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Original Research Article

Narrative Review and Diagnostic Performance Assessment of Paired Blood Cultures in Children with Cancer and Febrile Neutropenia: An Analysis of Four Studies

Aida Correia de Azevedo[1,2*], Tereza Oliva[2], Ana Maia Ferreira[2], Cristiana Couto[2]

[1]Department of Paediatrics, Médio Ave Hospital Centre, Vila Nova de Famalicão, Portugal
[2]Department of Paediatrics, Portuguese Institute of Oncology, Porto, Portugal

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Abstract: Children receiving cancer treatment face a heightened risk of bloodstream infections, posing challenges in care. Accurate diagnosis is crucial, and paired blood cultures (BC) from central venous catheter (CVC) and peripheral vein (PV) are a promising diagnostic approach. This review assesses the diagnostic accuracy and clinical utility of pediatric paired BC in children with cancer. A PubMed search (2003-2023) yielded 1042 titles; four articles meeting inclusion criteria were included. Studies on diagnostic accuracy or clinical utility of pediatric paired BC in ages 0-18 were reviewed by two independent assessors. Data extraction covered study characteristics, demographics, and diagnostic parameters. Observing 825 positive paired BC with a 23.5% false-positive rate, PV exclusively detected bacteremia in 22.7%, while CVC culture exclusively detected it in 54.7%. Both methods detected bacteremia in 54.0%. Variable sensitivity, specificity, PPV, and NPV across studies necessitate nuanced interpretation. PV showed higher sensitivity, while CVC exhibited higher specificity. Method choice should align with clinical context, urgency, and potential consequences. False positives, particularly with CVC, underscore the need for cautious clinical decision-making. Personalized approaches balancing clinical and diagnostic considerations are essential. Collecting paired samples aids in avoiding false positives, reducing unnecessary interventions, but may involve causing pain.

Keywords: Bacteremia; central venous catheter blood culture; febrile neutropenia; paediatric cancer; paired blood cultures; peripheral vein blood culture; sepsis.

INTRODUCTION

Children undergoing cancer treatment are frequently confronted with heightened vulnerability to bloodstream infections, presenting a formidable hurdle in their care management [1-4]. The precise and prompt diagnosis of these infections holds paramount importance, serving as a linchpin for steering tailored therapeutic interventions and enhancing overall outcomes. In response to this imperative need, paired blood cultures (BC) have surfaced as a promising diagnostic approach. This method involves collecting two distinct blood samples from disparate sites—the central venous catheter (CVC) and peripheral vein (PV) [1-4].

Against this backdrop, our review aims to undertake a thorough examination of the diagnostic accuracy and clinical utility of paediatric paired BC, with a specific focus on children undergoing cancer treatment.

MATERIALS AND METHODS

Search Strategy:

We conducted a literature search on PubMed to identify relevant articles published from 2003 up to 2023. The following keywords and MeSH terms were used: <paired blood culture>, <children>, <pediatric cancer>, <febrile neutropenia> and <bacteraemia>. Additionally, a thorough search of the selected articles bibliography was done in order to look for more articles.

***Corresponding Author:** Aida Correia de Azevedo
Department of Paediatrics, Médio Ave Hospital Centre, Vila Nova de Famalicão, Portugal

Inclusion Criteria:

- Studies published in English;
- Studies reporting on the diagnostic accuracy or clinical utility of pediatric paired blood cultures;
- Studies involving paediatric populations (age range [0-18]).

Exclusion Criteria:

- Studies with inadequate data on diagnostic accuracy or clinical utility;
- Case reports, reviews, or conference abstracts;
- Studies conducted in adult populations exclusively.

Study Selection:

Two independent reviewers screened the identified articles based on title and abstract for eligibility. Full-text articles were then assessed for inclusion according to the predefined criteria. Any discrepancies were resolved through discussion or consultation with a third reviewer.

Data Extraction:

Data extraction was performed independently by two reviewers using a standardized form. Extracted information included study characteristics, patient demographics, diagnostic accuracy parameters (sensitivity, specificity, positive predictive value, negative predictive value), and clinical utility outcomes.

RESULTS

We identified 1042 titles and abstracts through our search, and four complete articles were obtained for thorough examination. The principal features and specifics of the PV and CVC culture methods are outlined in table 1.

Table 1: Main characteristics and details of the PV and CVL culture techniques

	Definitions of bacteremia and contamination	**Number of paired cultures**	**Blood culture technique**		
			Timing between cultures	**Initial blood discard**	**Total volume cultured**
***Doganis 2013* [1]**	Bacteremia: if a recognized pathogen (such as *S. aureus*, Gram-negative *bacilli*, etc) was isolated from any source. In the case of possible contaminants (ex.: *S.* Coagulase-negative, etc), an episode of infection was classified as true blood stream infection if more than one BC from any source were positive for the same organism. If only one BC was positive and chills and/or hypotension were present, this episode was also classified as true-positive.	597	Within 2 hours apart	N/M	N/ M
***Burcham 2022* [2]**	True positive BC were defined if either the PV or CVC BC grew a microorganism known to be a pathogen causing invasive disease. Organisms that are commonly considered skin flora (Corynebacterium spp., coagulase-negative Staphylococcus, etc.) were considered contaminants and not analyzed with the true positive culture data, unless: the organism was isolated in both culture types at the same blood draw episode; or the organism was isolated from the same culture type on separate blood draws (typically within 24 hours).	190	At the same time	N/M	N/M
***Handrup 2015* [3]**	The pair of BC was regarded as true negative if both cultures were negative. If the same microorganism was found in cultures obtained from both the PV and the CVC, the pair of BC was regarded as true positive. If the result of the pair of cultures was discordant, a blood culture was regarded as true positive if: the patient had symptoms of sepsis and/or a localized site of infection; and a known pathogen was found. Microorganisms that are common skin contaminants were regarded as contaminants if they were cultured from a single BC from a patient without a known focal site of infection or clinical signs of sepsis.	654	Within 2 hours apart	First 5 mL	N/M
***Schheinemann 2010* [4]**	Positive blood cultures with common contaminants were considered true bloodstream infections if multiple cultures were positive for the same organism or if sepsis was present.	318	Within 24 hours	N/M	1-3 mL per BC bottle

N/M: Not mentioned N/C: Not calculable

We observed a total of 825 positive paired BC, with a false positive rate of 23.5% (n=194 cases). Out of the total positive BC, 22.7% (n=143) exclusively detected bacteremia through PV culture, while 54.7% (n=345) exclusively detected bacteremia through CVC culture. The proportion of bacteremia detected by both methods was 54.0% (n=341). Only two studies reported instances where both CVC and PV BC yielded negative results.

Table 2 illustrates the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each study (specificity and NPV were not calculated in two studies due to missing data, as mentioned above).

Table 2. Sensitivity, specificity, PPV, NPV and false-positives per study

	PV					**CVC**				
	Sens. (%)	**Spec. (%)**	**PPV**	**NPV**	**FP (n)**	**Sens. (%)**	**Spec. (%)**	**PPV**	**NPV**	**FP (n)**
Doganis 2013	93.9%	89.7%	57.5%	99.0%	5	83.0%	98.5%	94.8%	94.8%	26
Burcham 2022	89,9%	N/C	74,9%	N/C	14	85,4%	N/C	87,4%	N/C	25
Handrup 2015	90.0%	89.0%	53.3%	98.4%	9	79.9%	94.8%	80.9%	94.5%	31
Scheinemann 2010	76.1%	N/C	62.7%	N/C	45	81.6%	N/C	87.7%	N/C	45

Sens.: Sensitivity; Spec.: Specificity; FP: False-positive

DISCUSSION

The presented data offer insights into the diagnostic performance of blood cultures obtained via PV and CVC in children with cancer and febrile neutropenia, as reported in four studies.

Across the studies, BC from PV demonstrated consistently higher sensitivity than those from the CVC. For instance, Doganis *et al.*, (2013) reported a sensitivity of 93.9% for PV compared to 83.0% for CVC [1]. This suggests that, in the context of febrile neutropenia in pediatric cancer patients, PV may be more effective in identifying true positive cases, which is concordant with literature [1-4].

Specificity, on the other hand, showed an opposite trend. CVC-based cultures generally exhibited higher specificity compared to PV. This is evident in studies such as Doganis *et al.*, (2013) and Handrup *et al.*, (2015), where specificity for CVC was notably higher than for PV [1,3].

PPV represents the probability that a positive test result is correct. In most cases, CVC-based cultures showed higher PPV, indicating a higher likelihood that a positive result accurately reflects the presence of infection. NPV reflects the probability that a negative test result is correct. PV-based cultures consistently exhibited higher NPV, suggesting that a negative result from PV is more reliable in ruling out infection.

The number of false positives is an important consideration, especially in clinical settings where unnecessary interventions can have significant consequences. Notably, the number of false-positives for CVC was higher in most studies, implying a potential for overdiagnosis when using CVC-based cultures [1-3].

The observed variations in diagnostic performance between PV and CVC emphasize the importance of considering the clinical context and weighing the trade-offs associated with each sampling method. The choice between these methods should be carefully tailored to the clinical scenario, the urgency of diagnosis, and the potential consequences of false positives or negatives.

Limitations and Future Directions:

It is essential to acknowledge certain limitations in the interpretation of these findings. The limited number of studies and variations in reported metrics emphasize the need for additional research to establish a more comprehensive understanding of the diagnostic performance of PV and CVC-based BC in this specific patient population. Future studies should also address the gaps in specificity data, providing a more holistic view of the diagnostic landscape.

CONCLUSION

In conclusion, the presented data underscore the nuanced trade-offs between sensitivity and specificity in blood cultures obtained via PV and CVC in children with cancer and febrile neutropenia/ suspected sepsis. These findings contribute to the ongoing dialogue surrounding optimal diagnostic strategies in this vulnerable population, highlighting the need for personalized approaches informed by both clinical and diagnostic considerations.

Collecting a paired sample helps in avoiding false-positive results and subsequently reduces unnecessary interventions. On the other hand, obtaining a blood sample via peripheral venipuncture implies the need to cause pain and additional stress in an already suffering child. Thus, choosing to collect paired blood cultures for sepsis/bacteremia diagnosis is a balance between diagnostic accuracy and minimizing discomfort. Further research and larger-scale studies are warranted to refine our understanding and guide evidence-based clinical practices.

Conflicts of Interest: The authors have no conflicts of interest to declare

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