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REVIEW ARTICLE

# The evolving value of older biomarkers in the clinical diagnosis of pediatric sepsis

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Sepsis remains the leading cause of childhood mortality worldwide. The evolving definition of pediatric sepsis is extrapolated from adult studies. Although lacking formal validation in the pediatric population, this working definition has historically proven its clinical utility. Prompt identification of pediatric sepsis is challenging as clinical picture is often variable. Timely intervention is crucial for optimal outcome, thus biomarkers are utilized to aid in immediate, yet judicious, diagnosis of sepsis. Over time, their use in sepsis has expanded with discovery of newer biomarkers that include genomic bio-signatures. Despite recent scientific advances, there is no biomarker that can accurately diagnose sepsis. Furthermore, older biomarkers are readily available in most institutions while newer biomarkers are not. Hence, the latter's clinical value in pediatric sepsis remains theoretical. Albeit promising, scarce data on newer biomarkers have been extracted from research settings making their clinical value unclear. As interest in newer biomarkers continue to proliferate despite their ambiguous clinical use, the literature on older biomarkers in clinical settings continue to diminish. Thus, revisiting the evolving value of these earliest biomarkers in optimizing pediatric sepsis diagnosis is warranted. This review focuses on the four most readily available biomarkers to bedside clinicians in diagnosing pediatric sepsis.

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**IMPACT:**

- The definition of pediatric sepsis remains an extrapolation from adult studies.
- Older biomarkers that include C-reactive protein, procalcitonin, ferritin, and lactate are the most readily available biomarkers in most pediatric institutions to aid in the diagnosis of pediatric sepsis.
- Older biomarkers, although in varying levels of reliability, remain to be useful clinical adjuncts in the diagnosis of pediatric sepsis if used in the appropriate clinical context.
- C-reactive protein and procalcitonin are more sensitive and specific among these older biomarkers in diagnosing pediatric sepsis although evidence varies in different age groups and clinical scenarios.

## INTRODUCTION

Pediatric sepsis remains the leading cause of childhood mortality worldwide. It is recognized as a global health emergency by the United Nations World Health Assembly with an estimated mortality of 1.6 million annually.[1–4] There is no dedicated definition of pediatric sepsis to date that is not an extrapolation from adult studies. Since 2001, the evolving definition of pediatric sepsis has continued to aim for higher accuracy to encompass the syndrome yet it has remained a mirror of the adult definition (Table 1). Even the newest definition of pediatric sepsis in 2017 based on the Third International Consensus for Sepsis and Septic Shock using the Sequential Organ Failure Assessment (SOFA) was designed for adults albeit this working definition has historically served an effective surrogate to perform its function. The main highlight of this new definition is the emphasis on the presence of life-threatening organ dysfunction as a dysregulated host response to infection in sepsis compared to an uncomplicated bacterial infection.[5] Pediatric logistical organ dysfunction-2 (PELOD-2) is a derived predictive validation of SOFA in pediatric intensive care unit patients with promising results albeit its clinical validity is not generalizable outside the intensive care setting.[6–8] In addition to the absence of a cohesive understanding of the mechanisms of sepsis, the inherent time lag of conventional microbiological tests creates a significant loophole that may preclude optimal outcome through timely intervention. Thus, adjuvant interventions that aid in timely diagnosis of pediatric sepsis such as biomarkers have become invaluable tools in the hopes of addressing this issue. This review article intentionally limits its exclusive focus on C-reactive protein, procalcitonin, ferritin, and lactate, which are the most readily available biomarkers to the bedside pediatric clinicians across most hospitals in the United States.

A literature search was generated in Ovid Medline and Elsevier Scopus for the following diagnostic markers in pediatrics: C-reactive protein, procalcitonin, ferritin, and lactate. The Ovid Medline search consisted of medical subject headings for the diagnostic terms and pediatric-related terms. The Scopus search

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**Table 1.** Evolution of sepsis definition over time since its original definition based on international sepsis consensus.

| Sepsis severity | Sepsis 1 SIRS (Systemic Inflammatory Response Syndrome) | Sepsis 2 | Sepsis 3 qSOFA (quick Sequential Organ Failure Assessment) |
|---|---|---|---|
| Sepsis | Sepsis defined by 2 or more of SIRS criteria<br>Temperature >38 °C or <36 °C<br>Heart rate >90 beats per minute<br>Respiratory rate >20 breaths per minute or $PaCO_2$ < 32 mmHg<br>White blood cell count >12,000/cu mm, <4000/cu mm, or >10% immature (band)<br>**Meeting 2 or more of SIRS criteria** | Arterial hypotension (mean arterial pressure <80 or systolic blood pressure <90 mmHg, or systolic blood pressure decrease in >40 mmHg in adults or <2 SD below for normal age) + mixed venous oxygen saturation >70% with cardiac index >3.51 $min^{-1}$ $m^{-2}$ | Must have an increase of 2 or more in the score should raise suspicion of sepsis and organ dysfunction<br>Altered mental status (GCS score <15)<br>Systolic blood pressure <100 mmHg<br>Respiratory rate >22/min<br>**qSOFA score ≥ 2 points** |
| Severe sepsis | SIRS + organ dysfunction, hypoperfusion or hypotension | Arterial hypoxemia ($PaO_2/FiO_2$ < 300, acute oliguria (<0.5 mL/kg/h), coagulation abnormalities (INR > 1.5 or aPTT >60, thrombocytopenia <100,000/μL), ileus, AKI, thrombocytopenia, hyperbilirubinemia (>4 mg/dL), hyperlactemia (>3 mmol/L) | |
| Septic shock | Severe sepsis with hypotension despite adequate fluid resuscitation with perfusion abnormalities (lactecemia, oliguria, altered mental status); patients on vasopressors | | Sepsis + vasopressor requirement to maintain mean arterial pressure ≥ 65 and lactate >2 mmol/L despite adequate fluid resuscitation |

consisted of keywords for the diagnostic terms listed above and pediatric terms in the title, abstract, and keyword fields. The search was limited to the past 5 years and English references only. Only articles deemed to have significant clinical impact or contribution to pediatric clinical practice are included.

## OVERVIEW OF BIOMARKERS

In 2001, the National Institutes of Health defined "biomarker" as "a characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention". The United States Food and Drug Administration made recent clarifications around this broad definition to better understand appropriate applications of biomarkers for a particular function in different contexts.[9] We will use the term "biomarker" in this article as a "test performed on some body fluid that provides clinicians with patient information not readily obtainable otherwise using current diagnostic or monitoring modalities."[10] It is also important to mention that a biomarker's accuracy, encompassed by its sensitivity and specificity, is reflected by its calculated area under the curve (AUC) value. The closer the AUC to 1, the more accurate the biomarker is.[10]

The putative function of biomarkers in sepsis hails from their presence or altered concentration secondary to an infectious insult. As a result, seminal purposes of biomarkers in sepsis focused on their function to delineate infectious from non-infectious processes. This long-standing emphasis on this function, coupled with technological advancement has resulted in the discovery of more sophisticated biomarkers and to the expansion of their clinical uses. Currently, more than a hundred biomarkers have been discovered with assorted clinical uses that include diagnosis and screening of sepsis, risk stratification, monitoring of response to therapy, and even in rational guidance on antimicrobial use.[11] Many biomarkers have not been well-studied needing further elucidation for their clinical use to be meaningful.[12] Although overlaps in the function of biomarkers exist, particular biomarkers have been noted to excel in particular use over another. Furthermore, no biomarker is a stand-alone test to perform a particular clinical use. Biomarkers need to be judiciously paired with the appropriate clinical context and interpreted along with other laboratory parameters. Moreover, different cut-off values depending on the purpose of use have been validated for any given biomarker.

One of the oldest applications of biomarkers is to assist in timely diagnosis of sepsis. With pediatric sepsis, the clinical presentation is often subtle and clinical deterioration may be rapid without early intervention. Thus biomarkers are potentially useful in early identification of sepsis or impending sepsis.[13] The earliest biomarkers have been the most studied for this clinical use in children. They are also the most readily available, least costly and most used by pediatricians as staple adjuncts to clinical acumen. With advancing technology, more robust research databases, and wider population data sets bringing about clearer but evolving evidence of their clinical uses, it is easy to confuse one application over another. For example, the use of multi-biomarker approach for risk stratification has risen over the past decade can easily be mistaken at face value for each individual component's clinical use. It is, therefore, crucial to define a comprehensive understanding of the utility of these older biomarkers specifically as pediatric sepsis diagnostic tools. This article focuses on C-reactive protein, procalcitonin, ferritin, and lactate in terms of updated literature about their importance in the diagnosis of pediatric sepsis.

## C-REACTIVE PROTEIN

C-reactive protein (CRP) is probably the most celebrated of all biomarkers.[14] It is an acute phase reactant discovered in 1930 in the serum of patients with pneumococcal pneumonia that precipitated with the C-polysaccharide of the pneumococcal cell wall.[15] It belongs to the pentraxin family of proteins that is synthesized by hepatocytes as an indirect response to an inflammatory trigger including infection. Tissue damage triggers the release of inflammatory cytokines, particularly IL-6, that stimulate the liver to produce CRP. It increases within 4–6 h of the inflammatory insult with doubling time of about 8 h. It usually peaks around 36–50 h with a half-life of 4–7 h (Fig. 1).[16] CRP facilitates phagocytosis by macrophages and dendritic cells as well as activation of the complement cascade resulting in pertinent immune response.[16] The effect of steroids and immunosuppression on CRP levels is very limited, one of its main beneficial characteristics over other biomarkers. Furthermore, its level is not affected by renal dysfunction or dialysis making it a practical biomarker for this subset of patients.[11]

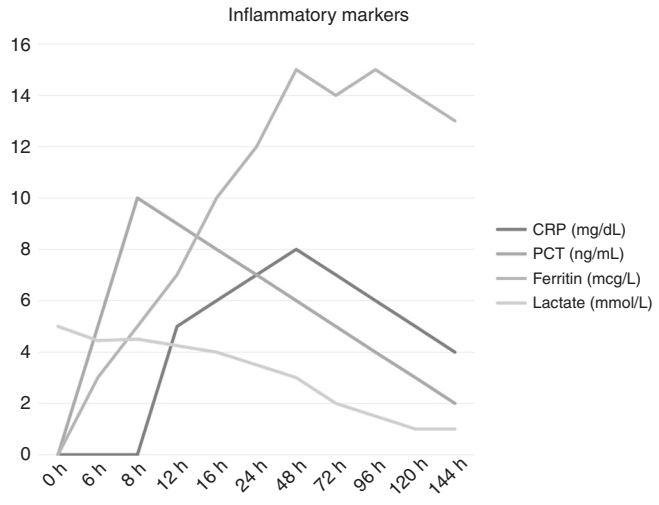


**Fig. 1 Kinetics of CRP, procalcitonin, ferritin, and lactate in relation to their response to an inciting infectious or inflammatory agent.** This diagram shows the differences in the dynamics between these older biomarkers and an inciting event (inflammatory or infectious) over time depicting heterogenous peaks and duration of elevation.

CRP binds to apoptotic cells eliminating them through phagocytosis.[16] It also binds to components of bacterial cell wall enhancing their clearance through binding to Fc receptors.[17] Elevated CRP is seen in a myriad of scenarios including trauma, surgical procedures, rheumatologic disorders, certain malignancies, viral, fungal, bacterial infections or a combination of these conditions. Physiologic rise in CRP was also demonstrated among term and preterm babies.[18] This non-specific trigger of CRP elevation has subjected its role in sepsis to rigorous scrutiny. However it has proven its value when used in the correct clinical context.

Although findings are variable from heterogeneity of sampling times and cut-off thresholds, one subset of patients where CRP has robust evidence in terms of its discriminatory performance for serious bacterial infections (SBI) is in the neonatal population. A meta-analysis that aimed to evaluate the diagnostic value of CRP in detecting neonatal septicemia among 1819 neonates has suggested the appropriateness of CRP for this purpose with AUC of 0.9.[19] This study, however, did not discriminate between early- and late-onset neonatal sepsis. A larger meta-analysis of 31 studies comprising 5698 participants found CRP as a valuable tool in diagnosing neonatal sepsis with AUC of 0.8458. In this particular study, meta-regression, and subgroup analysis were done showing heterogeneity in the studies included was irrelevant to test time, cut-off value, assay method, and sepsis type.[20] Smaller studies have shown the same findings. A prospective study among 187 febrile infants 0–90 days old demonstrated that CRP has superb performance in identifying serious bacterial infections defined as urinary tract infection, pneumonia, meningitis, osteomyelitis/septic arthritis, and sepsis with a AUC of 0.815.[21] CRP was also significantly higher in septic neonates in a cohort of 90 full-term babies when 7.2 mg/L ($p < 0.001$) is used as a cut-off value with sensitivity, specificity, PPV, and NPV of 91, 100, 100, and 85.7%, respectively.[22] Identical findings showing acceptable clinical utility of CRP to aid in empiric antibiotic initiation in neonatal sepsis were seen in other small studies.[23,24]

Some differences in its performance is demonstrated between early- and late-onset neonatal sepsis. A cross sectional study done among 385 neonates has shown its low screening validity in early-onset neonatal sepsis (EOS) compared to late-onset neonatal sepsis (LOS).[25] A similar result showed that CRP is higher in late- versus early-onset sepsis in a prospective cross sectional study among 320 subjects. CRP in this study with cut-off value 3.6 ng/mL showed pooled sensitivity of 78% and specificity of 70% in diagnosing neonatal sepsis.[26] CRP at a cut-off value >40 mg/L had poor sensitivity, specificity and predictive values for meningitis in culture negative early-onset neonatal sepsis.[27]

One of the largest recent systematic reviews assessing the diagnostic value of CRP looked into its diagnostic accuracy as an index test in the evaluation of late-onset neonatal sepsis in 22 cohort studies involving 2255 infants.[28] The authors found that at a pre-specified cut-off of 5–10 mg/L, the median specificity was 0.74 with a pooled sensitivity of 0.62 (95% CI 0.50–0.73). This implicates that for a hypothetical cohort of 1000 newborns at a prevalence of late-onset neonatal sepsis of 40%, CRP would misdiagnose 159 infants and miss 156 septic neonates. This study suggested against using CRP as a sole index test for diagnosis of late-onset neonatal sepsis. Limitations, however, of this review include considerable heterogeneity of sample population and absence of subgroup analysis because of insufficient data. A similar conclusion was found in another meta-analysis of 28 studies among 2661 patients in four different continents: Asia, North America, Africa, and Europe. Pooled CRP sensitivity varied across geographic location being highest in Africa (0.92 (0.8–1.00)) and lowest in Europe (0.63 (0.47–0.79)). This study showed that a cut-off value of >10 mg/L has a high sensitivity and specificity to diagnose neonatal sepsis but not a reliable stand-alone test for this function.[29]

In addition, the diagnostic value of CRP among the extremely-low-birth-weight and very-low-birth-weight infants remains controversial in a recent review of 39 studies.[30] In a retrospective cohort study done in Canada among 416 blood culture confirmed late-onset neonatal sepsis among very-low birth weight babies, CRP at a cut-off value of >10 mg/L demonstrated a meager sensitivity of 49%. The diagnostic sensitivity rose to 66% (95% CI 58–73) if combined with an abnormal CBC defined as WBC < 5000/mm$^3$, I/T ratio of >0.10 or platelet count <100,000/μL.[31]

In older children, the performance of CRP has been heterogeneous. Among 213 children less than 18 years old with fever and possible sepsis and/or meningitis in a prospective study, CRP showed moderate accuracy in detecting serious bacterial infection with AUC of 0.7.[32] In 102 infants identified with serious bacterial infection among 892 total participants 3 months or younger, CRP is a better diagnostic marker compared to WBC and considered a valuable test in assessing febrile infants.[33] A systematic review showed that CRP provides moderate and independent data on ruling in and ruling out serious bacterial infection in children with fever at first presentation with pooled sensitivity was 0.77 and specificity was 0.79.[34] Similar results are found in smaller studies done among heterogeneous age groups ranging from 7 days to 36 months old and with varying levels of cut-off values that range from 40–70 mg/L demonstrating sensitivity of 62–79% and specificity of 79–90% in detecting serious bacterial infections in pediatric patients without localizing source.[35–38] CRP less than 20 mg/L has shown to effectively rule out significant joint infections including osteomyelitis and septic arthritis in 265 children aged 3 months–5 years.[39]

In patients with febrile neutropenia, CRP is significantly elevated with culture-positive infections compared to culture-negative infections or fever of unknown source.[40] This is echoed in a meta-analysis that examined 25 studies that looked into 14 different biomarkers in 3585 episodes of febrile neutropenia wherein CRP showed to be the only biomarker that has consistently demonstrated value in detecting infection beyond clinical decision rules.[41] Furthermore, CRP > /=90 mg/L together with absolute monocyte count <100/μL significantly suggests invasive fungal infection in neutropenic patients with cancer who have been persistently febrile for 4 days from admission.[42]

On the contrary, a prospective cohort study looking into the value of CRP as a predictor of serious infection, whose definition

**Table 2.** Summary description of older biomarkers in terms of their strengths, limitations, and clinical applications in detection of pediatric sepsis.

| Biomarker | Advantages | Disadvantages |
|---|---|---|
| C-reactive protein | Low cost<br>Readily available in most hospital settings<br>Fast turn-around time<br>Threshold values more defined in pediatric population<br>Not affected by prior receipt of steroids, biologicals, poor renal function or dialysis status<br>Point-of-care test that can be performed at bedside or at home available (faster turn- around time)<br>Helpful in fungal infection | Low specificity<br>Can be falsely elevated in autoimmune conditions, surgery, trauma<br>Can be falsely lower in liver dysfunction |
| Procalcitonin | Readily available in most hospital settings<br>Fast turn-around time<br>High specificity and sensitivity<br>Less affected by surgery<br>Better differentiator between viral and bacterial infection (may be controversial in neonates)<br>Point of care testing is emerging although not available in all centers | Higher cost<br>Controversial cut-off values for different types of infection.<br>Cut-off values may differ depending on assay type.<br>Cut-off values are age-specific especially in preterm infants.<br>Can be falsely elevated in severe trauma, kidney injury/ disease, surgery, respiratory distress syndrome<br>Can be falsely low in liver dysfunction |
| Ferritin | Readily available in most hospital settings<br>Fast turn-around time | Low specificity and sensitivity<br>Marker of inflammation in non-septic state (can be confounder) |
| Lactate | Readily available in most hospital settings<br>Fast turn-around time<br>Quickly obtained with blood gas | Can potentially have different values (venous versus arterial)<br>Marker of tissue hypo-perfusion in non-septic state<br>Low specificity for sepsis |

included sepsis has shown its very limited clinical relevance for this function.[43] One caveat to this study is that it used point-of-care capillary blood CRP test (Nyocard) extrapolated from a small cross-sectional validation.[44]

Recent literature shows that CRP is a valuable clinical tool in the diagnosis of pediatric sepsis when used in the appropriate clinical context and population.

## PROCALCITONIN

The earliest literature describing elevated procalcitonin levels in septic children was written in 1993.[45] It was noted that among the 79 children, all but two with procalcitonin above 5 ng/mL were diagnosed with severe bacterial sepsis in this study. Furthermore the procalcitonin level correlated with the severity of the infection. Since then, studies elucidating the role of procalcitonin in pediatric sepsis have proliferated although its biological role in sepsis remains largely unknown. Procalcitonin (PCT) is the precursor of calcitonin and is presumed to be produced by the neuroendocrine cells in the thyroid and lungs at very low levels under physiologic conditions although all tissues have the potential to elaborate PCT in distinct conditions.[46] In bacterial sepsis, PCT levels can attain thousands-fold higher than normal.[47] It has been postulated that infection is the primary pathophysiological trigger of supra-physiologic levels of PCT. Lipopolysaccharide and lipotechoic acid in Gram-negative and Gram-positive bacterial cell walls, respectively, interact with immune cells through toll-like receptors resulting in increased levels of TNFa, IL-1B, and IL-6. These cytokines are the most proximate stimuli to the release of PCT.[48] PCT level is attenuated by interferon gamma, a cytokine released during viral infection, further suggesting its elevation to be specific to bacterial sepsis.[11,32] PCT usually rises within 2 h of the onset of bacterial infection and peaks at 24–36 h (Fig. 1).[32]

With CRP being the older and more studied biomarker for sepsis, it has been unavoidable to compare the clinical utility of PCT to it (Tables 2 and 3). Just like CRP, procalcitonin has been subjected to rigorous inquiry because it may also be elevated in non-septic states. For instance, physiologic peak of PCT occurs in term infants at 1 day of life. This peak timing may be different in preterm and late-preterm infants confounding its value in predicting neonatal sepsis during this time period.[49] PCT may also be elevated in major trauma, surgery, respiratory distress, or even in certain cancers.[50] However, like CRP, it becomes a valuable clinical adjunct to diagnose pediatric sepsis when used in the appropriate clinical context.

**Table 3.** Range sensitivities and specificities of CRP, PCT, lactate, and ferritin in terms of their clinical utility in pediatric sepsis.

| Statistical attribute | CRP | Procalcitonin | Lactate | Ferritin |
|---|---|---|---|---|
| Sensitivity | 62–89% | 70–96% | 34–97% | 24–71% |
| Specificity | 67–90% | 68–94% | 27–82% | 36–79% |

Variations in reported cut-off values have not been specified in the ranges noted.

Studies about PCT show diverse outcomes from heterogeneity in patient population, sample timing, cut-off values, and even in the definition of sepsis.[30,50] Overall, PCT studies have shown promising results as a diagnostic marker for pediatric sepsis. Several studies have been done in the neonatal population. One recent review of 39 studies directly comparing PCT and CRP, the mean sensitivity for EOS, LOS, and EOS + LOS was 73.6, 88.9, and 76.5%, respectively, showing its superiority to CRP. However, only 4 studies comprised VLBW neonates in the analysis making its utility in in this particular subset of neonates unclear.[30] Smaller studies have shown that PCT is significantly higher in septic neonates and is more sensitive than CRP with better positive and negative predictive values in the early diagnosis of neonatal sepsis.[51–56] PCT, however, is less useful in determining fungal sepsis in neonates.[52]

Mixed results have been shown in older children. A large prospective cohort study of 2047 infants 7 to 91 days showed that PCT has better diagnostic accuracy in detecting invasive bacterial infection (IBI defined as bacteremia and meningitis) compared to CRP when a cut-off value of 0.3 ng/mL is used. However, PCT and CRP have similar performance in detecting serious bacterial infection (SBI defined as UTI and gastroenteritis).[57] In a prospective study of 73 children 16 years and younger with median age of 32.4 months, PCT was noted to be significantly

higher in patients with sepsis with AUC 0.738 compared to non-septic patients.[58] Another study in 60 septic children 0-6 years old showed that PCT is an independent predictor of pediatric sepsis with AUC 0.787.[59] A meta-analysis of 8 studies involving 616 children demonstrated PCT to have very good accuracy in rapidly differentiating between bacterial and viral meningitis and is superior to CRP with pooled sensitivity and specificity of 96 and 89%, respectively.[60] Similar finding was seen in a smaller study done in 50 children ages 3 months–15 years.[61]

In children with fever and central line, one of the largest studies done among 523 patients 0–23 years old demonstrated that PCT is a sensitive predictor of bacteremia in this population.[62] The same result was observed in 49 patients 0–18 years old.[63] Particularly in pediatric cancer patients, the cut-off value of 0.49 ng/mL demonstrated superior diagnostic accuracy compared to CRP in excluding bacteremia in 300 patients with a NPV of 94.67%.[64] Similar result was demonstrated in 492 patients with acute lymphoblastic leukemia (ALL).[65]

One meta-analysis of 12 studies aimed to evaluate diagnostic accuracy of PCT in detecting SBI or IBI in 7260 children without a source showed that PCT is a helpful diagnostic adjunct to detect meningitis, bacteremia, and sepsis at a threshold of 0.5 ng/mL. The pooled sensitivity and specificity were, however, lower in detecting SBI compared to IBI.[66] A retrospective study in 318 infants younger than 3 months of age that aimed to analyze utility of PCT, physical exam, CRP, WBC, and ANC in detecting IBI has shown that PCT is superior to all in detecting IBI but has missed 30% of infants with IBI and therefore lacks sufficient accuracy.[67] Similarly, a recent study of 213 children showed that PCT has only moderate diagnostic accuracy for SBI in the ED using a point-of-care PCT BRAHMS 1B10 PCT test.[32] Same finding was shown in a meta-analysis of 17 studies comprising 1408 patients (1086 neonates and 322 children). The EOS and LOS were grouped together with a sensitivity of 0.85 and specificity of 0.54 when a cut-off value of 2.0–2.5 ng/mL is used. Pooled analysis was not done in older patients because of paucity of studies.[68]

PCT has shown some limitations in specific patient populations. For instance, in burn patients, PCT has demonstrated poor diagnostic performance in detecting sepsis. In the same way, PCT was elevated in neonates with meconium aspiration syndrome irrespective of the presence of bacterial infection.[69] In a study done in 420 critically ill patients admitted in the PICU with about 1226 PCT analyzed, PCT was not shown to reliably detect localized bacterial infection, neither did it differentiate bacterial versus viral infection.[70] The same result was observed in a prospective single-center blinded study of 181 PICU patients where PCT did not reliably predict presence or absence of confirmed bacterial infection to be considered clinically useful. Although in this study, the authors found that PCT was higher in children with confirmed bacterial infection.[71]

Overall, PCT is higher in the setting of bacterial sepsis but it has not been found to function as a stand-alone test to diagnose it. It is also found to be more sensitive than CRP.

## FERRITIN

Ferritin has long been known as an indicator of iron stores and less commonly as an acute phase reactant. It is found to be circulating in high amounts in critically ill children who have sepsis and is shown to be associated with poor outcome. Increased ferritin production is known to be part of acute phase reaction to infection attributed to reduction of available serum iron. This theory has been speculated to evolve as a defense mechanism for invading organism since nearly all microorganisms depend on iron. Iron is sequestered by transferrin in the bloodstream and stored in ferritin.[72] In vitro, macrophages harbor CD163 that binds to free hemoglobin–haptoglobin complexes triggering transcription and production of intracellular ferritin. Heme is then recycled by heme oxygenase 1 leaving a cleaved free iron. Ferritin sequesters the free iron to prevent generation of free radicals.[73] This becomes important in the diagnosis of hemo-phagocytic lymphohistiocytosis, which is characterized by pathologic pro-inflammatory activity of T cells and macrophages that may closely mimic an infectious process.

Hyperferritinemia has been observed in critically ill children. A retrospective analysis in 60 term neonates where blood samples were collected to analyze the levels of ferritin pre and post treatment for sepsis revealed that ferritin had sensitivity of 64.3% and specificity of 43.5% on patients with bacteremia.[74] Analysis of ferritin levels in a cohort of 36 children found high levels of ferritin in patients with severe sepsis and septic shock.[75] In this cohort 58% of children had ferritin >500 ng/mL with an associated relative risk of death of 3.2 suggesting that elevated ferritin is associated with poorer outcome. Interestingly, ferritin levels >3000 ng/mL in 171 patients was associated increased mortality and intensive care unit admission.[76] However, due to low specificity and sensitivity correlated with infection, ferritin is often not the first choice to assess for sepsis in children (Table 3). Rather, it can be a useful marker to assess the degree of inflammation during sepsis.

## LACTATE

Lactate is part of anaerobic metabolism and is elevated during tissue hypoxia.[77] As such, lactate is a known biomarker for tissue perfusion. The production of lactate occurs during anaerobic glycolysis where glucose is converted into pyruvate. In aerobic conditions, pyruvate enters the Krebs cycle where ADP is converted into ATP.[78] In oxygen-deprived conditions, pyruvate is converted to lactate via lactate dehydrogenase and lactate accumulates which subsequently results in lactic acidosis. However, once there is enough oxygen, lactate can be converted to back to pyruvate.[79]

Lactate was first clinically observed in 1964 when levels at 4 mmol/L was shown to be associated with poor outcomes in children with shock.[78] It has been shown that prolonged elevated lactate is associated with increased risk of mortality and organ dysfunction.[80] As such, measuring lactate levels can be a useful tool in assessing severity of sepsis.

Lactate is predominantly found in the muscles.[78] A normal lactate in a human is <1 mmol/L. This level is maintained by production in the muscle and metabolism in the kidney and liver. The definition of elevated lactate remains unclear. In children who are symptomatic and have signs of sepsis, lactate >2 mmol/L require intervention.[81]

A prospective cohort study assessed initial lactate levels and length of hospital stay in 74 pediatric patients with severe sepsis in a pediatric ICU. Results revealed that initial lactate levels correlated with PRISM-III, which is a well-validated illness severity score used for prognostication, suggesting that lactate may play a role as an early biomarker of disease severity.[82,83] This finding suggests that baseline lactate during admission could predict severity of sepsis.

A multi-center cohort study comprising children <16 years of age with a diagnosis of sepsis or septic shock admitted in the ICU was done with a goal to develop a sepsis score based on laboratory parameters. Their findings showed that mortality was independently correlated with lactate levels on admission and that a lactate of >2, >3, and >4 was associated with an adjusted respective mortality of 7.4, 8.4, and 9.5%, respectively.[84] These findings show the importance of measuring lactate to assess severity of sepsis. However, lactate cut-off values remain unclear.

In a prospective study of 77 pediatric patients in the emergency department with infection and acute organ dysfunction, lactate was measured at 2 and 4 h after the initial lactate was drawn and compared with other markers indicative of organ dysfunction. The

authors defined lactate clearance as a decrease of >10% from the lactate level on admission and a level <4 mmol/L was considered normal or back to baseline. Their study revealed that lactate normalizing to baseline within 4 h was associated with decreased risk of organ dysfunction, suggesting that serial lactate measurement may be prognostic in the first few hours of diagnosing sepsis.[81] This study shows that lactate >4 could be correlated with worse outcomes. However, because lactate is a measure of tissue perfusion and sepsis often present in shock with poor perfusion, arterial lactate is typically drawn after a high venous lactate is obtained to confirm as levels can be different. A 3-year retrospective study involving 60 PICU patients comparing venous and arterial lactate and concluded that venous lactate >2 mmol/L requires arterial lactate confirmation as the limits of agreement between the two becomes large.[85] Interestingly, an observational study of 1299 children with suspected sepsis in the emergency department with initial venous lactate >36 mg/dL is associated with increased mortality (OR 3 with 95% CI, 1.10–8.17). This finding suggests that although venous lactate can be falsely elevated due to tissue perfusion, a level >36 mg/dL can be a useful tool in assessing severity of sepsis at initial presentation.[86–92]

## AVENUES FOR RESEARCH

Newer biomarkers continue to inundate the pipeline of sepsis diagnostics, although their practical use in the clinical setting seem to be limited to theoretical implications at the moment. With advancing technology, the quest to discover the ideal sepsis molecular testing should definitely move forward especially in pediatrics. However, with now larger demographic data sets and more sophisticated epidemiologic tools, an emphasis on more robust clinical studies looking into the clinical utility of older and more readily available biomarkers should also be a concomitant priority. More recently, the role of combination biomarkers have been explored. Perhaps, instead of pairing newer biomarkers together, more studies looking into combination of older biomarkers bundled with staple laboratory values (e.g., complete blood count), demographic factors, and clinical features to elicit clinical signatures that will better define sepsis syndromes should be a focus. Although there is no universal scenario to suggest the command of any biomarker in its application in the diagnosis of sepsis, evidence continues to show the demonstration of their clinical value only in light of clinical acumen. Thus there is an essential role to explore, elucidate, and incorporate their use in variable clinical settings.

## CONCLUSION

Pediatric sepsis remains a global health concern. The definition of pediatric sepsis has continued to be an extrapolation from adult studies although it has historically proven an effective working definition for pediatric clinicians. While newer biomarkers continue to proliferate, the value of older and more readily available biomarkers to the pediatric bedside clinician cannot be abrogated. Older biomarkers which include CRP, PCT, lactate, and ferritin, although in varying levels of reliability are helpful adjuncts to clinical practice when used in the appropriate clinical context. They should, however, not be used as sole drivers of therapy. Newer evidence continues to suggest that biomarkers cannot supplant clinical decision making. Instead, biomarkers continue to demonstrate their clinical value only when clinical acumen is incorporated in the interpretation of their values. Furthermore, there is no single biomarker that can adequately diagnose sepsis. Although PCT has generally been found to be the most sensitive and specific among the four, all of these biomarkers need to be used in the correct clinical context along with other laboratory parameters to optimize their use in pediatric sepsis diagnosis.

## DISCLAIMER

This review article has not been previously published and is not currently under consideration by another journal.

## DATA AVAILABILITY

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

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## AUTHOR CONTRIBUTIONS

P.P.C.L., D.J.B., and A.M.E. made substantial contributions to the conception of this manuscript, drafting or revising it critically for important intellectual content and final approval of the version to be published. C.M.H. and C.G.M. helped with drafting or revising it critically for important intellectual content and final approval of the version to be published.

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## ADDITIONAL INFORMATION

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