Jurnal Ilmiah Kesehatan Vol 17 (2) September 2025 p-ISSN: 2301-9255 e:ISSN: 2656-1190

Page: 117-146

Positive Blood Culture as a Marker of Sepsis and MODS Risk in Critically Ill Children: A Narrative Literature Review

Rafly Bayu Surya Wardhana[1], *Arina Setyaningtyas[2], Rebekah Juniati Setiabudi[3] Neurinda Permata Kusumastuti[4]

[1] Medical Programme, Universitas Airlangga, Surabaya, Indonesia
[2] Department of Pediatrics, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[3] Department of Medical Microbiology, Universitas Airlangga, Surabaya, Indonesia
[4] Department of Pediatrics, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Correspondence author: Arina Setyaningtyas, *arina-s@fk.unair.ac.id*, Surabaya, and Indonesia

DOI: 10.37012/jik.v17i2.3063

Abstract

Blood culture is an essential examination for establishing the diagnosis of bloodstream infection (BSI) in critically ill children, as it enables the detection of causative pathogens and guides appropriate antimicrobial therapy. This study aims to examine the association between positive blood culture results and disease severity in children admitted to the pediatric intensive care unit (PICU). A literature review was conducted by searching articles in PubMed, Google Scholar, NCBI, and ScienceDirect over the past 15 years, which were then selected based on topic relevance and methodological quality. Analysis of ten studies revealed that positive blood cultures were strongly associated with increased mortality, longer hospital stay, and a higher incidence of multiple organ dysfunction. Frequently reported risk factors included younger age, the use of central venous catheters, immunocompromised conditions, and infections caused by drug-resistant Gram-negative bacteria. Parameters such as time to positivity (TTP), procalcitonin levels, and organ dysfunction scores (PELOD-2) were identified as important prognostic indicators reflecting infection severity. Thus, a positive blood culture serves not only as a diagnostic tool but also as a crucial prognostic marker for risk stratification and clinical decision-making in critically ill children.

Keywords : Blood culture, Critically ill children, Pediatric sepsis, Time to positivity, Organ dysfunction

INTRODUCTION

Blood culture is the gold standard method for establishing the diagnosis of bloodstream infections (BSIs) in critically ill children, as it directly detects the presence of pathogens and guides timely antimicrobial therapy. The success of this examination is highly dependent on the quality of pre-analytic procedures from the timing and technique of collection to adequate sample volume in order to maximize sensitivity while minimizing contamination rates. In the era of automated culture systems, clinically significant positive results generally appear within 12–48 hours, with clinical attention often focused on time to positivity (TTP) as a reflection of microbial burden and host immune status. In the pediatric population within the pediatric intensive care unit (PICU), the median TTP has been reported to be approximately 13.3 hours, and shorter TTP is associated with immunosuppressive conditions and a higher likelihood of

severe infection. Commonly detected pathogens include Enterobacterales, *Staphylococcus aureus*, and various *Streptococcus* species, all of which are linked to significant morbidity. (Yasechko *et al.*, 2024) Diagnostic stewardship efforts emphasize the rationalization of culture requests through evidence-based protocols to balance sensitivity and specificity without triggering excessive testing. (Woods-Hill *et al.*, 2021, 2022)

Interpretation of positive results requires integrating microbiological data with clinical context distinguishing intermittent from continuous bacteremia and determining whether the isolate represents true infection or contamination. In critically ill children, most clinically significant positive cultures are detected early, with 95% of cases appearing within 36 hours, reinforcing the need for rapid and targeted antimicrobial decisions. Patterns of intravascular (e.g., endocarditis) and extravascular sources of infection, along with time to positivity and the number of positive bottles, assist in assessing prognosis and the need for further source evaluation. This distinction is crucial to avoid unnecessary therapy and minimize adverse effects as well as healthcare costs. (HK *et al.*, 2019; Yasechko *et al.*, 2024)

Clinically, the association between positive blood cultures and severe illness in children is reflected in systemic symptoms such as high and persistent fever, lethargy, feeding difficulties, and abdominal pain accompanied by abnormal vital signs like tachycardia and tachypnea. Inflammatory markers (CRP, procalcitonin) and leukocyte profiles (neutrophilia, lymphopenia) further strengthen risk assessment, while ancillary examinations such as urinalysis, lumbar puncture, and imaging are selected based on the suspected source of infection. At the population level, vaccination has reduced the incidence of classic bacteremia, yet vigilance remains essential in children who are incompletely immunized or immunocompromised. (Ogunkunle *et al.*, 2022; Guo *et al.*, 2023)

The impact of positive cultures on clinical outcomes is significant. Several pediatric studies have linked bacteremia with longer hospital stays, early organ dysfunction, and higher mortality compared to patients with negative cultures. On the other hand, certain evidence particularly in adult populations suggests that culture positivity is not always an independent predictor of mortality after adjusting for comorbidities and severity scores, highlighting the importance of assessing the patient's overall status, the timeliness of antibiotic administration, and host response. (Hazwani *et al.*, 2020; Paquette *et al.*, 2021; Meena *et al.*, 2025) In pediatric patients, multi-organ involvement in the context of sepsis characterized by respiratory, cardiovascular,

coagulation, and even neurological dysfunction further reinforces the relevance of positive cultures as a risk marker, in line with contemporary pediatric sepsis classification systems and definitions that emphasize organ dysfunction. (Morin *et al.*, 2022; Schlapbach, Goertz, *et al.*, 2024)

Pathophysiologically, the presence of pathogens in the circulation triggers the activation of PAMPs/DAMPs, endothelial dysfunction, perfusion disturbances, and ultimately microvascular thrombosis leading to multi-organ failure. The integration of biomarkers (procalcitonin, lactate), organ dysfunction scores (such as PELOD-2), and TTP dynamics enhances risk stratification and decision-making, particularly in situations involving resistant organisms or high microbial burden. A comprehensive approach combining standardized blood culture collection practices, context-based interpretation, and rapid, targeted therapy is essential to halt progression toward septic shock and reduce mortality in pediatric patients with positive blood cultures. (M. *et al.*, 2012; Carcillo *et al.*, 2017; Clemens *et al.*, 2024; He *et al.*, 2024)

METHODS

This study is a literature review using a narrative review approach. This method was employed to analyze various collections of literature relevant to the main topic of this research. The subjects of this study were prior research articles related to the title of this study. Literature sources were obtained through searches in databases including PubMed, Google Scholar, NCBI, and ResearchGate. The keywords used to identify primary studies were “blood culture” and “critically ill children.” Search equations were applied without restrictions, considering titles, abstracts, theories, and methodologies used. The articles included in this review were those related to positive blood cultures as a risk marker for sepsis and MODS in critically ill children. The inclusion criteria for selecting articles were: (1) publication range from 2013 to 2025 (the last 13 years); (2) articles written in English; (3) article themes relevant to the research topic; and (4) availability of complete and specific full text. Articles written in languages other than English, as well as reports and editorials, were excluded.

The search identified a total of 30,057 articles, consisting of 45 articles from PubMed, 25,100 from Google Scholar, 2,520 from NCBI, and 2,392 from ScienceDirect. A total of 17,510 duplicates were removed, leaving 12,547 articles. Subsequently, 8,612 articles were excluded

because they did not meet the inclusion criteria (13-year range), followed by the exclusion of 3,824 articles due to irrelevant titles. Twelve articles were removed due to incomplete text. A total of 99 articles were screened, yielding 33 articles that met the criteria. A critical appraisal was then conducted on these articles, resulting in 10 eligible studies. This research process followed the framework developed by Arksey and O'Malley, which consists of five essential stages: (1) clearly and objectively identifying the research question, (2) identifying relevant sources of studies, (3) selecting the obtained studies, (4) data extraction, literature collection, and aggregation, and (5) presenting the findings of the selected studies. (Bettany-Saltikov, 2018) From the 10 articles used in this review, data extraction was conducted in tabular form, including the author, year of publication, number of participants, and key findings. The purpose of creating a data extraction table was to facilitate the author in describing the review results. The 10 selected articles were first identified to ensure data quality and validity. This procedure involved the following steps: (1) examining the titles to determine relevance to the research subject, (2) reviewing the article authors, (3) evaluating the journal name, volume, issue, and year of publication, and (4) assessing the abstracts, as the abstract serves as a summary of the study that may contain either brief or detailed data. The research article abstracts provide readers with a synopsis of the study, beginning with its context and continuing through the objectives, methods, and conclusions. This method allows for a complete and systematic selection process, thereby improving the accuracy of article selection.

RESULTS

1. Study selection

   The search identified a total of 30,057 articles, consisting of 45 articles from PubMed, 25,100 from Google Scholar, 2,520 from NCBI, and 2,392 from ScienceDirect. A total of 17,510 duplicates were removed, leaving 12,547 articles. Subsequently, 8,612 articles were excluded for not meeting the inclusion criteria (13-year range), followed by the exclusion of 3,824 articles due to irrelevant titles. Twelve articles were excluded due to incomplete text. A total of 99 articles were screened, resulting in 33 articles that met the criteria. A critical appraisal was then conducted on these articles, yielding 10 eligible studies. The detailed flow diagram is presented in Figure 1.

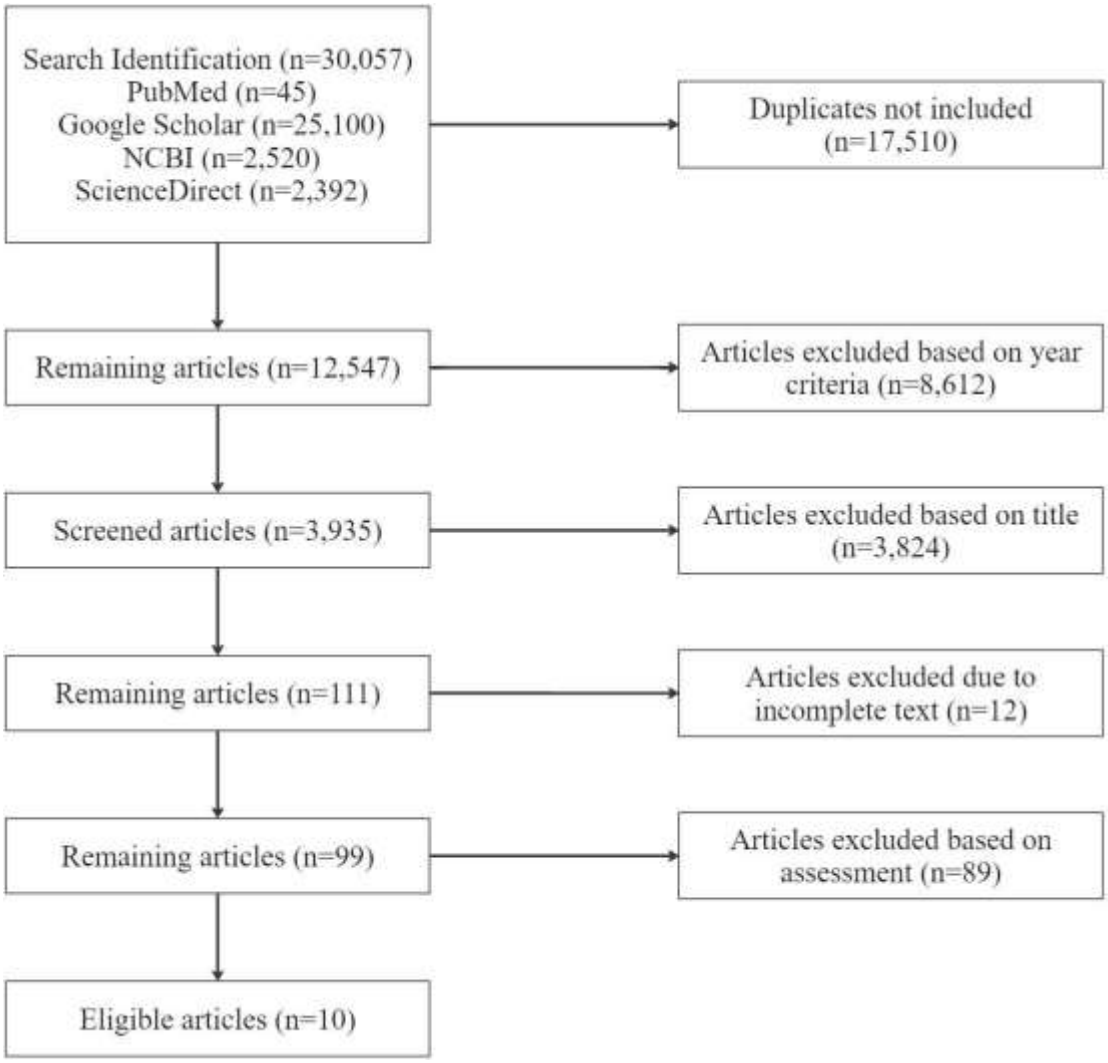


Figure 1. Study selection

2. Positive Blood Culture as a Risk Marker for Sepsis and MODS in Critically Ill Children

   This literature review generally focuses on positive blood culture as a risk marker for sepsis and MODS in critically ill children. The following are research findings demonstrating positive blood culture as a risk indicator for sepsis and MODS in critically ill children, as presented in Table 1.

Table 1. Results of Research Journal Assessment

No.	Author, year	Research Title	Number of Study Subjects	Research Conclusion
1	Han *et al*., 2024	*Early detection of bloodstream infection in critically ill children using artificial intelligence*	263 patients	We developed a machine learning model capable of predicting bloodstream infection (BSI) with acceptable performance. Further studies are needed to validate its effectiveness. *Candida albicans* was the most frequently detected pathogen, with a median BSI confirmation time of 3 days (range, 3–4 days). Patients with BSI demonstrated significantly higher in-hospital mortality and longer pediatric intensive care unit (PICU) stays compared to those without BSI. The random forest classifier achieved the highest area under the receiver operating characteristic curve, at 0.874 (0.762 for the validation dataset).
2	Vicenzi *et al*., 2025	*Risk Factors for Bloodstream Infections in Critically Ill Children: Gram-Negative Predominance and Complex Chronic Conditions*	148 BSI cases	Gram-negative bacteria predominated and were associated with oncohematologic diseases. Recognizing risk factors can improve empirical therapy in critically ill children. A total of 148 bloodstream infection (BSI) cases were analyzed in children with a median age of 33.5 months [IQR 5–110]; 60.0% were male. Gram-negative bacteria accounted for 43.2% of cases, Gram-positive for 41.2%, and fungi for 15.5%. Carbapenem resistance was detected in 26.5% of Gram-negative isolates. Methicillin-resistant *Staphylococcus aureus* (MRSA) represented 40.0% of *S. aureus* isolates. Gram-negative infections were associated with older age and oncohematologic conditions. Fungal infections were strongly associated with catheter use (OR 9.0; p = 0.039). The overall mortality rate reached 24.3%. The use of vasoactive drugs was the only independent predictor of mortality (RR 3.2; p = 0.004).
3	Lochan *et al*., 2013	*Blood cultures in sick children*	47.677 BC specimens	This study revealed a very high blood culture (BC) contamination rate, emphasizing the importance of sterile procedures during BC specimen collection. The proportion of contaminated specimens ranged from 5.9% to 7.2% per year (p = 0.4). Coagulase-negative staphylococci (CoNS) were the dominant isolates, accounting for 53.8% of all contaminated blood cultures. Children under 1 year of age experienced a higher contamination rate compared to those over 1 year (8.7% vs. 4.7%; relative risk 1.84; 95% confidence interval [CI] 1.71–1.97). Pathogenic organisms were isolated in 6.2% (95% CI 6.0–6.4) of all BC specimens. Among Gram-positive organisms, the proportion of *Streptococcus pneumoniae* isolates decreased from 14.3% to 4.7% (p < 0.00001), while there was a significant increase in Gram-negative organisms (51.8% to 57.9%; p = 0.04) over the 5-year period. *Klebsiella pneumoniae*, the most frequently isolated Enterobacteriaceae, decreased from 45.8% to 31.7% (p = 0.004).

4	Berger *et al*., 2018	*Blood Cultures Drawn From Arterial Catheters Are Reliable for the Detection of Bloodstream Infection in Critically Ill Children*	138 patients	Arterial catheter blood cultures are reliable for detecting bloodstream infections in pediatric intensive care units (PICUs). Two specialists, blinded to the source of the blood sample, evaluated each positive culture to determine whether the result represented a true bloodstream infection or contamination. The sensitivity, specificity, and positive and negative predictive values of arterial catheter blood cultures and peripheral blood cultures for diagnosing bloodstream infection were calculated. Of the 56 positive cultures, 41 (15% of the total samples) were considered true bloodstream infections. The remaining 15 cultures (5%) were categorized as contamination. The rate of false-positive results was higher in arterial catheter blood cultures compared to peripheral venipuncture cultures (4% vs. 1.5%), but this did not lead to unnecessary prolonged antibiotic therapy. Statistical analysis showed that arterial catheter blood cultures had high sensitivity (85%) and specificity (95%) for diagnosing true bloodstream infections, with performance comparable to that of peripheral blood cultures.
5	Pan *et al*., 2018	*Value of Time to Positivity of Blood Culture in Children with Bloodstream Infections*	808 strains	Our data show that time to positivity (TTP) is an important index for the early prognosis of bloodstream infection (BSI). TTP not only provides additional value as a general predictor of bacteria based on smear results, but also offers information regarding drug-resistant organisms. A total of 808 strains were isolated from 15,835 blood cultures collected, with 145 strains (17.9%) classified as Gram-negative, 636 strains (78.7%) as Gram-positive, and 27 strains (3.3%) as fungi. These microorganisms were categorized into definite pathogens (174), probable pathogens (592), fungi (27), and contaminants (15). The average TTP of all positive blood cultures was 30.97 hours, ranging from 3.23 to 92.73 hours. The TTP of Gram-negative strains was significantly shorter than that of Gram-positive strains ($P<0.001$) and fungi ($P=0.032$). The mean TTP for *Escherichia coli* (15.60 hours) was the shortest among Gram-negative isolates, while the mean TTP for *Streptococcus* (17.34 hours) was the shortest within the Gram-positive group. Significant differences in TTP were observed between methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*, ESBL-positive and ESBL-negative *Enterobacteriaceae*, as well as extensively drug-resistant and non-XDR *Acinetobacter baumannii*. The median TTP in patients with bloodstream infection (BSI) was significantly shorter than in patients without BSI ($P<0.001$). ROC curve analysis indicated TTP cutoff values for coagulase-negative staphylococci (CoNS), *S. aureus*, *E. coli*, and *Klebsiella pneumoniae* of 22.72 hours, 19.6 hours, 18.58 hours, and 16.43 hours, respectively, with the highest sensitivity and specificity as BSI predictors.
6	Aygun *et al*., 2019	*Infections with Carbapenem-Resistant* *Gram-Negative Bacteria are a Serious Problem Among Critically Ill Children: A Single-Centre Retrospective Study*	477 pediatric patients	These findings indicate that infections—particularly those involving carbapenem-resistant bacteria are a major concern in the management of critically ill children. A total of ninety patients (18.9%) developed bacterial infections, with gram-negative bacteria being the dominant infectious agents. Patients with positive cultures were younger than those with negative cultures, and age was associated with mortality as well as various clinical factors. Bacterial infections with positive cultures in the pediatric intensive care unit (PICU) were linked to increased use of invasive mechanical ventilation (odds ratio [OR]: 2.254), red blood cell transfusions (OR: 2.624), and inotropic drugs (OR: 2.262). Carbapenem resistance was found in approximately one-third of gram-negative bacteria, most frequently identified in tracheal aspirate specimens and in cases involving *Klebsiella* spp. Total parenteral nutrition was a significant risk factor (OR: 5.870). Positive blood culture results were associated with poorer patient survival compared to other culture results.

7	Agyeman *et al*., 2017	*Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study*	1.096 children	The burden of culture-proven bacterial sepsis on child health remains substantial. We observed important differences in dominant organisms, severity, and clinical outcomes among neonates, previously healthy children, and children with comorbidities. Although most episodes of culture-proven bacterial sepsis did not involve organ dysfunction, its presence was strongly associated with mortality. Of the 1,181 episodes of culture-proven bacterial sepsis, 382 episodes (32%) occurred in 379 previously healthy children, 402 episodes (34%) in 391 neonates, and 397 episodes (34%) in 341 children with comorbidities. The incidence was 25.1 cases per 100,000 children (95% CI 23.8–26.4) and 146.0 cases per 100,000 neonates (133.2–159.6). Central line-associated bloodstream infections and primary bloodstream infections accounted for 569 episodes (48%) of the total 1,181 episodes, with organ dysfunction detected in 455 episodes (39%). *Escherichia coli* (242 of 1,181 [20%]), *Staphylococcus aureus* (177 of 1,181 [15%]), coagulase-negative staphylococci (135 of 1,181 [11%]), and *Streptococcus pneumoniae* (118 of 1,181 [10%]) were the most common pathogens in this study, comprising 57% of all episodes. The overall case fatality rate was 7% (82 of 1,181 episodes; 95% CI 5.6–8.6), with higher rates observed in neonates (11%, 45 of 402 episodes; 8.4–14.8; adjusted odds ratio [OR] 4.41, 95% CI 1.75–11.1) and children with comorbidities (7%, 27 of 397 episodes; 4.6–9.9; OR 4.97, 1.84–13.4) compared with previously healthy children (3%, 10 of 382 episodes; 1.3–4.9). The case fatality rate among children without organ dysfunction was 1% (5 of 726 episodes [95% CI 0.3–1.7]) and increased to 17% (77 of 455 episodes [13.7–20.8]) when organ dysfunction was present (adjusted OR 4.84, 95% CI 1.40–16.7).
8	Puthawala *et al*., 2024	Persistent bloodstream infection in children: examining the role for repeat blood cultures	405 patients	Fungi or *Staphylococcus aureus* were associated with persistent bloodstream infection (BSI), whereas anaerobes and *Streptococcus* species were never observed to persist. Patient characteristics at the time of blood collection could not predict persistence unless the patient had a prior positive blood culture or was using a central venous catheter. These data may serve as a guide for when repeat blood cultures have clinical value and help reduce unnecessary blood sampling in children. A total of sixty-seven cultures (13.2%) showed persistent positive results. Anaerobic organisms (0 of 37) and *Streptococcus* species (0 of 104) were never detected in repeat cultures. *Staphylococcus aureus* (OR 9.45, CI 5.15–17.35) and fungi (OR 78.18, CI 9.45–646.6) were statistically associated with persistent BSI. Patients with a prior positive culture (OR 1.44, CI 1.12–1.84) or those with a central venous catheter (OR 2.20, 95% CI 1.04–3.92) were also at risk of persistence. Immune dysfunction and elevated inflammatory markers at the time of the index blood culture were not significantly associated with persistence.
9	Verstraete *et al*., 2018	*Blood culture indications in critically ill neonates: a multicenter prospective cohort study*	212 infants	There was significant heterogeneity in sampling practices between centers. Optimization of sampling practices is highly recommended. The proportion of laboratory-confirmed healthcare-associated sepsis (HAS) per suspected episode was 30 out of 192 (center 1), 28 out of 60 (center 2), and 8 out of 47 (center 3) ($p < 0.001$). The median C-reactive protein levels and the number of clinical signs at the time of culture collection differed between centers 1, 2, and 3 (11 vs. 5 vs. 3 mg/L, $p = 0.001$; 1 sign [IQR 0–2, center 1] vs. 3 signs [IQR 2–4, centers 2 and 3], $p < 0.001$). The median NOSEP score at the time of culture collection was 5 (IQR 3–8, center 1), 5 (IQR 3–9, center 2), and 8 (IQR 5–11, center 3) ($p = 0.016$). Differences were also observed in the initiation of antibiotic therapy (ABT) (82% vs. 93% vs. 74%, $p = 0.05$).

10	Woods-Hill *et al*., 2016	*Association of a Clinical Practice Guideline With Blood Culture Use in Critically Ill Children*	4.560 patients visits	A systematic approach to blood cultures reduced the overall number of cultures and those taken from central venous catheters, without an increase in mortality, readmissions, or suspected infection and suspected septic shock episodes. After the intervention, there was a 46.0% reduction in the blood culture rate (incidence rate ratio 0.54; 95% CI, 0.50–0.59). There was an immediate 25.0% reduction in the culture rate per 100 patient care days (95% CI, 4.2%–39.7%; P = 0.02) and a continued monthly decrease of 6.6% (95% CI, 4.7%–8.4%; P < 0.001) in the culture rate per 100 patient care days. Cultures taken from central venous catheters were significantly fewer after the intervention compared to before (389 [39.5%] vs 1321 [73.1%]; P < 0.001). The rate of episodes defined as suspected infection and suspected septic shock decreased significantly after the intervention, but the frequency of culture collection in patients meeting these criteria did not differ between before and after the intervention (52.1% vs 47.0%, P = 0.09, compared with 56.7% vs 55.0%, P = 0.75). In-hospital mortality (45 vs 37; P = 0.23) and hospital readmissions (107 vs 103; P = 0.42) did not change following the intervention.

The study by Han *et al*. (2024), titled *Early Detection of Bloodstream Infection in Critically Ill Children Using Artificial Intelligence*, involved 263 patients. This study developed a machine learning model capable of predicting bloodstream infection (BSI) with acceptable performance, and the authors emphasized the need for further validation. *Candida albicans* was identified as the most common pathogen, with a median BSI confirmation time of three days. Patients with BSI had higher in-hospital mortality rates and longer stays in the pediatric intensive care unit (PICU) compared to patients without BSI. The random forest model demonstrated the best performance, with an area under the ROC curve of 0.874.

Vicenzi *et al*. (2025), in a study titled *Risk Factors for Bloodstream Infections in Critically Ill Children: Gram-Negative Predominance and Complex Chronic Conditions*, analyzed 148 BSI cases. The findings showed a predominance of Gram-negative bacteria associated with oncohematologic diseases. Fungal infections were strongly linked to catheter use, while the use of vasoactive drugs emerged as the only independent predictor of mortality. The overall mortality rate reached 24.3%, with carbapenem resistance identified in more than one-quarter of Gram-negative isolates.

The study by Lochan *et al*. (2013), titled *Blood Cultures in Sick Children*, examined 47,677 blood culture (BC) specimens and revealed a high contamination rate ranging from 5.9% to 7.2% per year. Coagulase-negative staphylococci (CoNS) were the predominant isolates in more than half of the contaminated cultures. Children under one year of age had a higher contamination rate compared to older children. Pathogenic organisms were isolated from 6.2% of the specimens,

with a significant decline in *Streptococcus pneumoniae* and an increase in Gram-negative organisms over the five-year observation period.

Berger *et al*. (2018), in their study *Blood Cultures Drawn from Arterial Catheters Are Reliable for the Detection of Bloodstream Infection in Critically Ill Children*, involving 138 patients, concluded that arterial catheter blood cultures are reliable for detecting BSI in critically ill children. Although the rate of false-positive results was slightly higher compared to peripheral blood cultures, it did not lead to prolonged unnecessary antibiotic therapy. Overall, the sensitivity reached 85% and the specificity 95%, comparable to peripheral blood cultures.

In the study by Pan *et al*. (2018) titled *Value of Time to Positivity of Blood Culture in Children with Bloodstream Infections*, a total of 808 strains from 15,835 blood cultures were analyzed. The study highlighted that time to positivity (TTP) is an important index for the early diagnosis and prognosis of BSI. TTP was shorter in Gram-negative bacteria compared to Gram-positive bacteria and fungi, and it demonstrated predictive value for antibiotic resistance. *Escherichia coli* showed the shortest TTP among all isolates, while TTP cutoff values varied by species, with high sensitivity and specificity in predicting BSI.

Aygun *et al*. (2019), in their study *Infections with Carbapenem-Resistant Gram-Negative Bacteria are a Serious Problem Among Critically Ill Children*, analyzed 477 pediatric patients. They found that bacterial infections, particularly those resistant to carbapenems, are a serious issue in the PICU. Approximately 18.9% of patients experienced bacterial infections, predominantly caused by Gram-negative organisms. These infections were associated with the need for mechanical ventilation, blood transfusions, and inotropic support. Total parenteral nutrition was identified as a significant risk factor, while carbapenem resistance was observed in one-third of the cases.

The study by Agyeman *et al*. (2017), titled *Epidemiology of Blood Culture-Proven Bacterial Sepsis in Children in Switzerland*, involved 1,096 children and observed 1,181 episodes of bacterial sepsis. The findings indicated that sepsis remains a significant burden on pediatric health, particularly among neonates and children with comorbidities. *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* were identified as the predominant pathogens. The overall mortality rate was 7%, with higher rates observed in neonates and children with underlying conditions, especially when organ dysfunction was present.

In the study by Puthawala *et al*. (2024), titled *Persistent Bloodstream Infection in Children: Examining the Role for Repeat Blood Cultures*, 405 patients were included. The study found that fungi and *Staphylococcus aureus* were associated with persistent BSI, whereas *Streptococcus* species and anaerobic organisms did not show persistence. Key risk factors included a prior positive culture and the use of a central venous catheter. The study emphasized the importance of rationalizing repeat blood cultures to avoid unnecessary procedures.

Verstraete *et al*. (2018), in their study *Blood Culture Indications in Critically Ill Neonates: A Multicenter Prospective Cohort Study*, examined 212 infants and found significant variation in sampling practices between centers. Differences were observed in C-reactive protein levels, the number of clinical signs, and NOSEP scores at the time of culture collection. They recommended optimizing sampling practices to improve the accuracy of neonatal sepsis diagnosis.

Woods-Hill *et al*. (2016), in their study *Association of a Clinical Practice Guideline with Blood Culture Use in Critically Ill Children*, involved 4,560 patient visits. The implementation of a clinical practice guideline significantly reduced the number of blood cultures without increasing mortality or readmission rates. Cultures taken from central venous catheters decreased by nearly half, and the culture rate per 100 patient-days continued to decline each month, demonstrating the success of the intervention in optimizing blood culture use in the PICU.

DISCUSSION

Understanding blood cultures requires appreciation of their crucial role in establishing the diagnosis of bloodstream infections (BSI), especially in critically ill children, as early and accurate detection directly impacts clinical outcomes. Blood cultures are performed by collecting patient blood samples under sterile conditions and incubating them in specialized media to detect microbial growth. This methodology emphasizes optimal timing of collection, adequate blood volume, and proper handling to maximize sensitivity while minimizing contamination that could obscure clinical interpretation. Modern automated blood culture systems continuously monitor samples and typically report positive results within 12–48 hours, allowing for timely therapeutic interventions. (Jennifer and Erin, 2016).

In pediatric intensive care, the relationship between positive blood culture results and disease severity is highly significant. Studies have shown that time to positivity (TTP) the interval from blood collection to detectable microbial growth can reflect bacterial load and the host's immune

status. In critically ill children admitted to the pediatric intensive care unit (PICU), the median TTP was approximately 13.3 hours; shorter TTP is associated with immunosuppressive conditions, indicating a higher microbial burden and a greater likelihood of severe infection. The most frequently identified pathogens include Enterobacterales, *Staphylococcus aureus*, and various *Streptococcus* species known to cause significant morbidity. (Yasechko *et al.*, 2024).

The principles of blood culture collection in children require special attention to sample volume and timing, as pediatric patients often present challenges due to limited blood volume and small vessel size. Evidence shows that adherence to weight-based blood volume collection protocols improves pathogen recovery while reducing false positives caused by contaminants. Contamination is a significant issue that can lead to unnecessary antibiotic use, increased healthcare costs, and prolonged hospital stays. Advances in diagnostic stewardship promote the rational use of blood cultures through multidisciplinary quality improvement efforts, optimizing the timing and method of sample collection to balance sensitivity and specificity without causing excessive testing. (Woods-Hill *et al.*, 2021, 2022).

The association between positive blood cultures and severe critical illness is also evident in persistent bacteremia or multiple positive results, which often correlate with worse clinical outcomes, such as sepsis or septic shock the leading causes of pediatric mortality worldwide. Diagnostic stewardship programs emphasize reducing nonselective culture collection while maintaining vigilance for true infections, which is essential given that bloodstream infections can progress rapidly in this vulnerable population. Additionally, clinical factors such as immune status, the presence of invasive devices like central venous catheters or extracorporeal membrane oxygenation (ECMO), and prior antibiotic exposure influence blood culture results and their interpretation. (Schmoke *et al.*, 2025)

The interpretation of positive blood cultures depends not only on the detection of microbial growth but also requires integration of microbiological data with the clinical context. Bacteremia can be continuous or intermittent; intermittent bacteremia occurs more frequently and is usually associated with transient invasion into the bloodstream during procedures or from localized infections. In contrast, continuous bacteremia is often linked to infections of intravascular devices or endovascular structures. The source of bacteremia can be intravascular such as infective endocarditis or an infected graft or extravascular, when pathogens enter the

bloodstream from an infected organ via the lymphatic system. Distinguishing these patterns aids in prognosis assessment and tailoring management strategies. (HK *et al.*, 2019)

The relationship between positive blood cultures and severe critical illness in children is multifactorial. Bloodstream infections contribute to systemic inflammatory response syndrome (SIRS) and sepsis, leading to prolonged PICU stays and increased mortality. A study on bloodstream infections in critically ill pediatric patients demonstrated that children with confirmed bacteremia had longer intensive care stays and higher hospital mortality compared to patients without bacteremia. These findings underscore that positive blood cultures are not merely diagnostic markers but also prognostic indicators associated with severe disease. (Han, Kim and Park, 2024)

The interpretation of positive blood cultures also involves distinguishing true pathogens from contaminants. Some organisms, such as coagulase-negative staphylococci, may be considered contaminants if they are isolated in only one of several samples or if the time to positivity (TTP) is delayed beyond the typical range. However, early growth within 24–36 hours accompanied by clinical signs of infection usually indicates a true bloodstream infection. In the context of pediatric intensive care, this distinction is crucial, as it influences decisions to continue or discontinue empirical antibiotics and determines the need for further investigations. (Dierig *et al.*, 2018)

Bacteremia in children, defined as the presence of bacteria in the bloodstream, is a clinical condition with a wide spectrum of symptoms depending on the causative pathogen and the severity of infection. The condition can range from occult bacteremia where fever is the only symptom and the child appears well to severe systemic inflammation and critical illness requiring immediate intervention. Understanding the clinical manifestations of bacteremia is important in pediatric care, as positive blood culture results are closely associated with disease severity and serve as the basis for crucial management decisions. (Randolph and McCulloh, 2014)

In many cases, the main clinical sign of bacteremia in children is fever, often high, reaching ≥39°C (102.2°F). This fever can persist for several days; a longer duration, particularly more than 4–7 days, is associated with an increased likelihood of bacteremia and greater disease severity. In addition to prolonged fever, other common symptoms in children with bacteremia include lethargy, poor feeding, and abdominal pain signs indicating systemic involvement and

potential progression to critical illness. Gastrointestinal manifestations, such as diarrhea and vomiting, also frequently accompany bacteremia, especially in cases caused by nontyphoidal *Salmonella*. (Ogunkunle *et al.*, 2022).

Vital signs provide important diagnostic clues. Tachycardia and tachypnea are frequently observed in children with bacteremia and correlate with greater disease severity. These signs may reflect systemic inflammatory responses and early sepsis physiology. Additionally, physical examination may reveal signs of respiratory distress, such as groaning and nasal flaring, underscoring the need for close monitoring and early intervention. (Ogunkunle *et al.*, 2022)

Laboratory markers also provide supporting evidence. Elevated inflammatory markers, such as high C-reactive protein (CRP) and neutrophilia accompanied by lymphopenia, have been reported as predictors of severe bacteremia in pediatric patients. It is important to note that leukopenia may paradoxically occur in some cases of severe bacteremia, reflecting variation in host response depending on the pathogen and host factors. (Ogunkunle *et al.*, 2022; Guo *et al.*, 2023).

It is important to remember that occult bacteremia, particularly in vaccinated populations, may present without prominent clinical symptoms other than unexplained fever. Vaccination against common bacterial pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* has drastically reduced the incidence of classic severe bacteremia. However, vigilance remains necessary in children who are unvaccinated or immunocompromised. (Randolph and McCulloh, 2014)

Laboratory correlations play a crucial role in confirming bacteremia and assessing its severity. Elevated body temperature at triage, increased neutrophil counts, and elevated inflammatory markers such as C-reactive protein (CRP) and procalcitonin (PCT) are significant predictors of bacteremia in febrile infants. Furthermore, lymphopenia has been identified as a useful marker, particularly for bacteremia caused by pathogens such as *Salmonella* spp., with children exhibiting low lymphocyte counts having a substantially higher risk of bacteremia. Absolute neutrophil count (ANC) is considered more predictive than total white blood cell count. These laboratory findings enable physicians to stratify febrile children by risk and make informed decisions regarding hospitalization and antibiotic therapy. (Ogunkunle *et al.*, 2022; Guo *et al.*, 2023)

Blood culture remains the gold standard for definitive diagnosis, ideally with two samples obtained from separate sites to minimize false positives due to contamination. Early availability of culture results, typically within 24 hours, is crucial for guiding antimicrobial management. Complementary tests, such as urinalysis and cerebrospinal fluid examination, are tailored based on clinical suspicion. Meanwhile, imaging studies support the identification of hidden sources of infection or complications. For example, in cases where abdominal pain or gastrointestinal symptoms accompany bacteremia, ultrasound or computed tomography scans can reveal infections or abscesses that require targeted therapy. (Dierig *et al.*, 2018).

The severity of critical illness in children is strongly correlated with clinical and laboratory findings that predict bacteremia. Children hospitalized with bacteremia tend to exhibit prolonged fever, more frequent hospital admissions, and a higher prevalence of systemic signs such as diarrhea and abdominal pain symptoms associated with increased illness severity. Early recognition through a combination of clinical assessment, laboratory parameters, and imaging contributes to improved outcomes by enabling timely initiation of antibiotics and appropriate supportive care. (Ogunkunle *et al.*, 2022)

The presence of a positive blood culture in critically ill children is a significant clinical marker often associated with the severity of infection and related outcomes such as mortality and morbidity. A retrospective cohort study focusing on children with severe sepsis or septic shock found that mortality was higher in children with positive bacterial blood cultures compared to those with negative cultures. Specifically, the mortality rate was 43% in the culture-positive group versus 20% in the culture-negative group. Additionally, children with positive cultures exhibited higher rates of organ dysfunction upon admission, indicating a relationship between bacteremia and more severe systemic illness. However, the progression to multiple organ dysfunction syndrome during the early days of intensive care did not differ significantly between the groups, suggesting that early severity may be a critical determinant of outcomes rather than ongoing progression alone. (Hazwani *et al.*, 2020).

The presence of a positive blood culture in critically ill children is a significant clinical marker, often associated with severe infection and related outcomes such as mortality and morbidity. A retrospective cohort study focusing on children with severe sepsis or septic shock found that mortality was higher in those with positive bacterial blood cultures compared to those with negative cultures. Specifically, mortality was 43% in the culture-positive group versus 20% in

the culture-negative group. Furthermore, children with positive cultures exhibited higher rates of organ dysfunction upon admission, indicating a link between bacteremia and more severe systemic illness. However, the progression to multiple organ dysfunction syndrome during the early days of intensive care did not differ significantly between groups, suggesting that early severity may be a more important determinant of outcomes than ongoing progression alone. (Meena *et al.*, 2025)

Another prospective cohort study examining blood culture positivity and time to positivity found no significant difference in 90-day mortality based on the presence of bacteremia or the culture's time to positivity. This further underscores the complexity of sepsis outcomes, which depend on multiple factors such as host response, pathogen virulence, and comorbid conditions rather than solely on culture results. (Paquette *et al.*, 2021).

In pediatric critical illness, the relationship between positive blood cultures and clinical outcomes such as mortality and morbidity is significant. Positive cultures are generally associated with higher early disease severity and organ dysfunction, which correlate with an increased risk of death. However, bacteremia is only one of many factors influencing outcomes in critically ill children. Underlying disease severity, the timeliness and appropriateness of antimicrobial therapy, and the child's baseline condition all play crucial roles. Additionally, culture-negative sepsis cases may reflect diagnostic or temporal limitations but can still carry substantial risks of morbidity and mortality, underscoring the need for comprehensive clinical assessment beyond culture results alone. (Hazwani *et al.*, 2020)

Positive blood cultures indicate bloodstream infection, which is a major cause of morbidity and mortality in critically ill patients, including children. These infections often require prolonged hospitalization and intensive care, highlighting the importance of timely diagnosis and appropriate management. A study focusing on critically ill children in a large tertiary PICU found that 95% of clinically significant blood cultures turned positive within 36 hours, regardless of the child's immune status. This rapid detection facilitates early intervention, which can influence both the length of hospital stay and overall patient prognosis. However, disease severity and immune dysfunction also play crucial roles in clinical outcomes. (Yasechko *et al.*, 2024)

Contrary to the intuitive expectation that positive blood cultures would increase hospital and ICU length of stay, recent data suggest that this relationship is complex and not always straightforward. A comprehensive study analyzing clinical outcomes in patients with culture-positive versus culture-negative sepsis found no significant differences in hospital length of stay (LOS) or ICU stay between the groups. In fact, the average hospital stay was 14 days for culture-positive patients compared to 16 days for culture-negative patients, with ICU stay being similar in both groups. Furthermore, blood culture positivity was not independently associated with increased 30-day mortality after adjusting for age, disease severity scores, and comorbidities. These findings imply that factors beyond bloodstream infection status such as underlying disease severity, organ dysfunction, and comorbidities substantially influence both hospital and ICU stay durations. (Meena *et al.*, 2025).

Bloodstream infections confirmed by positive cultures are often associated with a more severe clinical course, requiring prolonged supportive therapies such as vasopressors and mechanical ventilation, which can indirectly extend ICU length of stay. Some studies indicate that patients with positive blood cultures tend to be more severely ill compared to those with negative cultures, logically suggesting longer ICU stays for sicker patients. However, this effect may be modulated by targeted antimicrobial therapy and enhanced supportive care, potentially mitigating the impact on length of stay. (Issa, 2005)

Contaminated blood cultures distinct from true bloodstream infections can also contribute to adverse clinical outcomes, such as prolonged hospitalization and unnecessary procedures in children. Although contamination results in false-positive findings, it can prolong the diagnostic process, delay appropriate treatment, and increase length of stay, emphasizing the importance of proper technique and accurate interpretation of blood cultures in clinical practice. (Hall *et al.*, 2013)

Biomarkers play a crucial role in assessing the severity of infection in pediatric patients, particularly those with positive blood cultures indicating bloodstream infection. Among various biomarkers, C-reactive protein (CRP) and procalcitonin (PCT) are the most extensively studied and used in clinical practice for this purpose. CRP is an acute-phase protein synthesized by the liver in response to inflammation, such as bacterial infection. Elevated CRP levels correlate with the presence of infection but have limitations in specificity, as CRP can also rise in viral infections or non-infectious inflammatory conditions. However, several studies in children with

community-acquired pneumonia (CAP) have shown that higher CRP levels are associated with more severe disease presentation and outcomes, such as progression to severe pneumonia or the need for intensive care. Thus, CRP serves as a useful marker for inflammation and severe infection but is best interpreted alongside clinical findings. (Omaggio *et al.*, 2024)

Procalcitonin, a precursor of the hormone calcitonin, is produced in various tissues in response to bacterial infection. Unlike CRP, PCT demonstrates greater specificity for bacterial infections compared to viral etiologies. Pediatric studies have shown a stronger correlation between elevated PCT levels and severe bacterial infections, sepsis, and critical illness. For example, in children with febrile neutropenia or community-acquired pneumonia (CAP), higher serum PCT levels have predicted bacterial etiology, severe disease, and adverse outcomes, making it a valuable marker for assessing severity and guiding antibiotic therapy. (Nahar *et al.*, 2023)

In the context of positive blood cultures, elevated levels of PCT and CRP have been associated with worse clinical outcomes, such as sepsis and systemic inflammatory response syndrome (SIRS), indicating more severe infections. Recent evidence also highlights the usefulness of combining these biomarkers with clinical assessments to improve diagnostic and prognostic accuracy in critically ill children. More advanced markers, such as pancreatic stone protein and chemokines like IP-10, have also been explored, although they remain under investigation for routine use. (Nowak *et al.*, 2023)

Procalcitonin has gained particular attention as an emerging biomarker with strong prognostic implications. Studies have shown that elevated PCT levels correlate with increased disease severity and mortality risk in pediatric populations with bacterial bloodstream infections (BSIs). Its rapid rise in response to pathogenic bacteria makes it a promising marker for early risk stratification, enabling clinicians to identify children at higher risk of developing critical illness or organ dysfunction. Furthermore, the utility of PCT in guiding antibiotic stewardship has been supported by evidence suggesting that its levels can help determine the need for antimicrobial therapy, thereby reducing unnecessary antibiotic exposure in children with less severe infections. (Jain, 2017; Heilmann, Gregoriano and Schuetz, 2019; Miura, Katsuta and Nakamura, 2024)

In addition to PCT, other biomarkers such as lactate levels and blood gas parameters have emerged as valuable indicators of severe disease in pediatric sepsis and bacteremia. Elevated lactate levels, often reflecting tissue hypoperfusion and metabolic dysregulation, have been associated with higher mortality and more severe clinical courses. Blood gas analysis, including

parameters such as pH and coagulation markers like prothrombin time (PT-INR), provides further assessment by revealing acid-base disturbances and coagulopathies linked to poorer outcomes. The integration of these biomarkers into severity scoring systems such as PELOD-2 and PRISM-3 enhances their predictive capacity for mortality and critical illness in children with infectious diseases. (Miura, Katsuta and Nakamura, 2024)

Recent research emphasizes that no single biomarker can effectively represent the degree of disease severity on its own. Instead, a combination of markers such as PCT, lactate, CRP, and hematologic indices can provide a more comprehensive picture of a patient's condition. For instance, studies have shown that integrating biomarkers with clinical assessments enhances prognostic accuracy, helping to identify children who require immediate intensive care interventions. Moreover, newly investigated biomarkers targeting specific pathophysiological pathways, such as cytokine responses (e.g., IL-6), hold promise for future applications in dynamic monitoring and personalized therapeutic strategies for pediatric infections. (Jacobs and Wong, 2016; Jain, 2017; Heilmann, Gregoriano and Schuetz, 2019; Bernardi *et al.*, 2024)

The relationship between positive blood culture results and organ dysfunction, particularly multi-organ involvement, is a key aspect in understanding the severity of critical illness in children. A positive blood culture indicates the presence of bloodstream infection, which is a major contributor to sepsis and subsequent organ dysfunction. Sepsis, defined as a dysregulated host response to infection, often leads to multiple organ dysfunction syndrome (MODS), which drastically increases the risk of mortality in critically ill pediatric patients. Several prospective studies analyzing pediatric populations with culture-proven sepsis have demonstrated that positive blood cultures are strongly correlated with the risk and extent of organ dysfunction. In a large-scale study involving children across emergency departments, pediatric intensive care units (PICUs), and general wards, various organ dysfunction scoring systems such as the Pediatric Sequential Organ Failure Assessment (pSOFA), Pediatric Logistic Organ Dysfunction-2 (PELOD-2), and the International Pediatric Sepsis Consensus Conference (IPSCC) criteria were used to assess organ involvement at the time of blood culture sampling. These scoring systems identified a majority of children with organ dysfunction, particularly affecting the neurological, respiratory, and cardiovascular systems. The predictive accuracy of these scores for 30-day mortality was notably strong, underscoring the association between positive blood culture results, severe organ dysfunction, and clinical outcomes. (Schlapbach, Goertz, *et al.*, 2024)

The pathophysiology of multi-organ dysfunction in children with positive blood cultures involves a complex interplay between immune responses, endothelial injury, and impaired tissue perfusion. Bacterial toxins and host inflammatory mediators trigger a systemic inflammatory response, leading to widespread endothelial damage and capillary leakage. These changes disrupt organ perfusion and can result in dysfunction across multiple systems, including the lungs (acute respiratory distress syndrome), kidneys (acute kidney injury), liver, cardiovascular system (shock), and central nervous system (encephalopathy). The severity of organ involvement typically reflects both the microbial burden and the magnitude of the host response, underscoring blood culture positivity as a marker of severe infection with potential multi-organ sequelae. (Upperman *et al.*, 2017).

In clinical practice, blood cultures not only confirm the diagnosis of bloodstream infection but also guide targeted antimicrobial therapy, which is crucial for halting the progression of sepsis and limiting organ damage. A positive blood culture requires careful clinical evaluation to identify the presence of organ dysfunction, as early recognition and supportive management of multi-organ involvement can improve outcomes in pediatric patients. Furthermore, multi-organ dysfunction scoring systems and biomarkers are often integrated into clinical workflows to aggressively monitor disease progression and predict mortality risk in children with bloodstream infections. (Lin *et al.*, 2022; Schlapbach, Goertz, *et al.*, 2024)

The pathophysiological relationship between positive blood cultures and organ dysfunction is primarily mediated by the host's immune response to invading pathogens. When bacteria or other pathogens enter the bloodstream, they release pathogen-associated molecular patterns (PAMPs), which are recognized by pattern recognition receptors of the immune system. This recognition triggers an inflammatory response aimed at containing and eliminating the infection. However, in severe cases, this response becomes dysregulated and excessive, resulting in what is commonly referred to as a "cytokine storm" or cytokinemia. The overproduction of proinflammatory cytokines recruits immune cells and leads to widespread endothelial dysfunction, capillary leakage, and microvascular thrombosis. These processes impair organ perfusion and function, ultimately culminating in multiple organ dysfunction syndrome (MODS). (Carcillo *et al.*, 2017; Clemens *et al.*, 2024).

More specifically, in children with positive blood cultures, studies have demonstrated a direct correlation between the presence of pathogenic bacteria in the bloodstream and the occurrence of severe organ dysfunctions such as acute respiratory distress syndrome (ARDS), acute kidney injury, and hepatic dysfunction. Inflammatory mediators produced in response to bloodstream infection induce epithelial and endothelial cell apoptosis, mitochondrial dysfunction, and metabolic disturbances that disrupt organ homeostasis. For instance, mitochondrial autophagy (mitophagy) and dysfunction contribute to cellular energy failure and catabolism in affected organs. These pathophysiological alterations observed in pediatric patients support clinical observations that positive blood cultures signify a higher risk of critical illness and increased mortality rates. (Carcillo *et al.*, 2017; Clemens *et al.*, 2024)

The concept of damage-associated molecular patterns (DAMPs) plays a crucial role in amplifying organ injury during sepsis. DAMPs are cellular molecules released during tissue damage that subsequently activate immune responses, exacerbating the early inflammatory disturbances initially driven by pathogen-associated molecular patterns (PAMPs) from infectious microorganisms. This vicious cycle leads to sustained inflammation, immune cell apoptosis, and ineffective microbial clearance, thereby prolonging and worsening organ dysfunction. In clinical pediatric MODS, biomarkers of PAMPs and DAMPs correlate with disease severity, underscoring the biological basis for the observed relationship between positive blood cultures and organ failure in critical illness. (Carcillo *et al.*, 2017)

A positive blood culture not only confirms the diagnosis of a bloodstream infection but also serves as an important prognostic indicator of disease severity in children. The presence of pathogenic organisms in the bloodstream triggers a cascade of immune and metabolic disturbances, leading to dysfunction across multiple organ systems and increasing the risk of adverse outcomes. Careful recognition of blood culture positivity, combined with early and aggressive management of subsequent inflammatory and metabolic disturbances, is crucial for improving clinical outcomes in pediatric critical illness associated with sepsis. (Lin *et al.*, 2022; Clemens *et al.*, 2024).

Sepsis in pediatric patients remains a major global health concern and is critically defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Historically, the 2005 International Pediatric Sepsis Consensus Definition utilized the criteria of systemic

inflammatory response syndrome (SIRS) in combination with suspected or confirmed infection to identify sepsis in children. This framework also distinguished severe sepsis and septic shock, associating these conditions with cardiovascular and respiratory dysfunction or multiple organ failure. Although widely used, these criteria demonstrated limitations, such as poor predictive value and redundancy in classification terminology, thereby necessitating revision based on evolving clinical evidence. (Richard J. Brilli FCCM and Brahm Goldstein FCCM, 2005; Miranda and Nadel, 2023)

More recent developments particularly the 2016 adult Sepsis-3 definition redefined sepsis as infection accompanied by organ dysfunction, quantified by the Sequential Organ Failure Assessment (SOFA) score. However, this adult-focused criterion excluded the pediatric population. In response, an international task force composed of pediatric critical care experts developed the Phoenix Sepsis Score, specifically adapted for children. This score defines pediatric sepsis as a Phoenix score of two points or higher in the presence of suspected infection. The scoring system incorporates organ dysfunction across respiratory, cardiovascular, coagulation, and neurological systems. Importantly, septic shock in children is defined as sepsis combined with cardiovascular dysfunction such as severe age-adjusted hypotension, elevated lactate levels greater than 5 mmol/L, or the need for vasoactive support. (Schlapbach, Watson, *et al.*, 2024).

This refined classification aligns with evidence showing a significant increase in mortality 7.1% in high-resource settings and up to 28.5% in lower-resource settings among children meeting the Phoenix sepsis criteria, underscoring the clinical severity associated with organ dysfunction. Notably, septic shock carries a poorer prognosis, with mortality rates exceeding 10% to 33.5%, reflecting the critical impact of cardiovascular failure in pediatric septic patients. (Morin *et al.*, 2022; Schlapbach, Watson, *et al.*, 2024)

In the context of the relationship between positive blood cultures and the severity of critical illness, the updated pediatric definition highlights the crucial role of infection-confirmed organ dysfunction as the defining feature of sepsis. A positive blood culture, as an indicator of bloodstream infection, therefore serves as a significant prognostic marker, often correlating with a more severe clinical course and higher organ dysfunction scores. This relationship reinforces the need for early detection and targeted interventions in children with confirmed bacteremia to

prevent progression to multiorgan failure and septic shock. (Morin *et al.*, 2022; Schlapbach, Watson, *et al.*, 2024)

Recent updates, such as the 2024 consensus from the Society of Critical Care Medicine (SCCM) for ICUs, have moved away from SIRS-based criteria and redefined pediatric sepsis as life-threatening organ dysfunction caused by infection mirroring the adult Sepsis-3 definition but specifically adapted for children. This new definition employs the Pediatric Sepsis Phoenix Score, which assigns points for dysfunction across respiratory, cardiovascular, coagulation, and neurological systems. Children with a Phoenix score of at least 2 demonstrate a significantly increased risk of mortality (7.1% in high-resource settings and 28.5% in low-resource settings), indicating that this scoring system reflects disease severity more accurately than previous criteria. Within this framework, septic shock is specifically defined as sepsis accompanied by cardiovascular dysfunction, evidenced by severe age-adjusted hypotension, elevated lactate levels (>5 mmol/L), or the need for vasoactive medications. Mortality is even higher in cases of septic shock, exceeding 10% in high-resource environments and over 33% in low-resource settings. (Schlapbach, Watson, *et al.*, 2024).

Understanding the distinctions between sepsis, severe sepsis, and septic shock is essential in pediatric care, as it guides clinical urgency, treatment intensity, and prognosis. Sepsis broadly refers to infection-induced organ dysfunction; severe sepsis highlights significant organ failure without the immediate need for cardiovascular support; and septic shock represents the stage in which cardiovascular collapse leads to persistent hypotension despite fluid resuscitation. The refined definitions emphasize organ dysfunction rather than inflammation alone, aligning more closely with clinical outcomes and enabling earlier risk stratification. (Morin *et al.*, 2022)

The presence of a positive blood culture a direct indicator of bloodstream infection correlates strongly with disease severity in pediatric sepsis. A positive blood culture not only confirms infection but may also indicate a higher microbial burden or a more invasive disease, which is often associated with organ dysfunction and progression toward septic shock. Recent analyses from critical care settings have shown that children with confirmed bacteremia or fungemia identified through blood cultures tend to experience more severe clinical illness, higher organ failure scores, and increased mortality rates. This relationship underscores the importance of timely blood culture acquisition for diagnosis and highlights that a positive blood culture serves

as a marker of elevated risk for severe critical illness in children with sepsis. (Morin *et al.*, 2022; Schlapbach, Watson, *et al.*, 2024)

Clinical predictors associated with positive blood cultures help explain the relationship between infection status and the severity of critical illness in pediatric patients. Recent studies have emphasized the importance of timely detection and specific clinical factors that anticipate positive blood culture results, facilitating improved clinical management and outcome prediction. One key clinical predictor is the time to positivity (TTP) of blood cultures. Research among critically ill children in pediatric intensive care units (PICUs) has shown that most clinically significant blood cultures become positive within 36 hours of sampling, with an average TTP of approximately 13.3 hours. This rapid timeframe applies broadly regardless of host immune status whether in previously healthy children, those at standard risk, or immunocompromised patients. These findings highlight that early detection within this window is crucial for guiding the initiation and adjustment of antimicrobial therapy, underscoring the need for frequent reassessment of empirical antibiotic use to balance therapeutic aggressiveness with antimicrobial stewardship. (Yasechko *et al.*, 2024).

Clinical severity scoring systems, such as the Pediatric Logistic Organ Dysfunction (PELOD-2) score assessed on the day of bacteremia diagnosis, have also been identified as strong prognostic factors. Higher PELOD-2 scores correlate with poorer outcomes and are independently associated with mortality in critically ill children with bloodstream infections caused by pathogens such as Klebsiella pneumoniae. This supports the notion that the clinical severity at the time of infection serves as a reliable predictor of disease progression and outcomes in cases of bacteremia. (Maia dos Santos *et al.*, 2022)

Host immune status and underlying conditions further influence prognosis. For instance, children with immunodeficiency may exhibit a shorter time to positivity (TTP), indicating a higher bacterial load or faster bacterial proliferation. Additionally, hypoalbuminemia, which is frequently observed in critical illness often due to sepsis or systemic inflammatory response serves as a marker of severe disease. Low serum albumin levels reduce plasma colloid osmotic pressure, disrupt circulatory integrity, and can potentially worsen clinical outcomes in children with bacteremia. (Xu *et al.*, 2020).

Common pathogenic bacteria detected in pediatric bloodstream infections include Enterobacterales, Staphylococcus aureus, Streptococcus agalactiae, and Streptococcus pneumoniae. These organisms vary in virulence and antibiotic susceptibility, which in turn influence the degree of disease severity and therapeutic response. Rapid identification of these pathogens through blood cultures, alongside clinical predictors, optimizes targeted therapy and improves prognosis. (Yasechko *et al.*, 2024).

One of the key laboratory predictors is the time to positivity (TTP) of blood cultures. Studies have shown that among critically ill children, 95% of clinically significant blood cultures yield positive results within 36 hours, with an average TTP of approximately 13.3 hours. This value remains relatively consistent regardless of host immune status, demonstrating its robustness as a prognostic tool. Pathogens such as Enterobacterales, Staphylococcus aureus, Group B Streptococcus, and Streptococcus pneumoniae are commonly isolated, and TTP does not differ significantly between Gram-positive and Gram-negative organisms. A shorter TTP often correlates with higher bacterial loads and, consequently, more severe infections, implying a poorer prognosis and greater urgency for targeted antimicrobial therapy. (Yasechko *et al.*, 2024)

In addition to microbiological timing, biochemical and clinical severity indicators also predict positive blood cultures and outcomes. Elevated procalcitonin levels (>2 µg/L) have been shown to be strongly associated with positive blood cultures in critically ill patients. Similarly, higher severity scores such as a Simplified Acute Physiology Score II (SAPS II) above 43 and a Sequential Organ Failure Assessment (SOFA) score greater than 4 correlate with an increased risk of bacteremia and poorer prognosis. These factors reflect severe systemic illness and organ dysfunction that commonly accompany bloodstream infections. Moreover, the presence of liver failure further increases the likelihood of a positive blood culture, underscoring the interaction between organ injury and infection risk. (M. *et al.*, 2012)

In children with bloodstream infections caused by multidrug-resistant organisms, such as Klebsiella pneumoniae producing carbapenemase, prognostic indicators include clinical scoring systems like the Pediatric Logistic Organ Dysfunction (PELOD-2) score. Increases in the PELOD-2 score both during the early phase of infection and within 48 hours thereafter are significantly associated with higher mortality rates, emphasizing the importance of dynamic monitoring of severe organ dysfunction. Notably, children with such infections often present with underlying chronic conditions, malnutrition, and multi-organ failure at the time of diagnosis

factors that further elevate risk and worsen clinical outcomes. Resistance patterns that limit therapeutic options compound the poor prognosis in this vulnerable pediatric population. (Maia dos Santos *et al.*, 2022)

Immunological parameters also contribute valuable prognostic insights. Lymphopenia at admission specifically a lymphocyte count below 1.5×10^9 /L has been identified as an independent predictor of poorer outcomes in pediatric critical illness involving bloodstream infections. Patients with lymphopenia exhibit higher mortality rates and reduced 90-day survival compared to those with normal lymphocyte counts. These findings underscore the role of immune competence in combating systemic infections and highlight peripheral immune cell profiles as useful early prognostic biomarkers. (He *et al.*, 2024)

CONCLUSION AND RECOMENDATION

Blood culture remains a cornerstone diagnostic tool in critically ill children, as it provides direct evidence of bloodstream infection and is closely linked to disease severity assessment. Early detection reflected by a time to positivity (TTP) typically under 36 hours guides more targeted antimicrobial decisions. In clinical practice, a combination of systemic symptoms, vital sign abnormalities, and inflammatory and hematologic markers aids in screening high-risk patients.

Precision in sampling procedures and adherence to diagnostic stewardship principles form the foundation for maximizing accuracy while minimizing contamination. In terms of outcomes, positive blood cultures are often associated with greater initial severity, organ dysfunction, and increased mortality risk, although they may not always serve as independent predictors once comorbidities and severity scores are accounted for.

The underlying pathophysiological mechanisms systemic inflammatory activation, endothelial injury, and hypoperfusion explain the progression toward multi-organ involvement. The integration of biomarkers, organ dysfunction scores, and microbiological parameters such as TTP enhances risk stratification and guides targeted therapy. This comprehensive approach is key to improving outcomes in the vulnerable pediatric population.

REFERENCE

Bernardi, L. *et al.* (2024) ‘Biomarkers for Serious Bacterial Infections in Febrile Children’,

Biomolecules, 14(1). doi: 10.3390/biom14010097.

Bettany-Saltikov, J. (2018) *How to do a systematic literature review in nursing: A stepby-step guide*. Maidenhead: McGraw-Hill/Open University Press.

Carcillo, J. A. *et al.* (2017) 'Pathophysiology of pediatric multiple organ dysfunction syndrome', *Pediatric Critical Care Medicine*, 18(3), pp. S32–S45. doi: 10.1097/PCC.0000000000001052.

Clemens, N. *et al.* (2024) 'Association between positive blood culture and clinical outcomes among children treated for sepsis in the emergency department', *American Journal of Emergency Medicine*, 76, pp. 13–17. doi: 10.1016/j.ajem.2023.10.045.

Dierig, A. *et al.* (2018) 'Time-to-Positivity of Blood Cultures in Children With Sepsis.', *Frontiers in pediatrics*. Switzerland, 6, p. 222. doi: 10.3389/fped.2018.00222.

Guo, B. C. *et al.* (2023) 'Predictors of bacteremia in febrile infants under 3 months old in the pediatric emergency department', *BMC Pediatrics*, 23(1). doi: 10.1186/s12887-023-04271-z.

Hall, R. T. *et al.* (2013) 'Reducing the blood culture contamination rate in a pediatric emergency department and subsequent cost savings', *Pediatrics*. American Academy of Pediatrics Elk Grove Village, IL, USA, 131(1), pp. e292–e297.

Han, H. J., Kim, K. and Park, J. D. (2024) 'Early detection of bloodstream infection in critically ill children using artificial intelligence', *Acute and Critical Care*, 39(4), pp. 611–620. doi: 10.4266/acc.2024.00752.

Hazwani, T. R. *et al.* (2020) 'Association Between Culture-Negative Versus Culture-Positive Sepsis and Outcomes of Patients Admitted to the Pediatric Intensive Care Unit', *Cureus*. doi: 10.7759/cureus.9981.

He, M. *et al.* (2024) 'Prognostic significance of blood immune cells in children with sepsis and establishment of a predictive model for PICU mortality: a retrospective study', *Frontiers in Pediatrics*, 12. doi: 10.3389/fped.2024.1455216.

Heilmann, E., Gregoriano, C. and Schuetz, P. (2019) 'Biomarkers of Infection: Are They Useful in the ICU?', *Seminars in Respiratory and Critical Care Medicine*, 40(4), pp. 465–475. doi: 10.1055/s-0039-1696689.

HK, C. *et al.* (2019) 'Approach to Positive Blood Cultures in the Hospitalized Patient: A Review', *Missouri medicine*, 116(4), pp. 313–317.

Issa, V. (2005) 'Clinical impact of positive blood cultures in intensive care patients'.

Jacobs, L. and Wong, H. R. (2016) 'Emerging infection and sepsis biomarkers: will they change current therapies?', *Expert Review of Anti-Infective Therapy*, 14(10), pp. 929–941. doi: 10.1080/14787210.2016.1222272.

Jain, K. K. (2017) 'Biomarkers of Infectious Diseases', *The Handbook of Biomarkers*, pp. 219–238. doi: 10.1007/978-1-4939-7431-3_9.

Jennifer, D. B. and Erin, M. T. (2016) 'Diagnosis of Bloodstream Infections in Children', *Journal of Clinical Microbiology*. American Society for Microbiology, 54(6), pp. 1418–1424. doi: 10.1128/jcm.02919-15.

Lin, P. C. *et al.* (2022) 'Revisiting factors associated with blood culture positivity: Critical factors after the introduction of automated continuous monitoring blood culture systems', *Medicine (United States)*, 101(30), p. E29693. doi: 10.1097/MD.0000000000029693.

M., P. *et al.* (2012) 'Predictors of positive blood cultures in critically ill patients: A retrospective evaluation', *Croatian Medical Journal*, 53(1), pp. 30–39.

Maia dos Santos, M. L. B. *et al.* (2022) 'Prognostic Factors of Severely Ill Children with Klebsiella pneumoniae Carbapenemase Blood Stream', *Int J Nurs Health Care Res*, 5, p. 1274.

Meena, D. S. *et al.* (2025) 'Impact of blood culture positivity on clinical outcomes in sepsis: a prospective observational study', *Infezioni in Medicina*, 33(3), pp. 294–302. doi: 10.53854/liim-3303-6.

Miranda, M. and Nadel, S. (2023) 'Pediatric Sepsis: a Summary of Current Definitions and Management Recommendations', *Current Pediatrics Reports*, 11(2), pp. 29–39. doi: 10.1007/s40124-023-00286-3.

Miura, S., Katsuta, T. and Nakamura, Y. (2024) 'Predictive biomarker of mortality in children with infectious diseases: a nationwide data analysis', *Frontiers in Pediatrics*, 12(July), pp. 1–7. doi: 10.3389/fped.2024.1381310.

Morin, L. *et al.* (2022) 'The Current and Future State of Pediatric Sepsis Definitions: An International Survey', *Pediatrics*, 149(6). doi: 10.1542/peds.2021-052565.

Nahar, A. *et al.* (2023) 'Procalcitonin versus C-Reactive Protein as a Biomarker for Prediction of Bacterial Infection in Children with Febrile Neutropenia in Acute Leukemia.', *Mymensingh medical journal : MMJ*, 32(1), pp. 76–82.

Nowak, M. *et al.* (2023) 'One Hundred Consecutive Neutropenic Febrile Episodes Demonstrate That CXCR3 Ligands Have Predictive Value in Discriminating the Severity of Infection in Children with Cancer', *Children*, 10(1). doi: 10.3390/children10010039.

Ogunkunle, T. O. *et al.* (2022) 'A Prospective Cohort Study of the Clinical Predictors of Bacteremia in Under-Five Children With Acute Undifferentiated Fever Attending a Secondary Health Facility in Northwestern Nigeria', *Frontiers in Pediatrics*, 9(February), pp. 1–10. doi: 10.3389/fped.2021.730082.

Omaggio, L. *et al.* (2024) 'Utility of C-reactive protein and procalcitonin in community-acquired pneumonia in children: a narrative review', *Current Medical Research and Opinion*, 40(12), pp. 2191–2200. doi: 10.1080/03007995.2024.2425383.

Paquette, K. *et al.* (2021) 'Neither Blood Culture Positivity nor Time to Positivity Is Associated with Mortality among Patients Presenting with Severe Manifestations of Sepsis: The FABLED Cohort Study', *Open Forum Infectious Diseases*, 8(7). doi: 10.1093/ofid/ofab321.

Randolph, A. G. and McCulloh, R. J. (2014) 'Pediatric sepsis: important considerations for diagnosing and managing severe infections in infants, children, and adolescents.', *Virulence*. United States, 5(1), pp. 179–189. doi: 10.4161/viru.27045.

Richard J. Brilli FCCM, M. D. and Brahm Goldstein FCCM, M. D. (2005) 'Pediatric sepsis definitions: Past, present, and future', *Pediatric Critical Care Medicine*.

Schlapbach, L. J., Watson, R. S., *et al.* (2024) 'International Consensus Criteria for Pediatric Sepsis and Septic Shock', *Jama*, 331(8), pp. 665–674. doi: 10.1001/jama.2024.0179.

Schlapbach, L. J., Goertz, S., *et al.* (2024) 'Organ Dysfunction in Children With Blood Culture-Proven Sepsis: Comparative Performance of Four Scores in a National Cohort Study', *Pediatric Critical Care Medicine*, 25(3), pp. E117–E128. doi: 10.1097/PCC.0000000000003388.

Schmoke, N. *et al.* (2025) 'Daily Surveillance Blood Cultures in Children Supported With Extracorporeal Membrane Oxygenation: Single-Center, Retrospective Cohort Study, 2021–2023', *Pediatric Critical Care Medicine*, 26(4), pp. e447–e453. doi: 10.1097/PCC.0000000000003699.

Upperman, J. S. *et al.* (2017) 'Specific etiologies associated with the multiple organ dysfunction syndrome in children: Part 1', *Pediatric Critical Care Medicine*, 18(3), pp. S50–S57. doi:

10.1097/PCC.0000000000001048.

Woods-Hill, C. Z. *et al.* (2021) 'Consensus Recommendations for Blood Culture Use in Critically Ill Children Using a Modified Delphi Approach', *Pediatric Critical Care Medicine*, 22(9), pp. 774–784. doi: 10.1097/PCC.0000000000002749.

Woods-Hill, C. Z. *et al.* (2022) 'Association of Diagnostic Stewardship for Blood Cultures in Critically Ill Children with Culture Rates, Antibiotic Use, and Patient Outcomes: Results of the Bright STAR Collaborative', *JAMA Pediatrics*, 176(7), pp. 690–698. doi: 10.1001/jamapediatrics.2022.1024.

Xu, H. *et al.* (2020) 'Prognostic role of time to positivity of blood culture in children with Pseudomonas aeruginosa bacteremia', *BMC Infectious Diseases*, 20(1). doi: 10.1186/s12879-020-05257-3.

Yasechko, S. M. *et al.* (2024) 'Time to Positive Blood Cultures among Critically Ill Children Admitted to the PICU', *Critical Care Explorations*, 6(7), p. e1115. doi: 10.1097/CCE.0000000000001115.