

# Practice update to optimise the performance and interpretation of blood cultures: 2022

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Blood cultures are an important diagnostic and antibiotic stewardship tool to aid in treatment, monitoring and prognosis of patients with infection. This guideline is intended to update our 2010 guideline on the optimal use of blood cultures. Since then, there have been significant changes to the definitions of sepsis, guidance on the number of blood cultures recommended per draw, central and peripheral line blood cultures, advances in mitigating culture contamination, updates on the indications for blood cultures, and guidance on performance of follow-up cultures.

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A guideline intended to optimise the use of blood cultures in South Africa (SA) through 'diagnostic stewardship' was published in 2010.<sup>[1]</sup> When used optimally, blood cultures are an important antibiotic stewardship tool, and directly influence patient management.<sup>[2,3]</sup> Positive blood cultures taken from patients attending emergency departments in Cape Town changed patient management in 95% of cases, with the culture isolate being resistant to empirical antibiotics in one-quarter.<sup>[2]</sup> This update to our 2010 guidelines considers changes in the definitions of sepsis and advances in the field of infection management.

## Definitions

- **Bacteraemia** is the presence of viable bacteria in the bloodstream. This may be 'transient' (e.g. after dental procedures), 'intermittent', as may occur in cases of suboptimal source control of an infected focus, or 'continuous', as seen in infective endocarditis. Persistent bacteraemia is defined as a positive blood culture collected >24 hours after collection of the last positive culture in the face of appropriate therapy.<sup>[4]</sup>
- **Blood culture** is the inoculation of blood into culture medium with the goal of growing the pathogenic bacterium or fungus to aid in the diagnosis and management of infection.<sup>[1]</sup>
- **Candidaemia** is the presence of viable candida in the bloodstream.<sup>[1]</sup> As in the case of bacteraemia, this may be transient, intermittent or persistent.
- **Contaminant** is an organism that grows in a blood culture that is not considered to be pathogenic in the clinical setting of the case in question.<sup>[5]</sup>
- **Contamination rate** is the proportion of total blood cultures that isolate a contaminant organism.<sup>[6]</sup>

## What's new

- Sepsis guidelines and nomenclature have changed with the removal of the terms severe sepsis and septicaemia, with changes to the definitions of sepsis and septic shock.
  - We recommend taking 2 aerobic blood cultures at 2 different sites.
  - Advances in mitigating culture contamination through phlebotomy teams, and diversion devices.
  - Recommendations for taking blood cultures from peripheral and central lines.
  - Blood cultures should preferably be taken in patients with an intermediate-to-high likelihood of having a positive blood culture.
  - Follow-up cultures should be performed for patients with infections due to *Staphylococcus aureus*, *Staphylococcus lugdunensis*, and *Candida* spp. to ensure clearance.
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- **Clinical infection** is the presence of local or systemic inflammatory response due to one or more micro-organisms and invasion of these micro-organisms into an area.
  - **Sepsis and septic shock.** The definitions pertaining to sepsis and septic shock were revised in 2016.<sup>[7]</sup> The term 'severe sepsis' has been removed from the 2016 guideline owing to redundancy, as has septicaemia, because it is overly narrow.<sup>[7]</sup> The 2021 guidelines, in comparison with 2016, suggest that clinical variables and tools such as the quick sequential organ failure assessment (qSOFA) score should not be used preferentially over others such as systemic inflammatory response syndrome (SIRS) criteria, the Modified Early Warning Score (MEWS) and the National Early Warning Score (NEWS).<sup>[7,8]</sup>
  - **Sepsis** is dysregulated host response secondary to a confirmed or suspected infection resulting in life-threatening organ

dysfunction. Screening variables, tools, and an elevated lactate level may assist in identifying patients with sepsis.<sup>[8]</sup>

- **Septic shock** is sepsis in which the cellular/metabolic abnormalities are profound enough to substantially increase mortality. Clinically, septic shock is defined as persistent hypotension despite adequate fluid resuscitation in a patient with sepsis, requiring vasopressors to maintain the mean arterial pressure  $\geq 65$  mmHg with a lactate level  $>2$  mmol/L, in the absence of hypovolaemia.<sup>[7]</sup>

## Types of blood culture

Standard blood cultures comprise aerobic and anaerobic bottles. Aerobic culture medium is able to support the growth of aerobic bacteria, facultative anaerobes, and yeasts. However, recovery of obligate anaerobes is compromised.<sup>[1]</sup> Anaerobic blood cultures are best suited for the isolation of anaerobes, but are also able to support the growth of some aerobic micro-organisms and fungi.<sup>[9]</sup>

The true incidence of anaerobic bloodstream infections (BSIs) remains contentious, with inconsistent findings reported.<sup>[10-14]</sup> One factor may be the type of culture medium used, as 13.5 - 15.8% of anaerobic blood culture bottles may be positive in the absence of growth in aerobic bottles.<sup>[9,15]</sup> Isolation of anaerobes from blood culture rarely leads to a change in antibiotic choice, as many empirical antibiotic regimens include anaerobic cover, particularly in clinical settings where anaerobes are likely.<sup>[16,17]</sup> The health economic argument for continuing to perform anaerobic blood cultures therefore remains controversial. We recommend using aerobic over anaerobic blood culture bottles. If anaerobic blood culture bottles are used, they should be inoculated first, as the final amount of blood in the syringe is most likely to be contaminated by air.<sup>[18,19]</sup>

Detection of candidaemia in relation to type of culture medium has demonstrated conflicting results. One study of 93 patients demonstrated earlier detection of candidaemia by at least 1 day and increased the yield by 24% if using Bactec Myco/F lytic medium (BD Diagnostics, USA) compared with standard aerobic and anaerobic cultures,<sup>[20]</sup> although this finding was not replicated in another study of 32 patients, which found no difference in sensitivity or time to positivity.<sup>[21]</sup> Furthermore, an *in vitro* study illustrated that time to detection of candidaemia was faster in aerobic culture compared with Myco/F lytic culture medium.<sup>[22]</sup> In resource-limited settings, we recommend standard culture bottles as sufficient for use in suspected candidaemia.

*Mycobacterium tuberculosis* (MTB) blood cultures (such as the Myco/F Lytic system) may be used as part of the work-up for tuberculosis and systemic non-tuberculous mycobacterial infections. The use of two MTB cultures increases the sensitivity of detection. Barr *et al.*,<sup>[23]</sup> in high-tuberculosis endemic settings, showed that 72/99 patients under investigation for tuberculosis cultured MTB from blood on the first culture specimen, with the remaining 27 patients testing positive on the second. We recommend obtaining at least one MTB blood culture, but where resources allow, 2 is preferable for the investigation of disseminated tuberculosis in hospitalised patients, adding to other diagnostic tests such as urine lipoarabinomannan or sputum Xpert MTB/RIF Ultra (Cepheid, USA).

## Number of blood cultures

Lack of consensus surrounds the number of blood cultures needed for the investigation of patients with suspected infective endocarditis (IE). The European Society of Cardiology advises 3 sets of blood cultures (total of 6 blood culture bottles) taken from different peripheral venepuncture sites, each separated in time by ~30 minutes.<sup>[24]</sup> One study showed that 2 blood culture sets is sufficient

for the diagnosis of IE, with a detection rate of 87%,<sup>[25]</sup> while another demonstrated that in cases of streptococcal IE, 96% of streptococci were cultured from the first blood culture set and a further 2%, i.e. 98%, when 2 blood culture sets were used.<sup>[26]</sup>

Increasing the number of blood cultures taken leads to incremental yield. A multicentre study of blood cultures that yielded 629 single bacterial pathogens demonstrated incremental yield of 73.1%, 89.7%, 98.2% and 99.8% positivity from 1, 2, 3 or 4 cultures, respectively.<sup>[27]</sup> It is thought that the diminishing return from subsequent cultures may relate to newer culture systems that are able to detect lower thresholds of bacteraemia, as well as the use of media in blood culture systems containing charcoal and resin.<sup>[18,27]</sup>

For suspected IE in low-resource settings such as SA, we recommend taking 3 aerobic blood culture bottles from different peripheral sites, each separated in time, ~30 minutes prior to antibiotic administration. For other infections when blood cultures are indicated, we recommend 2 aerobic blood cultures taken at the same time from 2 different sites.

## Timing of blood cultures

It is not necessary to take blood cultures at the time of fever, as the yield will not be increased.<sup>[28]</sup> However, blood cultures should be taken prior to administration of antibiotics whenever possible.<sup>[29]</sup> In patients with presumed sepsis or septic shock, where urgent administration of antibiotics is needed, blood cultures should be taken preferably before or within 45 minutes of administration of antibiotics.<sup>[8]</sup>

Blood culture positivity falls off sharply with pre-culture administration of antibiotics. A small study looking at outpatient antibiotic administration during the 2 weeks preceding culture in patients with IE demonstrated a drop-off in positivity from 100% to 64% if antibiotics were administered.<sup>[30]</sup> However, a study focusing on streptococcal IE showed a much smaller decline from 97% to 91% ( $p < 0.02$ ).<sup>[26]</sup> In patients with sepsis, antibiotic administration prior to cultures reduced sensitivity, from 31% to 19%, despite venepuncture occurring within 4 hours of administration in patients with sepsis.<sup>[31]</sup>

## Volume of blood

The optimal amount of blood per bottle will vary with the bottles (paediatric bottles, for example, are designed for lower volumes of blood). However, the majority of adult blood culture bottles are designed to accommodate 10 mL of blood to optimise the growth conditions and improve the yield. Underfilling blood culture bottles reduces the likelihood of isolating bacteria. For each millilitre of blood added to the culture bottle, there is an increase in yield of ~3% up to 10 mL.<sup>[32]</sup> Furthermore, Boyles *et al.*<sup>[2]</sup> demonstrated that the odds ratio (OR) of having a positive blood culture if  $<8$  mL blood was added to the culture medium, as opposed to  $\geq 8$  mL, was 0.56 (95% confidence interval (CI) 0.27 - 1.16).

Many guidelines recommend 2 bottles per set of blood cultures, and 2 sets of blood cultures, thus equating to a final volume of 40 mL. In the local setting, given resource limitations, we recommend that 2 bottles be taken as two separate procedures, recognising the limitations this introduces in terms of the total volume of blood collected.

Paediatric blood volume calculation is more complex, and a weight- or age-based approach can be adopted.<sup>[33,34]</sup> A review by Huber *et al.*<sup>[33]</sup> illustrated the heterogeneity in the volume of blood that needs to be drawn per weight. One approach is shown in Table 1.

## Culture contamination

Bacteria not usually considered as pathogens cultured from blood include common skin flora such as coagulase-negative staphylococci (CoNS, e.g. *Staphylococcus epidermidis*), *Cutibacterium acnes*,

**Table 1. Volume of blood required per weight category**

Weight (kg)	Blood volume (mL)
1.5 - 2.1	1.0
2.2 - 11.1	1.5
11.2 - 17.1	7.5
17.2 - 37.2	11.5
≥37.3	16.5

Adapted from Gaur *et al.*<sup>[34]</sup> and Huber *et al.*<sup>[33]</sup>

*Micrococcus* spp., *Aerococcus* spp., *Bacillus* spp. and *Corynebacterium* spp.<sup>[35,36]</sup> Contaminated cultures are more likely if only one of two culture sets becomes positive for such bacteria, or if multiple sets of blood cultures grow different bacteria that are incompatible with the clinical presentation of the patient.<sup>[5]</sup> Clinical context is critical. For example, CoNS may represent a true pathogen if isolated on blood culture in a patient with suspected prosthetic valve endocarditis.

Poor skin disinfection and venepuncture technique may lead to contaminated blood culture rates of up to 50%.<sup>[37]</sup> Specimen diversion devices, which siphon off the first 1 - 2 mL of blood drawn, demonstrated a reduced average culture contamination rate from 5.2% to 1%.<sup>[6]</sup> Furthermore, diversion of the first blood drawn using a diversion device into a sterile lithium heparin tube prior to filling of blood culture bottles decreased contamination rates by up to 60%.<sup>[38]</sup> A meta-analysis looking into changing needles between blood draw and inoculation of the blood culture bottle – also known as a ‘double-needle collection procedure’ – decreased contamination rates from 3.7% with a single needle used to 2% with the double-needle technique.<sup>[39]</sup> However, a large study involving 640 institutions did not find that a double-needle collection procedure influenced contamination rates.<sup>[40]</sup> The increased risk of needlestick injury if using the double-needle collection procedure is a further reason not to recommend this technique. Educational programmes, blood culture collection checklists, use of protocols, and feedback to healthcare workers have all been shown to decrease contamination rates.<sup>[36,41,42]</sup> The procedure for collecting a blood culture is summarised in Box 1, alongside.

Phlebotomy teams may be cost-effective and can decrease the number of contaminated blood cultures.<sup>[36,43]</sup> An SA private hospital phlebotomy team achieved contamination rates of only 1.3%, compared with public sector tertiary-, secondary- and district-level hospital contamination rates of 4.3%, 4.5% and 6.7%, respectively,<sup>[44]</sup> all of which exceed the goal of <3% contamination.<sup>[45]</sup>

The laboratory costs of processing contaminated blood cultures cannot be ignored. In the abovementioned SA study, 126 490 blood cultures were processed over a 3-year period with just over ZAR1 million spent on contaminated bottles.<sup>[44]</sup>

In addition to laboratory costs, blood culture contamination is costly to patients and the hospital in other ways. One systematic review from high-income countries found that up to 59% of patients received unnecessary vancomycin as a result of blood culture contamination, increasing length of hospital stay between 1 and 22 days, compared with 1 - 17 days in those with negative cultures, and increasing pharmacy costs between USD210 and USD12 611 per patient.<sup>[46]</sup> Additionally, laboratory costs increased between USD2 397 and USD11 152 per patient. Patient discomfort related to unnecessary phlebotomy and the adverse effects associated with antibiotics also need to be considered.<sup>[47]</sup>

## Skin disinfection

Skin disinfection prior to blood cultures prevents false-positive cultures, with comparable rates for alcohol-based antiseptics, alcoholic chlorhexidine and povidone iodine.<sup>[48]</sup> The optimal drying

## Box 1

Procedure for taking blood cultures (see accompanying demonstration video at <https://www.youtube.com/watch?v=c98rrufYr4o>)

1. Verify the patient's identity by asking their name or checking the patient's arm band ± their notes.
2. Explain the procedure to the patient and obtain verbal consent.
3. Assemble the correct materials required for blood culture:
  - a. blood culture bottle/s
  - b. syringe (≥10 mL)
  - c. needle (≥22 gauge)
  - d. sterile gloves
  - e. tourniquet
  - f. adhesive strip
  - g. alcoholic chlorhexidine for skin disinfection
  - h. sterile pack containing cotton/gauze swabs, sterile paper × 2 and waste bag
  - i. patient labels
  - j. sharps waste disposal bin.
4. The sterile blood culture pack needs to be opened onto the trolley. The sterile paper is removed and placed under the patient's arm. Add disinfection solution into the recess of the tray. Sterilely open the syringe and needle and place onto the sterile field.
5. Apply tourniquet to patient's arm and select a vein.
6. Perform hand hygiene, either by washing with soap and water or with alcohol-based solution. It is important to allow your hands to dry completely before attempting to put on the sterile gloves, as this will allow you to draw the gloves over your hands easily.
7. Using aseptic technique, clean the venepuncture area and the top of the blood culture bottle, allowing the solution to dry.
8. Place the green sterile paper with the opening over the venepuncture area.
9. Insert the needle into the vein, while ensuring that your other hand is not in front of the needle to prevent a needlestick injury, and withdraw 10 mL of blood. Collect blood for the blood culture first and then for other specimens.
10. After sufficient blood is drawn, release the tourniquet, and remove the needle and syringe. Place a swab or gauze over the area and apply pressure. You may then inoculate the blood culture bottle if this has not already been performed with the vacutainer system. **Do not** change needles between venepuncture and inoculating the culture bottles because of the risk of needlestick injury.
11. Gently rotate the blood culture bottle to mix the blood and culture media. Do not shake the bottle vigorously.
12. Label the blood culture bottle without covering the barcode of the bottle and without covering the base of the bottle. Some bottles may have an area in which to stick the patient label.
13. Laboratory request forms need to be completed with date, time of collection, site, contact details of clinician, and clinical information. If multiple blood cultures are sent with the same form, clearly indicate whether bottles were collected as two separate draws or in the same draw. Clinical information is of utmost importance for the laboratory to optimise processing of samples for different pathogens.
14. Ideally, blood culture bottles should be transferred as soon as possible to the laboratory for incubation, but if a delay is expected, leave at room temperature. Do not refrigerate the sample.

time prior to venesection varies depending on the disinfectant: 15 - 30 seconds, 30 seconds and 2 minutes for alcoholic chlorhexidine, iodine tincture and povidone iodine, respectively.<sup>[48]</sup> We recommend 70% alcohol/0.5% chlorhexidine gluconate solution in adults as it is as effective as iodine-based agents, does not carry risks of hypersensitivity reactions, and does not stain linen.

### Blood culture sites

Blood cultures should be taken peripherally rather than from a central line, owing to higher rates of contamination from the latter. A systematic review of 9 studies illustrated higher rates of contamination when blood was taken from central lines compared with peripheral blood cultures (mean OR 2.69; 95% CI 2.03 - 3.57). These studies included blood taken at the time of central line placement as well as from central lines that had been *in situ* for hours to days.<sup>[49]</sup> Contamination may be related to greater manipulation with taking blood from a central line.<sup>[50]</sup>

Blood cultures should not be collected at the time of insertion of a peripheral line. A study in a paediatric emergency department showed contamination rates to be 6.7% when blood cultures were taken at the time of peripheral line insertion, compared with 2.3% when obtained via a second venepuncture.<sup>[51]</sup>

The exception to the rule is when investigating suspected central-line associated BSI (CLABSI), which can be diagnosed by taking blood cultures from the central line with a paired peripheral blood culture.<sup>[52]</sup> A differential time to positivity of at least 2 hours in which the blood culture from the central line precedes culture positivity from the peripheral venepuncture suggests a CLABSI (assuming equal volumes of blood in both bottles, and collected at the same time).<sup>[53]</sup> In the absence of a differential time to positivity, correlation of cultured pathogens from the catheter tip with blood cultures taken from either a peripheral site or the central line is also suggestive of CLABSI.<sup>[53]</sup> However, we do not advise sending away catheter line tips if there is no clinical infection suspected, as it is not uncommon for lines to be colonised.

Some central lines may have two ports with associated two lumens (double-lumen catheters). In cases where CLABSI is suspected, we advise taking blood cultures from each port (as well as the peripheral culture), as one lumen may be infected while the other may not.

### The positive predictive value of blood cultures

The pre-test probabilities of a positive blood culture occurring in specific infections or in patients with single symptoms compatible with infection are shown in Table 2. We recommend blood cultures that should be done for adult non-neutropenic patients who have an intermediate or high pre-test probability of having a positive blood culture.<sup>[47]</sup>

### Follow-up blood cultures

Follow-up blood cultures are important in the management of specific infections. *S. aureus* BSI requires follow-up blood culture at 2 - 4 days following the start of appropriate antibiotics to ensure sterilisation of blood.<sup>[47,54]</sup> A study investigating blood culture follow-up for methicillin-resistant *S. aureus* (MRSA) showed 100% survival for those with negative follow-up blood cultures compared with 50% for those with a positive culture or when no follow-up culture was taken.<sup>[55]</sup> As *S. lugdunensis* BSI has been associated with equally poor outcomes, it is recommended that a similar algorithm is followed.<sup>[47]</sup>

The benefit of follow-up blood cultures for Gram-negative BSI is less clear. Some studies have shown no benefit,<sup>[4,47,54]</sup> while others argue the need based on identifying those patients at increased risk of death.<sup>[56,57]</sup> Further research is needed before routine follow-up blood cultures for Gram-negative BSI can be recommended.<sup>[58]</sup>

Daily follow-up blood cultures from the day of treatment initiation are recommended for candida BSI to guide the duration of treatment. If unfeasible, repeat cultures can be done 3 times a week until the first negative culture.<sup>[59,60]</sup> Treatment duration should be 14 days from the first negative blood culture following the initiation of appropriate antifungal treatment with clinical improvement.<sup>[59]</sup>

Repeat blood cultures have been suggested for patients with CLABSI to ensure clearance before insertion of a new catheter;<sup>[47]</sup> however, there is little published evidence to support this practice.

### Accelerating identification of cultured microbes

Matrix-assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF MS) allows the assessment of structural elements of bacteria and fungi with fast turnaround times. MALDI-TOF MS applied to positive blood cultures reduced bacterial identification times between 26 and 34 hours compared with conventional laboratory methods.<sup>[61]</sup> However, inability to determine the antibiotic resistance profiles limits its value.<sup>[62]</sup> Moreover, most low-resource settings will not have access to MALDI-TOF MS.

Polymerase chain reaction-based identification of bacterial cultures is becoming more common, with results available within 1 hour. Limitations include restricted microbial targets and/or their genetic mutation profile being identifiable on existing platforms. It is hoped that future platforms will allow for expansion of microbes and genes for analysis.<sup>[62]</sup>

### Conclusion

Blood cultures are an important diagnostic tool, which if used properly, improves patient management and enables antibiotic stewardship. A thorough understanding of the principles, practice and limitations of the test will aid healthcare workers in optimising its use.

**Table 2. Pre-test probability of blood cultures being positive depending on presenting infection**

Probability of blood culture positivity		
<10% (low)	10 - 50% (intermediate)	>50% (high)
Isolated fever and/or leukocytosis	Acute pyelonephritis	Catheter-associated bloodstream infection
Cellulitis (non-severe)	Acute cholangitis	Discitis or vertebral osteomyelitis
Lower urinary tract infections – cystitis and prostatitis	Cellulitis with comorbidities	Epidural abscess
Community-acquired pneumonia (non-severe)	Non-vascular shunt infections	Meningitis
Postoperative fever within 48 hours (very low)	Community-acquired pneumonia (severe)	Non-traumatic native septic arthritis
	Ventilator-associated pneumonia	Ventriculoatrial shunt infections
	Chills in a febrile patient	

Adapted from Fabre *et al.*<sup>[47]</sup>

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