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REVIEW

Blood cultures in Paediatrics: Clinical indications to obtain a blood culture

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Abstract

Globally there is no consensus on the ideal set of indications for obtaining a blood culture in paediatric and neonatal practice. In sub-Saharan Africa, where paediatric sepsis is associated with worse outcomes than other regions, early and accurate detection of bacteraemia is particularly important. However, use of blood culture in sub-Saharan Africa is complicated by resource limitation, variable availability of microbiological laboratory services, and prevalence of coinfections such as malaria, tuberculosis and HIV. Additional factors, such as different vaccination profiles and disease severity at presentation, limit generalisability of approaches developed for use in high-income countries. We review the literature on clinical indications for blood cultures in paediatric and neonatal practice, including current practices from sub-Saharan Africa and low-middle income countries, and propose a simple, practical set of clinical indications for blood culture in paediatric and neonatal practice in this setting.

Introduction

Sepsis incidence and mortality are greatest in neonatal and paediatric populations.(1) Despite ongoing improvements in quality of care, mortality rates for children and neonates with severe sepsis remain high, ranging from 9-25% globally.(1,2) Mortality associated with paediatric bacteraemia is reported to be much greater in sub-Saharan Africa,(3–5) even in regions in which there is access to a paediatric intensive care unit. (2,6,7) Early detection of sepsis in these at-risk populations is a priority.(8,9) Although biomarker and molecular approaches have emerged as key tools for detection of sepsis in high-income settings,(10–13) blood culture remains the gold standard for confirmation of bloodstream infection.(14–16) Unfortunately, in sub-Saharan Africa blood culture may not always be unavailable as a diagnostic modality.(17)

Clinical approaches to blood culture sampling

There is no consensus on the optimal set of indications for obtaining a blood culture in paediatric and neonatal practice. The epidemiology of neonatal and paediatric bloodstream infections has shifted considerably over the past few decades - in part due to changing characteristics of pathogens (e.g. emerging pathogens, antimicrobial resistance), patient populations (e.g. vaccination status, improved survival of immunocompromised patients), and increased access to and use of medical therapies (e.g. broad-spectrum antibiotics, chemotherapeutic agents, central vascular catheters). (15,18,19) This epidemiological shift has further complicated clinicians' decisions about when to obtain a blood culture. (17)

The Surviving Sepsis Campaign guideline recommends obtaining blood cultures in all children with suspected sepsis prior to administration of antimicrobial therapy, provided this does not substantially delay therapy.(9) No studies have assessed the direct impact of blood culture on paediatric sepsis outcomes, however multiple observational studies have demonstrated that a bundled approach to resuscitation that includes obtaining an early blood culture is associated with improved survival.(9,20–22)

Theoretically, any localised infection may disseminate to the bloodstream and can result in sepsis if left untreated. The most common sites of primary infection resulting in bacteraemia in children are the respiratory tract and sites of vascular cannulation, followed by the urinary tract and the peritoneal cavity.(2,23) There may additionally be no identifiable source of infection in 11-34% of bacteraemia cases, particularly in neonates and young infants, highlighting the need for blood cultures to be performed appropriately in this vulnerable population in order to diagnose and treat bacteraemia correctly.(24–26)

One rational approach to guide the suitability of blood culture sampling is to consider the pre-test probability of bacteraemia for a specific focal infection. Adult-based data on the bacteraemia risk associated with different clinical scenarios is available and illustrated in Table 1, however comparative paediatric data is limited.

Table 1. Pre-test probability of bacteraemia in common clinical syndromes in adults (27)

Bacteraemia risk **<10%**	Bacteraemia risk **10-20%**	Bacteraemia risk **20-50%**	Bacteraemia risk **>50%**
Uncomplicated Cellulitis Lower Urinary tract infection Pneumonia (Community-acquired and Healthcare associated)	Cellulitis in patients with severe comorbidities Ventilator associated pneumonia	Severe sepsis Rigors Pyelonephritis Cholangitis Pyogenic liver abscess Severe community-acquired pneumonia Non-vascular shunt infections	Septic shock Meningitis, epidural abscess Catheter-associated bloodstream infection Ventriculo-atrial shunt infection Septic arthritis, discitis, vertebral osteitis

Paediatric practice

A recent paediatric practice guideline strongly recommends performing blood cultures in the setting of clinically suspected sepsis or focal infections with a risk of bacteraemia >10%.(15) These include bacterial meningitis, infective endocarditis, septic arthritis, osteomyelitis, severe or complicated pneumonia (e.g. necrotising or cavitating pneumonia, lung abscess, empyema), deep soft tissue infections (e.g. pyomyositis, necrotising fasciitis) and complicated superficial soft tissue infections (e.g. following trauma, burns, surgery, or presence of prosthetic material), UTI in an infant <3 months old, and infections in patients with underlying risk factors (e.g. immunocompromised patients, patients with intravascular catheters). Blood culture is also recommended in cases of pyrexia of unknown origin associated with a >1.5% risk of occult bacteraemia, such as in infants <3 months old with a febrile illness necessitating hospitalisation. This guideline was developed for use in a high-income setting in Europe, potentially limiting the generalisability of its recommendations in less-resourced settings.

Notably, few guidelines have addressed blood culture indications in sub-Saharan Africa, where resource limitation, prevalence of coinfections (e.g. malaria, tuberculosis, HIV), vaccination profile, and disease severity at presentation may warrant a different approach to blood culture sampling. Simpler, more practical criteria for blood culture in both children and adults in LMICs have been proposed and summarised in Table 2, based on adaptations of predictive models for bacteraemia.(29,30)

Table 2. Proposed indications for blood culture in LMICs (28)

A	Temperature instability (axillary T◦ ≥ 38◦C or ≤ 36◦C) OR history of fever (last 48 h)
AND any one of the following:	
B	Organ dysfunction (e.g. hypotension; confusion; tachypnoea)
C	Severe focal infection (e.g. pneumonia; meningitis; osteomyelitis; complicated UTI; soft tissue infection; intra-abdominal infection)
D	Suspicion of other severe infection (e.g. severe malaria; typhoid fever; endocarditis)

Additionally, recommendations for blood culture collection in children with pneumonia have evolved. Previous international guidelines routinely recommended obtaining blood cultures in hospitalised children with community-acquired pneumonia (31); however, the rate of a positive blood culture in community-acquired pneumonia is only approximately 5%, and the blood culture result seldom influences management.(32) The yield of a positive relevant result is significantly higher when a blood culture is selectively performed in cases of severe or complicated pneumonia (14-20%) (33) and in HIV-infected children with community-acquired pneumonia (14%).(34) Current pneumonia guidelines recommend more selective use of blood culture.(35,36) Local guidelines published in South Africa and Nigeria recommend blood culture for children with community-acquired pneumonia who require intensive care unit admission, and in hospitalised children with pneumonia and poor response to initial antibiotic therapy (37,38), as well as for all cases of hospital-acquired and ventilator-associated pneumonia.(39,40)

Furthermore, institutions may have developed their own in-house indications for blood culture collection. One such example is a guideline that was developed for use within a South African tertiary hospital that recommended blood culture collection at a lower threshold (e.g. fever without source, focal infections usually associated with low risk of bacteraemia) in immunocompromised patients, such as children with HIV infection, severe acute malnutrition, malignancy, primary immunodeficiency, and children on immunosuppressive therapy where the risk of morbidity and mortality in untreated infection is higher.(41)

Neonatal practice

In neonatal practice, nonspecific presentation of sepsis is combined with a high risk of severe sequelae and death, resulting in a lower threshold for blood culture and empiric antimicrobial therapy. The World Health Organisation recommends that blood culture should be routinely performed prior to starting antibiotic therapy in neonatal practice, where possible.(42) Although few studies have addressed blood culture sampling in neonatal practice, there is a significant body of literature outlining indications for empiric antibiotic therapy in neonatal practice.(42–45) In young neonates (age <72 hours), empiric antibiotic therapy is recommended based on the existence of relevant risk factors, whether or not the neonate manifests clinical signs associated with sepsis. Risk factors for early-onset sepsis are chorioamnionitis, intrapartum maternal fever, maternal group B streptococcal colonisation, prematurity, low birth weight, prolonged rupture of membranes, and low APGAR scores. In older

neonates (age >72 hours), empiric antibiotic therapy is recommended for neonates with clinical signs associated with sepsis, particularly when there are co-existing relevant risk factors for late-onset sepsis (e.g. prematurity, prolonged hospital admission, use of a central venous catheter, mechanical ventilation, prolonged administration of antibiotic therapy or total parenteral nutrition).

Neonatal sepsis presents with non-specific clinical signs, which can be identical to features of non-infective disease entities, such as hyaline membrane disease, necrotising enterocolitis, and apnoea of prematurity.(46) One large multicentre prospective cohort study in Belgium reported correlations between confirmed bacteraemia and different clinical signs that prompted blood culture sampling.(47) Impaired peripheral perfusion, lethargy, and feeding intolerance were strongly associated with bacteraemia, whereas other features (e.g. fever, increasing oxygen demand, hyperglycaemia, oliguria, acidosis, and CRP>20) were not independently significant, although still potentially relevant given the non-specificity of clinical signs for infection in this population. Although a number of studies have reported pathogen prevalence and resistance patterns in neonatal units across sub-Saharan Africa (48–54), few have included clinical data or indications for blood culture. Respiratory distress, feeding intolerance, lethargy, convulsion, and fever were reported to be most associated with confirmed bacteraemia in two retrospective reviews conducted at large neonatal units in Tanzania and Nigeria.(55,56) These features are consistent with a prospective review that identified clinical danger signs for severe neonatal illness, including sepsis, at multiple sites across six LMICs.(57) The rate of blood culture positivity is also described to be greater in neonates with specific risk factors (e.g. central vascular access, mechanical ventilation, total parenteral nutrition), suggesting that a lower threshold for blood culture sampling may be appropriate in these patients. (47)

Summary

Although there is no consensus on the optimal set of indications for obtaining a blood culture in paediatric and neonatal practice, the literature supports obtaining a blood culture in the following scenarios:

Children with:

- Focal infection associated with a significant bacteraemia risk
  (e.g. meningitis, endocarditis, septic shock)
- Suspected infection associated with organ dysfunction
  (e.g. haemodynamic instability, respiratory failure, altered mental state, acute kidney injury)
- Suspected infection and a background of immunosuppression
  (e.g. neutropenia, advanced HIV infection, complicated severe acute malnutrition)
- New-onset infection and a risk factor for bacteraemia
  (e.g. central venous access, mechanical ventilation)

Neonates with:

- Risk factors for early-onset sepsis
  (e.g. invasive maternal infection, maternal GBS colonisation, prolonged rupture of membranes)
- Clinical features associated with sepsis, particularly if there are associated risk factors for infection
  (e.g. fever, respiratory distress, feeding intolerance, seizures)

Furthermore, blood culture should also be obtained based on clinical discretion, such as diagnostic uncertainty, fever of unknown origin and suspected hospital-acquired infections.

Although the majority of the world's children and their families live in less resourced countries, current recommendations for obtaining blood cultures in paediatric practice have been developed for use in high-resource settings. Further research is needed to describe current practices in obtaining blood cultures in paediatric practice in sub-Saharan Africa, and to define the distribution of microbiological laboratory services in the region. It would be beneficial to develop a consensus guideline with appropriate recommendations for use of blood cultures in paediatric practice in sub-Saharan Africa. We recommend formulation of a consensus guideline by a focus group of experienced clinicians and experts in paediatric infectious diseases from sub-Saharan Africa, using the Delphi technique and critical appraisal of existing evidence.

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