though this limitation is not important in treatment of candida infections

MANAGEMENT OF A POSITIVE BLOOD CULTURE

Microscopy using Gram stain should be carried out on broth from any blood culture bottle that signals positive on automated system. Some healthcare providers, especially in the developed countries, carry out the Gram stain procedure and provisional reporting even out of hours.

Recently, technology has been developed to identify the organism rapidly within only a few hours from positively flagged blood culture bottles. Some examples are QuickFISH (AdvanDx, Woburn, MA, USA), Verigene Gram-Positive Blood Culture (BC-GP; Nanosphere, Northbrook, IL, USA) and matrix-assisted laser desorption ionisation–time-of-flight mass spectrometry. The concordance of some of these methods with conventional

identification method is excellent for most commonly encountered pathogens. These methods can dramatically reduce the turnaround time for a provisional result and in turn can lead to timely and appropriate treatment of patients.[11]

A medical microbiologist or infectious diseases (ID) physician should be involved in communication of preliminary positive blood culture to clinician. Microbiologist/ID physician can assist with assessment of the significance of the probable organism(s), likely source of infection, further investigations to locate the source (e.g., imaging) and most appropriate antibiotic(s) to cover likely pathogens based on local susceptibility data. Organisms of public health importance, e.g., *Neisseria meningitidis*, according to local policy and laws, must be notified to appropriate authorities for appropriate preventative measures.

Clinical correlation

A clear understanding of pathogens, their pathogenesis and their potential to cause diseases is necessary for a microbiologist/ID physician to guide the therapy and management of the patient. A brief overview for common blood culture isolates is given in Tables 1-3. The plausible source of infection helps in directing the clinician on further investigation for a definitive diagnosis. The recommended antibiotics may change according to local epidemiology. All empirical treatment should be adjusted once full susceptibility results are available. Two of examples of managing patients with positive blood cultures are given below.

Case 1

A 25-year-old professional sportsman presented with rapidly spreading cellulitis on thigh after a sports-related bruise got infected. He was started on intravenous (IV) Piperacillin-Tazobactam by the admitting clinician. However, his condition was still deteriorating from a sepsis point of view and cellulitis was still spreading. A blood culture became positive after 10-h incubation with Gram-positive cocci in cluster, suggestive of Staphylococcus species. The microbiologist informed the treating clinician and reviewed the history and advised to add IV Vancomycin and IV Clindamycin. The rationale for adding Vancomycin was to cover for Methicillin-resistant *Staphylococcus aureus*. Clindamycin has shown anti-toxin properties in *in vitro* studies and is considered useful in toxin-mediated diseases such as necrotising fasciitis. The microbiologist also advised early surgical review. Outcome: The isolate was identified as Methicillin-resistant *S. aureus*, sensitive to Vancomycin and Clindamycin. Antibiotics were rationalised to Vancomycin and Clindamycin; Piperacillin-Tazobactam was stopped on microbiology advice. After seven days of IV treatment, antibiotics were changed to oral Linezolid which has very good oral bioavailability. The patient fully recovered. A transthoracic echocardiogram did not identify any vegetation on heart valve. Endocarditis is a known complication of *S. aureus* bacteraemia.

Case 2

A 46-year-old woman presented with sepsis and a recent history of recurrent urinary tract infections (UTIs) caused by *Escherichia coli*. She was started on IV Meropenem by the admitting clinician. A blood culture became positive after 12-h incubation, with Gram-negative rods. The microbiologist reviewed the recent urinary *E. coli* which were resistant to Meropenem at the time of blood culture being positive. Based on this information, the microbiologist advised to increase the dose of Meropenem and add IV Colistin to cover for carbapenemase-producing Enterobacteriaceae. The microbiologist also asked the laboratory technician to test for carbapenemase production in the Gram-negative rods from the blood culture. Outcome: The organism was identified as Extended-spectrum beta-lactamase-producing Klebsiella. Antibiotics were changed to once daily Ertapenem to complete 10-day therapy on microbiologist's advice. The patient became asymptomatic. An ultrasound of the urinary tract as well as appropriate gynaecology referral was recommended by the microbiologist in view of the repeated UTI.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA 2014;311:1308-16.
2. Shen HN, Lu CL, Yang HH. Epidemiologic trend of severe sepsis in Taiwan from 1997 through 2006. Chest 2010;138:298-304.
3. Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: A challenge for patients and hospitals. NCHS Data Brief 2011;(62):1-8.
4. Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. Indian J Pediatr 2008;75:261-6.
5. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, *et al.* Assessment of clinical criteria for sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:762-74.
6. National Institute of Health and Care Excellence: Tuberculosis: NICE Guideline; January, 2016. Available from: http://www.nice.org.uk/guidance/ng33. [Last accessed 2016 Sep 09].

7. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, *et al.* 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128.
8. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al.* Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
9. Connell TG, Rele M, Cowley D, Buttery JP, Curtis N. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. Pediatrics 2007;119:891-6.
10. Harvey DJ, Albert S. Standardized definition of contamination and evidence-based target necessary for high-quality blood culture contamination rate audit. J Hosp Infect 2013;83:265-6.
11. Martinez RM, Bauerle ER, Fang FC, Butler-Wu SM. Evaluation of three rapid diagnostic methods for direct identification of microorganisms in positive blood cultures. J Clin Microbiol 2014;52:2521-9.