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REVIEW

Blood cultures in paediatrics: a narrative review

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Abstract
Blood culture is one of the most important investigations to detect bloodstream infection, but in children, blood cultures are often omitted or poorly collected. This review outlines the procedural flow for blood cultures in paediatrics including the pre-analytical, analytical, and post-analytical phases, bearing in mind the differing contexts and resources available across Africa. The aim is to discuss clinical practicalities and laboratory logistics of blood culture samples, and to provide a summary of recommendations to assist with maximising the potential benefit of blood cultures. Key recommendations include collecting the maximum recommended volume of blood according to age or weight-based guidelines, optimising laboratory processes to facilitate the quickest identification and antimicrobial susceptibility testing methods feasible in local settings and ensuring prompt communication and discussion of results with clinicians in order to benefit patient management and antimicrobial stewardship. Microbiologistics, a new term referring to all possible improvements in the logistic chain from sampling to reporting of blood cultures, is also important.

Blood culture (BC) is one of the most important investigations to detect bloodstream infection. Rapid diagnosis, identification of the causative organism/s, and provision of antimicrobial susceptibility results guides the choice of antimicrobial therapy, leading to better patient outcomes. Surveillance of BC isolates provide understanding of the epidemiology of sepsis, which may differ in low and middle-income countries (LMICs), whilst cumulative antimicrobial susceptibility reports can be used for local empiric treatment guidelines and antimicrobial stewardship by facilitating streamlining of broad-spectrum empiric antibiotics at different levels of healthcare.

In children, BCs are often omitted because of perceptions that the procedure is impractical, insensitive or unhelpful due to the delay in receiving results. With poorly collected BCs, yield of pathogens may be relatively low with high contamination rates, emphasising the importance of recognising appropriate clinical indications for BC sampling (addressed by Harrison *et al*) as well as aseptic technique during sample collection, and optimal laboratory flow and interpretation of BC results. (1)

Analysis of laboratory testing procedures can be broken down into the pre-analytical, analytical, and post-analytical phases. This review covers these three phases of paediatric BCs, bearing in mind the differing contexts and resources available across Africa. The aim is to discuss clinical practicalities and laboratory logistics of BC samples, and to provide a summary of recommendations to assist with maximising the potential benefit of BCs.

Pre-analytical phase

The pre-analytical phase involves all aspects of the collection of BCs. The transport of BC specimens to the laboratory forms part of the pre-analytical phase, but for ease of discussion it is included in the analytical phase.

Volume of blood

The volume of blood collected for BC is one of the most important factors determining the diagnostic yield and time-to-detection of positive BCs in both adults and children.(2) Paediatric BC bottles typically require 0.5- 4 ml of blood, yet multiple studies reveal that the majority of (usually single) bottles submitted are under-filled. For example, in an international study on children aged 1-59 months hospitalised with severe pneumonia, the recommended volume for BC was 3 ml, with a minimum of 2 ml if the child's weight was ≥ 3 kg. (3) Yet the mean volume inoculated was 2.05 ml and only 12.4% of samples contained ≥ 3 ml. The same study also confirmed a significant increase in bacterial pathogen yield for samples ≥ 3 ml compared to those with ≤ 1 ml (OR 4.85). Similarly, in a study of community-acquired bacteremia in rural Kenya the proportion of children aged more than 60 days with a positive BC increased from 5.6% if 1 ml was inoculated, to 7.9% if 3 ml was used (p = 0.006).(4)

In children, obtaining adequate volumes of blood can be challenging, since it is considered that only 1-4% of blood volume can safely be withdrawn at any one time, including that required for other diagnostic tests.(5, 6) Removal of large amounts of blood may be technically demanding and painful to children and can lead to anaemia, which may necessitate blood transfusion.(7)
In the past smaller volumes were considered appropriate based on the understanding that children generally exhibited high-level bacteraemia.(8) However, more recent studies show that low-level bacteraemia is extremely common in children with 60. 3% having ≤ 10 CFU/ml and 23.1% having ≤ 1.0 CFU/ml.(9) Therefore, current guidelines suggest the larger the volume of blood obtained the higher the potential yield.(6)

Blood culture recommendations for adults consistently advise 2 or more sets of BCs, each containing 20-30 ml per set, on the first day of a septic episode. (6) (10) In contrast, there is a lack of consensus for paediatric blood cultures and recommended volumes vary considerably (Table 1).(2, 7) Recommendations are based either on the weight of the child which correlates with total blood volume, or on the age which is often considered easier to apply in practice. Most recommendations are based on volumes calculated for different studies, with many small and variable weight and volume subdivisions. More recent studies tend to choose more practical adaptations, e.g. a minimum of 1 ml, plus an additional 1 ml for every year of life up to a total of 10 ml or more uniform 5-10 kg weight categories.(11) (12) While many of the recommendations have shown increased performance relative to smaller inadequate volumes, there are no head-to-head comparisons of different recommended volumes. Most recommendations suggest that older children weighing ≥ 30 -37 kg should have at least 20 -40 ml sampled, corresponding to adult recommendations.(7) Age-based recommendations may be too low for children from 3 -10 years of age since the volumes appear much lower than likely corresponding weight-based recommendations (Table 1).

Obtaining adequate BC volumes in neonates is particularly problematic, especially in small preterm babies, and this frequently leads clinicians to doubt the accuracy of negative cultures. However, in a setting where clear guidelines and clinician education were in place, 93% of BCs in a neonatal ICU met the minimum blood volume of ≥ 1ml.(13) Other practical solutions include better risk assessment of the need for BC, prioritising BCs over blood sampling for non-definitive tests such as CRP, and using cord blood for culture.

Cord blood can be sampled at birth for diagnosing early-onset sepsis. The procedure is technically easier than venipuncture and can yield a larger volume, although there have been concerns about potential contamination leading to false positives. A systematic review and meta-analysis involving over 2000 neonates reported a sensitivity of 75% and specificity of 91.3% compared to peripherally collected BC. Given that peripherally collected BC may be an imperfect reference standard, both peripheral and cord BCs were compared to clinically defined early onset sepsis. Cord BC showed greater sensitivity - 42.6% versus 20.4%, whilst maintaining similar specificity – 97.8% compared to 100%.(14) A recent study minimised contamination rates using a strict aseptic technique, that included drying the umbilical cord segment prior to cleaning with antiseptic solution.(15)

Types and number of blood culture bottles

Paediatric BC bottles contain a reduced volume (compared to standard aerobic BC bottles) of an enriched broth designed to optimise the blood-to-broth ratio in the face of smaller blood volumes whilst supporting the growth of fastidious paediatric pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*.(2) There is limited data on the performance of paediatric bottles compared to standard aerobic bottles. One *in vitro* study using bottles seeded with varying concentrations of bacteria and blood, showed a benefit of paediatric bottles only for inoculated volumes of < 1 ml blood and ultralow bacterial concentrations ≤ 1 CFU/ml. (16) For larger volumes and higher concentrations, both bottle types performed well in general.

The value of anaerobic bottles in paediatric patients is debatable. Advantages of anaerobic bottles in adults include the potential detection of obligate anaerobes, as well as a growth advantage for certain facultative anaerobes leading to more rapid time-to-positivity (TTP). However, obligate anaerobic bacteraemia is considered uncommon in children at <1- 2%, (17) and therefore it is generally considered more important to use the available blood for inoculation of paediatric or aerobic bottles. Paediatric-specific anaerobic BC bottles are also not available commercially.

Table 1. Recommended sampling volumes for blood culture in children according to published weight and age-based recommendations

Weight category	**Recommended blood volume (5,6,9,13,23)**	**Approximate age corresponding to weight category (calculated for ease of comparison)**	**Age category**	**Recommended blood volume (7,27**
Neonates: less than 1.0 kg	1- 2 ml	Less than 1 month	Less than 1 month	0.5 - 1 ml or more if possible
Neonates: > 1.0 -2.0 kg	1 - 4.5 ml	Less than 1 month	Less than 1 month	0.5 - 1 ml or more if possible
Infants: > 2.0 -5.0 kg	1 -6 ml	1 month to 6 months	1-12 months	1 – 3 ml
Infants: > 5.0 – 10.0 kg	1.5- 6 ml	6 months to 1 year		
Toddlers: > 10.0 - 15.0 kg	1.5 - 23 ml	1 -3 years	1 -3 years	1 – 4 ml
Young children: > 15.0 - 20.0 kg	6- 23 ml	4-5 years	4-5 years	4 – 8 ml
Children: > 20.0 - 30.0 kg	10 - 23 ml	6-8 years	5-9 years	6 – 8 ml
Children: > 30.0 – 40.0 kg	10 – 60 ml	9-10 years		
	16.5 - 60 ml	10 -13 years	≥ 10 years	20 ml

The number of BC bottles inoculated depends on the volume of blood available for culture. Smaller volumes less than 4 ml should be inoculated into a paediatric bottle if available but larger volumes should be divided into standard aerobic bottles.

Number of draws

Traditionally in adults, multiple venipunctures were recommended over a single venipuncture, chiefly to determine the significance of potential contaminants. However, each venipuncture carries its own risk of contamination, Based on mathematical modelling, the collection of 6 bottles comprising a total volume of 35- 42 ml at a single venipuncture is considered the most rational strategy to maximise both sensitivity and specificity.(18) Contaminants can be distinguished since they are usually present only in the first of the multiple bottles collected. Two prospective studies in adults have confirmed that the single sampling strategy detects fewer contaminants whilst maintaining similar detection of pathogens.(19, 20)

In children with febrile neutropenia comparing multiple draws of 1-2 ml per set and up to 3 sets drawn within the first 24 hours to a single early draw of a large weight-based volume, the single-draw strategy showed improved detection of bacteraemia, prompting the call for multicentre trials in neutropenic and general paediatric populations.(21)

In practice many paediatric BCs are by default from a single draw because of volume limitations, although recent studies have encouraged multiple draws.(22)

Site of blood draw

Peripheral venipuncture is preferred over collection of blood via indwelling vascular catheters because of concerns about false positive results due to colonisation of the line. However, peripheral venipuncture is also liable to false positive results due to contamination from skin flora, and some studies have suggested no difference in contamination rates in paediatric patients.(23) An important consideration is that drawing blood through an indwelling catheter minimises pain for patients, technical difficulty for operators, and usually allows collection of larger blood volumes. Catheter draws are therefore used routinely in some paediatric ICUs or oncology settings.(21)

Timing of blood culture collection

In the past, it was recommended that BCs be taken during a temperature spike to maximise the chance of detecting (possibly intermittent) bacteremia. There is little evidence supporting the concept of intermittent bacteremia and past studies with intermittent positive cultures may simply reflect inadequate sensitivity of small volumes sampled.(10) Additionally, fever reflects a response to bacteremia that may only occur after the onset of bacteremia. Therefore, BCs should be taken as soon as an indication arises, and before the administration of (new) antibiotics.

Contamination of blood cultures

The introduction of contaminating organisms into BC samples can lead to false positives which can have adverse effects on patients, including misdiagnosis and delayed recognition of underlying illness, use of unnecessary antimicrobials as well as increased costs and prolonged hospital stay.(12, 24) Contaminants are organisms found in the normal flora of the skin or organisms from the environment. Usually, the particular contaminant is not present in multiple bottles, whether these are drawn from a single or multiple separate venipunctures.(18, 19) Contaminated samples may take longer to show evidence of growth, presumably due to the very small inoculum.

Certain organisms are more commonly suspected of being contaminants unless isolated from multiple bottles, e.g. most species of coagulase-negative staphylococci and *Corynebacteria*, *Bacillus* (other than *B. anthracis*) and *Micrococcus* spp., Other organisms, e.g. *Enterococci*, non-fermenting Gram-negative bacilli (GNB) such as *Acinetobacter* spp., viridans *Streptococci* and *Clostridium* spp., may automatically be assumed to be pathogens although their significance from a single culture may be difficult to interpret. (24, 25)

Typically, contaminants are less virulent organisms that do not account for the patients' clinical infection. However, in selected compromised patients, e.g. neonates, ICU or neutropenic patients, or in selected conditions, e.g. endocarditis or line sepsis, even relatively avirulent organisms can cause significant infection.

Classification as a pathogen or contaminant therefore requires knowledge of all microbiological investigations (including other BCs and cultures from other sites) as well as clinical information. A BC contamination rate of <3% is considered acceptable though it has been suggested that more stringent targets of < 1% should be established.(24) Unfortunately, higher contamination rates of up to 10% are frequent in LMICs.(26)

Some studies have shown an inverse correlation between blood volume sampled and contamination rate, i.e. small volume samples tend to have more contaminants. (23, 27, 28) Possible explanations include a dilutional effect with larger volumes limiting detection or an association with more difficult venipuncture attempts.(2)

Whilst the majority of contaminants likely originate from the site of venipuncture, contaminants can also be introduced via blood collection equipment including the needle or cleaning solution or be present in the BC bottle itself. Prevention of contamination depends on adequate skin antisepsis and the use of sterile equipment and aseptic technique. South African guidelines describing in detail the aseptic technique for taking BC have been published recently.(29)

Alcohol-based skin antiseptics significantly reduce BC contamination compared to aqueous solutions possibly because of more rapid drying. (30, 31) Alcohol-based antiseptics are also less likely to support the growth of environmental GNB. In addition, 2% chlorhexidine is frequently preferred to iodine-based antiseptics, although the exact contribution of chlorhexidine is difficult to determine as it is formulated with alcohol, which may on its own be adequate for skin antisepsis.(30, 31) There are some concerns about the use of chlorhexidine in infants < 2 months of age because of limited safety data. However, chlorhexidine is used frequently in many NICUs without adverse effects, and the safety concerns seem to be restricted to neonates with gestational age < 32 weeks. (32)

Prior to the HIV pandemic, a double-needle strategy was used whereby the first needle used for venipuncture was removed and a second needle was used for inoculation of BC bottles.(24) Subsequently to reduce the risk of needlestick injuries, a single-needle strategy was adopted that is associated with a small increase in contamination rates. A better alternative is to use devices such as vacutainers that allow direct inoculation of blood into culture bottles. Disinfection of the septum of BC bottles, usually with 70% isopropyl alcohol, is recommended.(24) Iodine containing solutions should not be used due to the risk of erosion of the rubber stopper.(24)

Blood culture diversion devices divert the initial portion of blood (0.15ml – 1ml), which may contain skin contaminants, into a separate chamber before switching to blood collection bottles.(33) A recent systematic review and meta-analysis showed their use in adults was associated with decreased contamination rates OR = 0.26 (0.13 -0.54), without affecting the detection of true infection OR = 0.85 (0.65 -1.11). (34) To date there are no studies showing benefit in children, and in a setting where obtaining adequate volumes of blood may be difficult, diversion may not be practical. (35)

Apart from specialized diversion devices, diversion can be achieved by simply discarding the initial blood, or potentially harvesting it in a collection tube suitable for any other test request. Traditional guidelines for BC have always stipulated that culture should be collected first to minimise contamination when using the traditional needle and syringe method. Recent authors have queried this assumption since the use of modern closed vacutainer systems means that it is possible for blood for culture to be sampled after an initial diverting blood specimen, provided that the cap of the first tube is sterile.

Additional measures that have been shown in some settings to reduce contamination include the collection of blood by phlebotomists, the use of sterile gloves, the provision of sterile packs, surveillance and feedback, multi-disciplinary performance improvement measures (including education, training and feedback usually with a quality improvement approach) and the use of consensus recommendations for BC use in children.(36)

Analytical phase

The analytical phase covers the laboratory analysis of paediatric BCs (Figure 1).

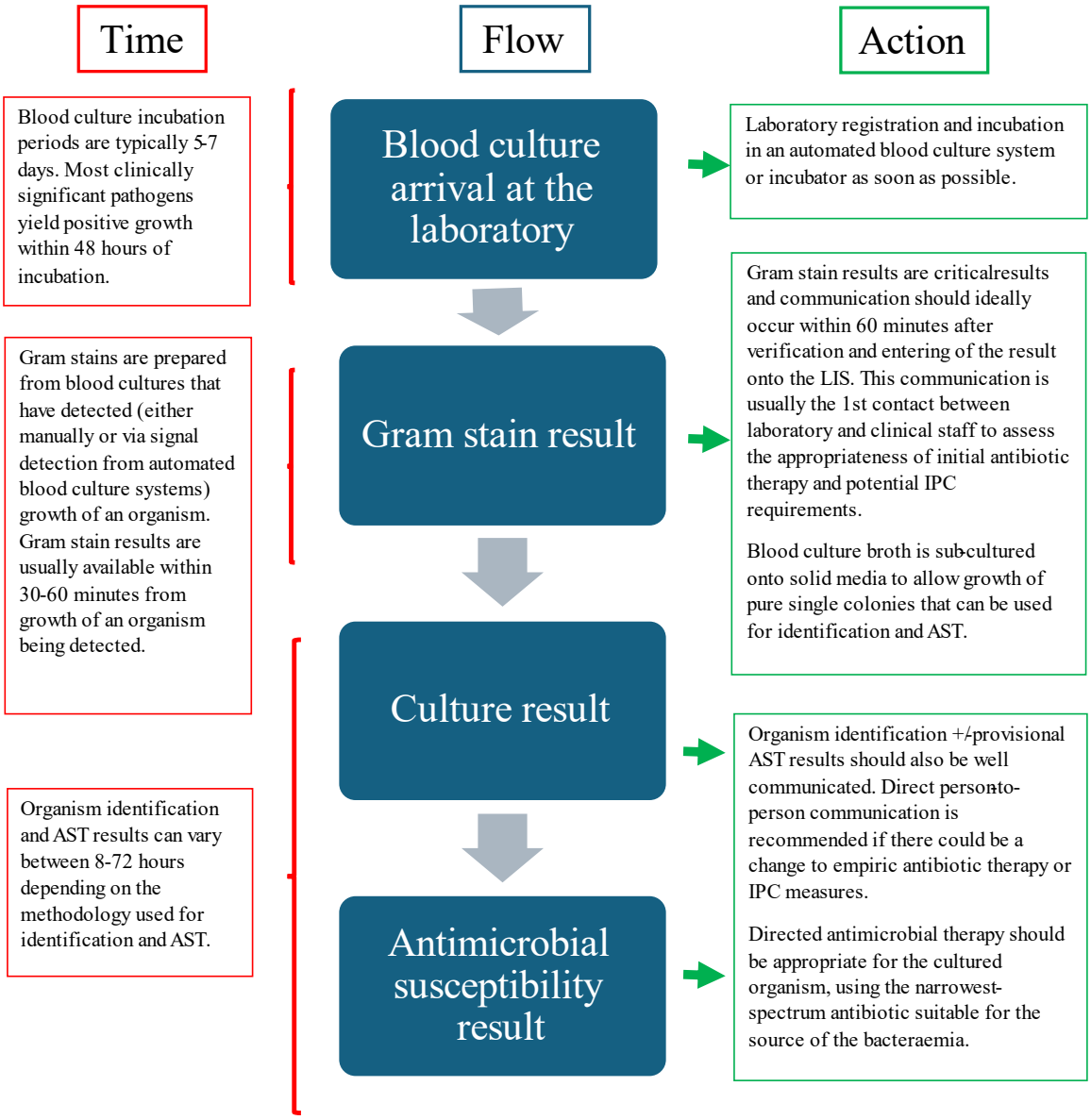

Figure 1: Flowchart showing laboratory processes involved for positive blood culture, including timeline and required actions

Blood culture systems

Automated continuous monitoring BC systems have become the standard of care in high-income countries (HICs) worldwide. These systems incubate and agitate BC bottles whilst monitoring

continuously and non-invasively for bacterial growth, by detecting carbon dioxide produced by growing bacteria.(37) Algorithmic interpretation of these measurements translates into early recognition of growth and the system then signals or 'flags' the potential positive bottle. (2, 26, 37) Commonly used automated systems include BD BACTEC (Becton Dickinson, East Rutherford, NJ, USA) and BacT/ALERT® 3D Microbial Detection System or BacT/ALERT® VIRTUO™ Microbial Detection System (both bioMérieux, Marcy l'Etoile, France). (2)

The latest, but more expensive BacT/ALERT® Virtuo system offers automated loading of bottles, more stable temperature regulation and improved detection algorithms that together result in increased sensitivity and shorter time-to-detection of growth. (37, 38) In addition, the ability to monitor blood volume levels in the BC bottle is useful though unfortunately to date this does not apply to paediatric BC bottles.

Automated BC systems may not be feasible in many LMICs as they are expensive and require reliable electricity supply and regular maintenance. (26) Manual BC systems are frequently used in these settings. Manual BC systems incubate BC bottles in standard incubators and rely on once or twice daily visual inspection for detection of bacterial growth. A variety of different systems using liquid broth +/- solid media are in use. (26)

Due to the difficulties with visual detection blind sub-culturing of apparently normal-appearing BC broth onto solid agar is recommended. However, sub-culturing risks introducing contamination as well as increasing needlestick injuries and workload.(5, 26) The timing of blind subcultures is debatable and involves balancing the need for early detection of growth versus the risk of false negatives if performed too early. (5, 39) Terminal sub-culturing at the end of the incubation period is not routinely recommended, but may be useful in certain situations, e.g. in immunocompromised patients where difficult to detect organisms such as *Pseudomonas aeruginosa* and yeasts might be expected(26)

The disadvantages of manual systems include longer time-to-detection of growth, decreased sensitivity, and increased workload.(26, 37) There has been a dearth of research on manual BC systems for the past 3- 4 decades since the development of automated systems, though this may be changing now. For example, a recent *in vitro* study using spiked BCs suggested that biphasic media, which had previously been considered advantageous in manual systems, demonstrated slower growth than broth media.(40) The yield of the broth media in the manual system was similar to that in the automated system, though the time-to-detection was longer even with blind subcultures at 24 hours. (40) Research is ongoing into new more sensitive methods to detect growth in manual systems as well as other potential improvements.(41)

Composition of blood culture broth

Most modern BC broth formulations for both automated and manual systems contain a base of soybean casein digest (trypticase soy broth) to support bacterial growth, together with an anticoagulant, sodium polyanethol sulfonate (SPS), which greatly reduces the time-to-detection for many micro-organisms.(26, 42) Antimicrobial-binding resins or charcoal may also be added. Modifications for paediatric BC bottles include decreased volume and modified media formulation, and lower SPS concentrations.(37)

Transport to the laboratory and time to incubation

Delayed entry of BC bottles into automated BC systems may negatively impact culture yield since bacteria may have transited the exponential growth phase and entered the stationary phase which is more difficult to detect. Generally, a maximum delay of 2- 4 hrs between inoculation of the BC bottle and incubation is recommended.(5) In a simulated model, a delay of more than 8 hours significantly decreased the culture yield in paediatric patients.(43) Prolonged delays of > 24 hrs are associated with decreased yields and prolonged time-to-detection in both automated and manual BC systems. (44) BacT/Alert BC bottles may be advantageous in situations where delays are expected as the

colorimetric growth indicator at the bottom of the bottle can detect growth prior to incubation and prompt immediate subculture. (44, 45)It is usually recommended that inoculated BC bottles should be kept at ambient temperature during transit. However, in certain LMICs environmental temperatures can be extreme and can exacerbate the negative impact of prolonged time to incubation. In these settings measures to protect BC bottles during transit e.g. cool boxes should be considered.(44) Manual BCs can be pre-incubated at 35° C if time to incubation is likely to be prolonged, but this is not recommended for automated bottles.(26)

Duration of incubation

The usual duration of incubation is 5 days for automated systems and 7 days for manual systems even for fastidious organisms such as the HACEK group. However, more than 90% of positive BCs show growth within 48 hours of incubation and the yield during the last two days of incubation is low and often of limited clinical value as many are contaminants.(6, 26, 46, 47)

Identification and antimicrobial susceptibility testing

Once growth is detected an aliquot of BC broth is withdrawn for Gram stain microscopy to confirm the presence and basic morphology of bacteria present. Thereafter traditional laboratory practice involves subculturing positive BC bottles onto solid agar media to generate pure colonies for subsequent identification and susceptibility testing. Consequently, it can easily take 48 hours or more to generate a final result (Figure 2).

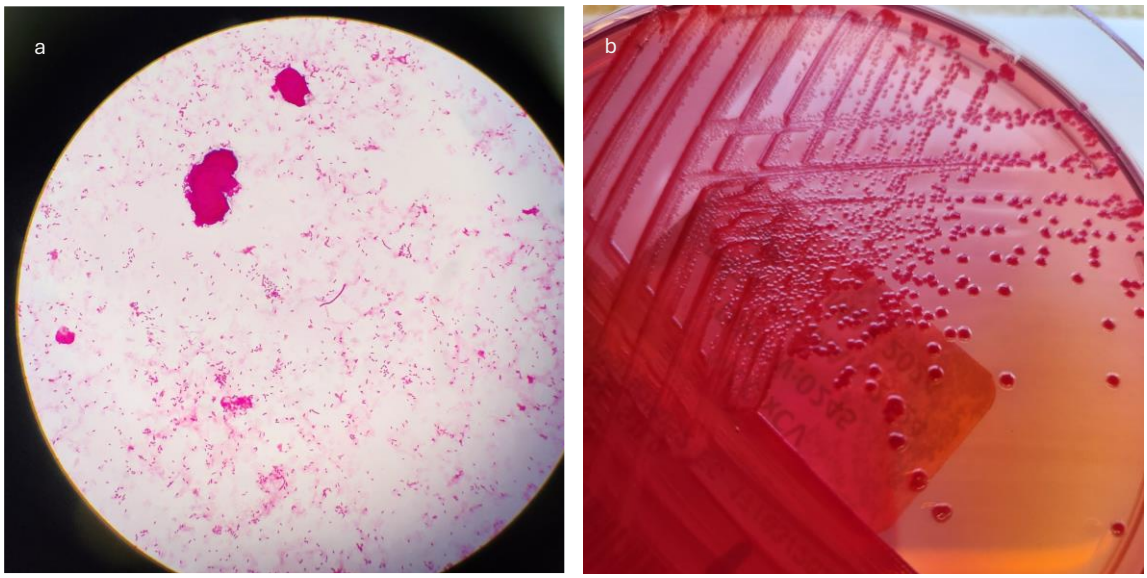

Figure 2. (a) Gram stain microscopy of Gram-negative bacilli in a positive blood culture. 100X magnification; (b) Subculture from a positive blood culture bottle showing growth of lactose fermenting Gram-negative bacilli on MacConkey agar after incubation for approximately 18 hours.

Performing identification and/or antibiotic susceptibility testing directly from BC broth can lead to faster diagnosis and decision-making. Over the years laboratories have developed in-house methods of direct inoculation into a variety of identification systems, both manual and automated, and onto agar for disc diffusion susceptibility testing, particularly for GN mono-microbial cultures.(48) However, the exact methods are not standardised and susceptibility results still necessitate an 8 to 24-hour delay.

More recently matrix-assisted laser desorption/ionization—time-of-flight (MALDITOF) testing has been widely introduced in HICs for identifying pathogens directly from BC broth or perhaps more commonly from a sub-cultured agar plate after a short 4–8-hour period of incubation.(11)

Standardised methods of rapid disc diffusion testing directly from positive BC bottles have also been developed and validated by both the Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).(49, 50) EUCAST provides breakpoints that are species and time-specific for reading at 4, 6 or 8 hours (and also after 16-20 hours incubation), whereas CLSI generally applies standard species breakpoints to reading at 8-10 hours and also at 16-18 hours). (51, 52)These methods can be implemented in routine microbiology laboratories without requiring major investment in new equipment and consumables. Potential drawbacks are that currently rapid reading breakpoints are only available for a limited number of organism-antibiotic combinations, and the method is labour-intensive unless automated plate readers are available.

Given the limitations of genotypic susceptibility testing e.g. variable expression of detected resistance genes, failure to detect novel resistance mechanisms, and the lack of a comprehensive antibiotic profile, there has been renewed interest in phenotypic susceptibility testing and the development of novel mechanisms for the rapid detection of bacterial growth directly from positive BCs. Two examples recently introduced into practice are the Accelerate PhenoTestBC kit and the Vitek ®Reveal TM system, both of which appear to have excellent accuracy and performance, and other novel phenotypic systems are likely to follow. (53, 54)

Molecular identification of pathogens directly from blood can provide rapid identification, as well as detection of selected important resistance determinants. Two approaches are possible, one using rapid nucleic acid amplification testing (NAAT) and one using next-generation sequencing (NGS) . (55) Rapid NAAT e.g. using multiplex polymerase chain reaction (PCR) technology can detect a specific set of target organisms/resistance determinants with a short 1- 3-hour turn-around-time (TAT). The use of rapid NAATs for identification and susceptibility results from positive BCs has been shown to decrease mortality by up to 34%.(56) NGS is unbiased in that it can detect all organisms and resistance genes and may overcome the limited sensitivity of low-volume paediatric BCs. However, NGS is less accessible as it requires more specialised equipment, and suitably trained staff and generally has a longer TAT of 12-48 hrs. Numerous potential NAAT and NGS systems are in varying stages of development and implementation with a recent review stating that “we are on the cusp of a revolution in the detection of pathogens causing bloodstream infections”.(55) Various technical challenges remain and there are still many difficulties in the interpretation of results, particularly for culture-negative/molecular test-positive samples. For LMIC the high costs and need for skilled staff are an additional barrier to implementation.

Post-analytical phase

The post-analytical phase involves reporting and interpretation of positive BCs (Figure 1).

Preliminary reporting of Gram stain results

Positive BCs are defined as critical or significant-risk results indicating life-threatening or life-altering results that need timely clinical management.(57) The Gram stain is the first step in the analysis of positive BCs.(37) It is a rapid and simple way to broadly characterise organisms before identification and susceptibility testing. Communicating the Gram stain result is usually the first point of contact between laboratory and clinical staff, where the appropriateness of initial antimicrobial therapy, based on clinical presentation and the Gram stain result, can be determined.(58, 59)

Furthermore, when these results are also communicated to multi-disciplinary antimicrobial stewardship teams, it positively impacts patient management by earlier initiation of effective antimicrobials.(60) Delays in reporting this result has been associated with increased mortality.(58) Ideally communication should be via direct person-to-person communication to a clinician with the authority to treat the patient (either telephonically, physically, or via text with confirmation of receipt) and occurring within 60 minutes of the result being verified and urgently entered onto the laboratory

information system (LIS). (57, 61) However due to unique challenges in different environments, the type and timeliness of communication should be agreed on by clinical and laboratory staff specifically reflecting the clinical needs of the environment and patient populations served e.g. clinical needs of patients in intensive care are different to those in outpatient facilities.(57) Often it is not always practical or feasible to communicate directly with treating clinicians, and in many circumstances intermediate clinical staff (e.g. nurses) are used to relay results to responsible clinicians – once again, timeliness and efficiency of communication needs to be maintained.(57) In settings where there is inadequate staff to facilitate timeous communication of all results, further prioritisation of urgent results may be required.

Reporting of time-to-positivity

Time-to-positivity, defined as the time from the start of incubation to a detectable positive signal in a continuous monitoring BC system, is a surrogate marker for bacterial biomass, which is dependent on the bacterial load and growth rate i.e. the shorter the TTP, the higher the bacterial load and growth rate. (62) TTP can be influenced by the volume of blood inoculated, the type of BC broth used, incubation conditions, transportation time to the laboratory and antibiotic therapy, and should therefore be interpreted with caution

Nevertheless, TTP has been used as a prognostication tool to identify patients at risk of severe disease and poorer outcomes. Conversely lack of growth at 48 hours can be used a potential antimicrobial stewardship tool allowing for early stopping or de-escalation of antibiotics.(62, 63) A differential TTP of ≥ 2 hours between simultaneously collected peripheral and central-line BCs is suggestive of catheter-related bacteraemia although recent studies show poor performance of this method. (64)

Reporting of Identification and Antimicrobial Susceptibility Testing (AST) results

Although Gram stain results mostly correlate with culture identification results,(65) antimicrobial susceptibility testing results will still be required as antimicrobial susceptibility is less predictable in the current era of increasing antimicrobial resistance. Organism identification and/or antimicrobial susceptibility results also need to be well-communicated. Written communication via the LIS is sufficient provided that the results from subsequent testing are not significantly different from that communicated initially and do not alter patient management.(57) However, given the approximate nature of empirical antibiotic therapy, directed therapy can often be narrowed for sensitive organisms, or may need to be escalated for resistant organisms, warranting direct person-to-person communication.

Laboratories may implement either or both selective or cascade reporting of antimicrobial agents as an antimicrobial stewardship strategy.(57, 61) Selective reporting reports antimicrobial agents based on criteria unrelated to AST results, e.g. based on the anatomical site of infection, clinical setting or patient demographics.(57) For example, selective reporting includes suppression of nitrofurantoin for bloodstream infections, as nitrofurantoin is only effective for the treatment of cystitis. Cascade reporting reports antimicrobial agents based on the antimicrobial resistance of the organism, with broader-spectrum antimicrobials only reported if there is resistance to narrower-spectrum antimicrobials,(57) e.g., inhibition of carbapenem results for Enterobacterales susceptible to third-generation cephalosporins. It was predicated that by suppressing certain AST results, those antimicrobial agents were less likely to be used.(57) This has been demonstrated in antimicrobial stewardship studies involving both bloodstream-related and non-bloodstream-related infections.(66, 67) Furthermore, any relevant interpretative or management comments can be added to the report, though the benefit has not been extensively studied despite widespread use.

Management of contaminants

Based on organism morphology, the microbiology laboratory may suspect the organisms growing in a particular BC to be contaminants, e.g. small Gram-positive bacilli from a single BC taken from a child > 1 month of age who is not in the ICU nor oncology ward are usually *Corynebacteria* or diphtheroids derived from the skin. To improve efficiency laboratories may develop a policy to limit the further testing of suspected contaminants, e.g. coagulase-negative staphylococci may be reported as such

without speciation and without susceptibility testing with the proviso that clinicians always have the possibility to request further testing if clinically indicated.

Ideally categorisation of isolates as contaminants requires ongoing communication with clinicians. This is particularly important for isolates that are not initially recognised as contaminants, e.g. environmental GNB. Such organisms may be difficult to identify, and a final result may only be available after a number of days. Preliminary results should be communicated at least daily on an ongoing basis, and should also highlight excluded organisms, e.g. Gram-negative bacilli, NOT Enterobacterales nor *Pseudomonas aeruginosa*. Such reports can allow clinicians to streamline antimicrobial therapy early in many cases based on clinical assessment. Since the majority of African laboratories do not currently have an attending microbiologist, clinicians may need to take responsibility for these discussions, as laboratory staff may be reluctant to act beyond their perceived scope of practice or standard operating procedures.

Reporting for Infection prevention and control

Provisional identification and susceptibility results of organisms (e.g. *Neisseria meningitidis*, *Salmonella typhi,* or Carbapenem-resistant Enterobacterales) that pose a threat to other people within the hospital, or the community should also be communicated as critical or significant-risk results. This is to ensure prompt infection prevention control measures such as transmission-based precautions are immediately implemented. In the case of outbreaks or organisms capable of causing outbreaks, the department of public health should be informed as a public health outbreak response may also need to be triggered based on these results.

Microbiologistics for all three phases

A new term microbiologistics has been coined in recent years that covers all possible improvements in the logistic chain from sampling to reporting.(11) A key component is embracing a 24/7 approach to the handling of BCs. Improvements in the pre-analytical phase include fast transport of bottles to the laboratory as well as ensuring that bottles can be loaded promptly into BC incubators at all times of the day and night. For the analytical phase rearrangement of the laboratory shifts and workflow may be needed to ensure that all stages of BC analysis happen promptly on a continuous basis without delays due to batching or bottlenecks. For example, many laboratories only report on growth and susceptibility results in the mornings. Plates put up in the afternoon or evening are then either read too early the following morning or are delayed an additional 24 hrs. In the post-analytic phase prompt reporting should also happen on a 24/7 basis. Microbiologistics complements other improvements in handling of BCs and may improve the time to results independently of the adoption of any rapid laboratory methods.

Conclusion

Blood cultures are invaluable in paediatrics. Settings in Africa may differ from established norms in HICs, due to variable availability of equipment, expertise, and other resources. This review discusses key factors related to paediatric BC testing and summarises recommendations for best practise (Table 2).

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Table 2: Summary of recommendations for the three phases of blood culture testing

Pre-analytical phase	Analytical phase	Post-analytical phase
Collect at least the minimum recommended volume of blood according to weight or age-based guidelines. Depending on the clinical circumstances try to obtain larger volumes, up to the maximum volume recommended, especially in older (> 5 years) or larger (more than 20 kg) children.	Automated continuous monitoring BC systems remain the reference standard in the paediatric population.	Ensure rapid communication of both initial Gram stain and subsequent identification and AST results to attending clinician.
Consider formally implementing one of the simpler weight or age-based guidelines that suits your setting e.g. the 1 + 1 ml/year guideline or the simpler 5 kg weight categories.	Manual blood culture systems which may be more practical in LMICs require a longer time for detection of growth, even with a policy of routine subculturing on day 1. However, the sensitivity of manual systems may be comparable with automated systems.	Link communication with clinical and antimicrobial stewardship advice whether this is through infectious diseases specialists/clinical microbiologists/antimicrobial stewardship teams.
Collect the total volume required via a single sterile peripheral venipuncture. Collection via indwelling vascular catheters is preferred in some ICUs and oncology settings.	Paediatric blood culture bottles contain media modified to improve culture yield in this population.	Use different reporting strategies to enhance optimal treatment of bloodstream infections.
Inoculate the correct volumes into paediatric or standard aerobic blood culture bottles. The number and type of bottle selected will be based on the amount of blood available for culture and the clinical indication.	The recommended duration of incubation is 5 and 7 days for automated and manual systems respectively. Most clinically significant organisms show growth within 48 hours of incubation.	Critically assess clinical significance of unusual organisms
Take blood cultures as soon as possible and preferably before administration of antibiotics. Transport the blood culture to the laboratory as quickly as possible.	Rapid methods for identification and susceptibility testing directly from positive bottles are recommended.	Implement infection prevention and control measures and/or inform department of public health for relevant communicable pathogens.
Use an alcohol-based skin antiseptic, preferably with 2% chlorhexidine (except in preterm infants < 32 weeks gestation), together with aseptic technique during blood culture collection.		
Microbiologistics Incorporate Microbiologistics to improve the entire logistic chain, with a focus on a 24/7 approach to blood cultures.		

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