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An Insight about Different Biomarkers in Pediatric Sepsis

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Abstract:Background: Sepsis remains a major contributor to pediatric hospitalizations and deaths, even with recent advancements. Screening, diagnosis, prognosis (risk stratification), monitoring of therapeutic response, and sensible use of antibiotics (determination of adequate treatment time, for example) are all made feasible by the existence of biomarkers throughout the response to an infectious insult. Research on biomarkers in pediatric sepsis is still in its infancy. Biomarkers such as C-reactive protein, procalcitonin, interleukin 6, 8, and 18, human neutrophil gelatinase, and proadrenomedullin are discussed in this study as they pertain to sepsis in pediatric patients. The treatment of pediatric sepsis might benefit from an evaluation of these biomarkers.

Keywords: Biomarkers, Pediatric, Sepsis

Introduction

A significant number of children end up in pediatric intensive care units due to sepsis.(1,2) Over the past ten years, numerous programs have been launched with the goals of better comprehending sepsis and making related concepts more clear (3,4). Another objective is to decrease the number of deaths and illnesses caused by sepsis by reducing the time it takes to diagnose the condition, start antibiotic treatment, and provide treatment guidelines for pediatric sepsis.(5) Sepsis still has a significant impact on children and adolescents, even though these strategies have reduced mortality rates relative to adults. The World Health Organization reports that sepsis is still one of the top causes of mortality for children and newborns worldwide.(4) The inadequacy of current clinical understanding of sepsis led to the development of a new conceptual approach in 2003. This approach, called the PIRO concept—an acronym for Predisposition, Insult, Response and Organ Dysfunction—was modeled after the tumor-node-metastasis (TNM) cancer staging system.(6) Dividing sepsis into these four categories enables therapeutic stratification through domain-specific individualized care.(7) It

is well-established that the host's reaction to infection can vary from person to person, with some engaging in an inflammatory response that includes elevated levels of biomarkers and biomediators. Local, regional, and systemic responses vary from patient to patient, and are dependent on factors such as the site of infection, the infectious agent, and the host (genetic susceptibility and comorbid conditions).
Screening, diagnosis, prognosis (risk stratification), therapeutic response monitoring, and rational antibiotic use (determining adequate treatment length, for example) are all made possible by the known presence of specific biomarkers during the response to an infectious insult. (Figure 1).

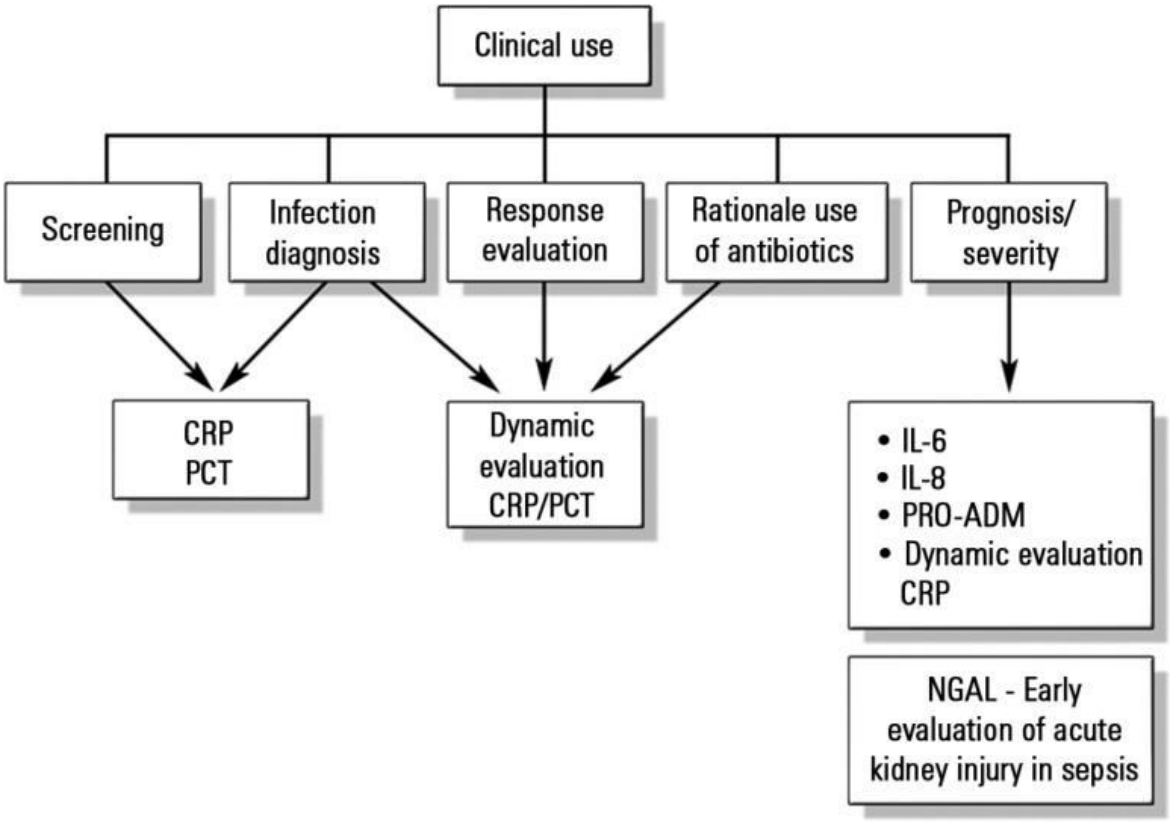

Figure 1: Biomarkers in pediatric sepsis.
CRP - C-reactive protein; PCT - procalcitonin; IL-6 - interleukin 6; IL-8 - interleukin 8; NGAL - human neutrophil gelatinase.

An objectively measurable and evaluated property that may serve as a sign of normal biological processes, pathological processes, and/or pharmacological responses to a therapeutic intervention is called a biomarker(8,9).
The available research on biomarkers supports the idea that their use should be prudent, and that clinical evaluation is essential for understanding their indications, use, and applicability.in (10,11)The utilization of biomarkers in the treatment of sepsis in pediatric patients is the subject of this review study.
Biomarkers have been the subject of research into their potential utility in screening and diagnosis for a while. There are currently accessible biomarkers that can be used as risk and prognostic stratifiers; these indicators have an improved connection with clinical severity and can detect illnesses with a worse prognosis at an earlier stage. Nevertheless, research on biomarkers' utility in children is still in its infancy compared to that in adults and even the newborn population. Here we will focus on a few biomarkers (Table 1) that have received more attention from studies involving children.

Table 1 - Main biomarkers in pediatric sepsis

Biomarker	Why use?	Limitations
CRP	Easily available and low cost Peaks 36 - 50 hours after an inflammatory trigger Serial use for therapeutic response assessment Not affected by immunosuppression, renal dysfunction or corticosteroid use	Variable sensitivity and specificity for detecting bacterial infection (lower when a single measurement is performed) Low accuracy
PCT	Peaks 24 - 36 hours after an inflammatory trigger More specific for bacterial infection	Variable sensitivity and specificity Altered serum levels in cases of renal dysfunction Lack of multicenter and prognostic and risk stratification studies Higher cost
IL-6 and IL-8	Increased accuracy when combined with other biomarkers Good correlation with severity Promising use in pediatric patients with cancer and febrile neutropenia	Few studies in the pediatric population
Adrenomedullin (proADM)	Correlation with severity and potential use as a risk stratifier Promising marker of diagnosis of infection in febrile neutropenic patients	Studies in the pediatric population are still scarce Not yet available for use in clinical practice
NGAL	Promising biomarker of acute kidney injury (organ dysfunction) Early increase in cases of acute kidney failure (48 hours prior to the increase of creatinine) Early introduction of renal protection measures	Lacks validation in pediatric patients with septic shock (low specificity as a kidney injury predictor) Low availability for use in clinical practice

CRP - C-reactive protein; PCT - procalcitonin; IL-6 - interleukin 6; IL-8 - interleukin 8; NGAL - human neutrophil gelatinase.

C-reactive protein

C-reactive protein (CRP) is a non-specific, acute-phase protein that has been used for a longer period of time as a biomarker for pediatric sepsis. It peaks 36 to 50 hours after being exposed to an inflammatory trigger, whether that trigger is infectious or not, and increases 4 to 6 hours afterward. The protein has an 8-hour doubling time. There is a 19-hour half-life for CRP. In invasive bacterial infections, its levels tend to be high but quickly drop when inflammation subsides.(12) When it comes to CRP as a diagnostic biomarker, its sensitivity and specificity aren't great for differentiating between serious bacterial infections and benign or non-bacterial infections, especially in situations of pediatric emergency, when regarded in a single dosage. A systematic analysis found that C-reactive protein (CRP) had an estimated sensitivity of 77% and specificity of 79% in diagnosing bacterial infection in children with fever who were not hospitalized.(13) On the other hand, its predictive power grows as the number of serial measurements increases, suggesting it could be an asset in treatment management. When C-reactive protein levels are measured serially and either stay high or go up after 48 hours of antibiotic treatment, it indicates that the treatment was unsuccessful.(12) C-reactive protein (CRP) elevations below 10 mg/L in 24-hour samples can be used to rule out infections and suspected cases of sepsis, according to research in neonates and young children.12 and 14This kind of tracking has the potential to let doctors stop prescribing antibiotics to some patients, which would save a lot of money and prevent them from being taken for longer than required.

Serial C-reactive protein measurements taken in the first 48 hours of antibiotic treatment in neonates with sepsis may indicate whether the infectious agent is responsive to the prescribed antibiotic regimen; consequently, serial C-reactive protein measurements can serve as a reliable indicator of whether or not empirical antibiotic treatment is sufficient. The organism's sensitivity was determined by the 89% sensitivity and 80% specificity of the CRP drop over this period.(15) Other biomarkers have been investigated in conjunction with CRP due of CRP's low specificity.(13) C-reactive protein testing was evaluated in studies of children with febrile neutropenia to determine the likelihood of severe sepsis. Elevated C-reactive protein levels seem to be a good diagnostic prediction within the first twenty-four hours when coupled with another biomarker, such as interleukin 8 (IL-8).(16) In patients with cancer and febrile neutropenia, the accuracy of CRP alone in diagnosing severe bacterial infection (sepsis/severe sepsis) is lower than that of other biomarkers, such as procalcitonin [PCT] and interleukin 6 [IL-6] (16).(17) Compared to relying solely on absolute values, studies in critically ill adults, particularly those with severe community-acquired pneumonia,

have demonstrated that tracking serial C-reactive protein (CRP) levels and how they change over the first 5 to 7 days of antibiotic treatment is a more useful prognostic indicator.(18–20) C-reactive protein (CRP) measurements are validated as a critical biomarker of antibiotic treatment response when evaluated dynamically, given their long history of use in clinical practice, accessibility, affordability, and availability in most healthcare facilities. Therefore, a comparable assessment in pediatric patients is warranted; indeed, such an assessment has previously been documented, albeit in a preliminary form.(21) Keep in mind that C-reactive protein is not a precise biomarker for identifying certain infectious agents or for distinguishing infection from inflammation. Bedside clinical evaluation of patients and other clinical decision-making criteria should always accompany its usage, as is the case with other biomarkers. The use of C-reactive protein (CRP) in conjunction with other biomarkers, such as procalcitonin (PCT), interleukin (IL)-6, and interleukin-8, has the potential to enhance its specificity in the diagnosis of infections (16,17) and to evaluate changes in therapeutic methods, such as antibiotic therapy, on the other hand.

The use of CRP in critically ill patients is beneficial because to its unique properties, despite its low specificity.(22) One of these is that systemic corticosteroids don't seem to have much of an effect on CRP levels; another is that immunosuppression doesn't seem to alter CRP levels when the source of the elevation is infectious (such as in seriously sick adult patients with sepsis and neutropenia). Beyond that, CRP levels are not impacted by renal failure or dialysis procedures, unlike other biomarkers like PCT.numbers 22 and 23 the Hence, C-reactive protein (CRP) has been a well-known inflammatory biomarker for a long time. However, there is significant value in using C-reactive protein in conjunction with other biomarkers and clinical criteria when evaluating treatment for sepsis (Table 2).

Table 2 - Main publications on the use of C-reactive protein in pediatric infection/sepsis

Authors	Type of publication	Main results	Conclusion
McWilliam et al.[12]	Narrative review	Single measurement of CRP is not sensitive or specific enough to identify severe bacterial infection Increased CRP suggests severe bacterial infection and requires further investigation	Serial measurements of CRP are useful in assessing the response to antimicrobial treatment CRP values that fail to decrease or continue to rise after 48 hours of antibiotic therapy suggest treatment failure
Sanders et al.[13]	Systemic review	Diagnostic accuracy of CRP for bacterial infection in non-hospitalized children with fever has 77% sensitivity and 79% specificity Increased predictive value with serial measurements	CRP is useful (moderately and independently) for the diagnosis and exclusion of severe bacterial infection Moderate sensitivity (77%) means that CRP may not be used to exclude all bacterial infections Serial measurements are even more useful
Santolaya et al.[16]	Prospective cohort	447 episodes of high-risk febrile neutropenia - 17% with diagnosis of severe sepsis Combination of 3 factors (age > 12 years, CRP > 90mg/L and IL-8 > 300pg/mL) on admission and/or 24 hours later identified risk for severe sepsis (6.7 RR)	Validation of the predictive risk model for severe sepsis in patients with high-risk febrile neutropenia in the first 24 hours of admission Proposal to incorporate this model in the initial evaluation of patients and more selective management of children at risk for severe sepsis
Kitanovski et al.[17]	Prospective cohort - 47 children	18 of 90 episodes of febrile neutropenia were classified as bacteremia/sepsis At days 1 and 2, CRP and other biomarkers had low to moderate diagnostic accuracy for sepsis with no significant difference between biomarkers The diagnostic accuracy of CRP was lower than that of IL-6 and PCT in severe sepsis	On admission and 24 hours later, the diagnostic accuracy of CRP alone for severe sepsis in children with febrile neutropenia was lower than that of PCT and IL-6
Lanziotti et al.[21]	Prospective cohort (preliminary results) - 57 children	50 of 57 patients were classified according to a CRP response pattern in the first week of antibiotic therapy in pediatric sepsis Mortality in the pediatric ICU was significantly different according to the CRP response pattern. Patients with decreased CRP had lower mortality than those without a decrease in CRP	Sequential CRP assessment (CRP ratio) is useful in the early identification of patients with poor prognosis Evaluation of CRP response in the first 7 days of antibiotic treatment may be useful in identifying an individual clinical course, influencing bedside decision-making

CRP - C-reactive protein; IL-8 - interleukin-8; RR - relative risk; IL-6 - interleukin-6; PCT - procalcitonin; ICU - intensive care unit.

Procalcitonin

The neuroendocrine C cells of the thyroid release PCT, a precursor to the calcitonin hormone, although in healthy individuals, serum levels are negligible. Nevertheless, PCT is released by various different tissues during a systemic infection, leading to a significant rise in serum levels. Because of this, PCT has been regarded as a trustworthy biomarker for distinguishing sepsis from SIRS that is not caused by an infection. PCT can help in deciding if antibiotics are necessary because it is reduced by interferon gamma (IFN-γ) when a virus is infecting a cell and its level determines whether bacteria are present in an infection. Values of PCT below 0.5ng/mL indicate inflammation without an infectious cause, while values above 2.0ng/mL indicate sepsis, taking into account the assay's highest sensitivity and specificity.(25)On the other hand, other adult studies(26) have employed alternative values, with PCT levels above 0.25 to 0.5ng/mL being indicative of a likely bacterial infection and the need for antibiotic treatment. Keep in mind that improvements in PCT detection technologies have also caused these numbers to fluctuate.

Typically, PCT levels rise 24–36 hours into an infection, which is earlier than CRP levels, and they peak at that point. Compared to other markers, particularly C-reactive protein (CRP), PCT assessment has shown superior accuracy in diagnosing bacterial infections in certain critically ill pediatric patients (27, 28). On the other hand, its specificity and sensitivity can differ.

Clinical evaluation should continue to be the primary factor in determining the therapeutic approach for febrile infants; however, a 2014 meta-analysis on the use of PCT levels for evaluating these patients (7 trials involving 2,317 patients) for severe bacterial infection suggested that serum values below 0.3ng/dL may be helpful for excluding severe infection when utilized in conjunction with clinical evaluation.(29)

whether deciding whether to start antibiotic treatment for a patient, clinical judgment is still the gold standard. Clinical examination, however, becomes less specific and, in some cases, happens too late to offer a foundation for decision-making for antimicrobial treatment as infectious diseases progress.(23) Biomarkers are crucial in this setting, and PCT has been the subject of substantial research in this area. Serial PCT measurements in pediatric patients with sepsis have been demonstrated in multiple trials to potentially serve as a reliable marker for determining when antibiotic therapy can be safely discontinued.28 and 30Therefore, PCT has the potential to shorten the time that bacteria are treated with antibiotics, which could help lower antibiotic resistance and lessen the negative side effects of these medications, such as nephrotoxicity and ototoxicity. While there are more studies examining the use of PCT to guide the discontinuation of antibiotic therapy in adult patients, even these studies have their limitations. Among these studies, there is a lack of consistent PCT use protocols, a high rate of patients being excluded, control group patients receiving long antibiotic therapy, and additional prognostic information such as length of hospital stay and mortality.

Researchers have looked for a correlation between this biomarker and illness severity, multiple organ failure, and mortality by measuring PCT serially at patient admission and throughout hospitalization.numbers 27, 28, 30, 31, and 32Serial PCT measures are being considered a potential prognostic sign, according to these research.

Children with bacterial sepsis who had continuously high PCT had a worse prognosis in a cohort study conducted in an American tertiary hospital. The study included 78 children who met the criteria for sepsis and septic shock, as well as 12 critically sick children who did not have sepsis.(31) In a different prospective observational study conducted in a pediatric intensive care unit in São Paulo, Brazil, the plasma levels of PCT upon admission enabled the distinction between sepsis and septic shock. The study included 689 patients admitted within a 2-year period, 59 of whom met the criteria for sepsis and 65 for septic shock.The results indicate that PCT can be used to diagnose septic conditions in children and determine the severity of the disease. This information can be helpful for evaluating whether a patient should be admitted to the pediatric intensive care unit, among other uses.

Results from a 2015 cohort research included 82 children with meningitis showed that PCT levels in the blood correlate with infection severity in bacterial meningitis patients and that a drop in PCT levels after therapy is an excellent indicator of a good prognosis.(34) Additionally same year, a meta-analysis demonstrated that PCT had a sensitivity of 96% and a specificity of 89% when it comes to distinguishing

between viral and bacterial meningitis in children.(35) In a more recent meta-analysis from 2015, researchers looked at PCT levels in pediatric patients diagnosed with acute pyelonephritis. They found that PCT values of 1.0ng/mL or higher had a better diagnostic performance (91% specificity) compared to values of 0.5ng/mL or higher (76% specificity and 86% sensitivity).Some studies have found that PCT is more accurate than CRP in indicating sepsis and bacteremia in cancer and febrile neutropenia children (36). The utilization of PCT values in the classification of cancer patients with febrile neutropenia has been promoted in recent years, and it appears that PCT values are unaffected by the use of corticosteroids and chemotherapy.22, 37, and 38

Researchers are currently studying the use of PCT to distinguish SIRS from sepsis in certain cases. For example, in the post-operative care of patients undergoing cardiac surgery, where antibiotics can worsen nephrotoxicity in patients exposed to intraoperative extracorporeal circulation, there is a need to differentiate between the two conditions. Although PCT testing has not yet been extensively used to predict infection or mortality in burned children, it has been evaluated for use in patients with severe burns.There is less published evidence of PCT's utility as a prognostic indicator in pediatric patients (41, 42). In the first five days of hospitalization, patients with Pediatric Logistic Organ Dysfunction (PELOD) scores of twelve or above had higher PCT values than patients with scores below twelve, according to a recent single-center prospective cohort study of sixty-two children diagnosed with SIRS and sepsis. Although there was no correlation between PCT levels and death in this investigation, there was a correlation between PCT levels and infection severity and organ failure in sepsis patients.(43) More rigorous research in pediatric patients is required, but there has been an uptick in the evaluation of PCT for risk stratification, prognosis, and mortality prediction. Most of the studies that have been conducted so far only involve one site and a relatively limited number of participants. As shown in Table 3, there is not yet enough data to establish PCT as a biomarker for widespread use in clinical practice as a risk stratifier, prognostic predictor, or even to dictate the length of antibiotic treatment or inform decisions made at the bedside. A larger number of patients, ideally from different parts of the world, should participate in multicenter trials. Keep in mind that Kryptor, the exclusive method for measuring PCT, is not available in many health facilities, particularly in developing nations, and that the cost of testing is still very high.

Table 3 - Main publications of the use of procalcitonin in pediatric infection/sepsis

Authors	Type of publication	Methods and main results	Conclusion
Rey et al.[27]	Observational prospective cohort	359 patient-days included in the study Evaluation of the use of PCT, CRP and leukocyte count to classify: absence of infection, SRIS, localized infection, sepsis, severe sepsis and septic shock Area under the receiver operating characteristic (ROC) curve for diagnosis of sepsis was 0.532 for leukocyte count, 0.75 for CRP and 0.912 for PCT	PCT is a better diagnostic marker for sepsis in critically ill patients than CRP PCT and CRP may be useful as clinical tools to stratify the severity of patients with SRIS
Fioretto et al.[28]	Prospective cohort	87 patients (46 patients diagnosed with sepsis and 41 patients diagnosed with septic shock) PCT and CRP measurement on admission and 12 hours later	PCT was better than CRP for the diagnosis of sepsis and septic shock, particularly on admission, and was related to disease severity
England et al.[29]	Systematic review	7 studies of 2,317 patients Evaluation of the use of PCT in the diagnosis of severe bacterial infection in young infants (≤3 months of age) 5 of 7 studies used the same cut-off value (0.3ng/mL) RR for diagnosis of severe bacterial infection with increased PCT was 3.97 RR for diagnosis of severe bacterial infection using clinical prediction was 30.6 (patients without antibiotic treatment) and 8.75 (patients using antibiotic)	PCT values < 0.3ng/mL may be useful in the exclusion of severe bacterial infection, as an additional test to clinical prediction, remaining as a key factor to guide the therapeutic approach in these patients
Arkader et al.[30]	Observational prospective cohort	PCT and CRP kinetics studied in patients undergoing heart surgery with cardiopulmonary bypass (Group 1 - SRIS) and in patients with confirmed bacterial sepsis (Group 2) The area under the ROC curve was 0.99 for PCT and 0.54 for CRP	PCT was able to differentiate patients with SRIS and sepsis, and CRP was not PCT concentrations varied according to the progression of sepsis
Han et al.[31]	Prospective cohort	87 patients with sepsis and septic shock 12 critically ill patients with no criteria for sepsis PCT values were elevated in patients with bacterial sepsis at days 1 and 3 of pediatric ICU admission Persistently elevated PCT values were found in patients with bacterial sepsis with persistent multiple organ failure and in those who died, but not in patients with non-bacterial sepsis (fungal, viral or sepsis with negative culture)	PCT is persistently elevated in children with bacterial sepsis and poor prognosis
Hu et al.[34]	Prospective cohort	Investigation of the relationship between the PCT SL and prognosis in children with bacterial meningitis 82 patients included Patients with bacterial meningitis have higher PCT SL than those with viral meningitis PCT SL were significantly higher in patients with severe sepsis and septic shock than in patients with non-severe sepsis and without sepsis A drop in PCT SL was observed in patients with a good response to antibiotic treatment PCT SL were significantly higher in patients who died than in survivors	PCT SL are related to disease severity in children with bacterial meningitis A decrease in PCT SL after treatment may indicate a favorable prognosis
Henry et al.[35]	Systematic review	8 studies were included (616 patients) PCT SL were highly accurate in differentiating the diagnostic etiology of meningitis in children, with 96% sensitivity and 89% specificity In 6 studies, the accuracy of PCT was higher than that of CRP	PCT SL are highly accurate in differentiating bacterial meningitis from viral meningitis in children
Hatzistilianou et al.[37]	Prospective cohort	Assessment of PCT, CRP, TNF-alpha, IL-1b, IL-8 and TNF-receptor II values in the rapid and early diagnosis of infection in patients with acute lymphocytic leukemia and febrile neutropenia and differentiation between bacterial and viral infection The SL of biomarkers were assessed on admission and for 7 consecutive days PCT SL were significantly different between bacterial and non-bacterial episodes, with 94% sensitivity and 96.5% specificity	Serial PCT measurements may be useful in predicting severe sepsis in patients with acute lymphoid leukemia and febrile neutropenia
Zurek et al.[43]	Prospective cohort	62 patients (0 - 19 years) with SRIS or sepsis were included Severity measured using the PELOD PCT SL were measured from day 1 to day 5 of admission and significantly higher PCT values were found in patients with PELOD >12 than with PELOD < 12	PCT SL from day 1 to day 5 of pediatric ICU admission are related to severity and multiple organ dysfunction in children with SRIS/sepsis

PCT - procalcitonin; CRP - C-reactive protein; SRIS - systemic inflammatory response syndrome; RR - relative risk; SL - serum levels; TNF-alpha - Tumor necrosis factor alpha; IL-1b-interleukin 1 beta; IL-8 interleukin 8; TNF-receptor II - tumor necrosis factor receptor II; PELOD - Pediatric Logistic Organ Dysfunction score.

Interleukin 6

An adult biomarker of sepsis, interleukin 6 (IL-6) is a pro-inflammatory cytokine that has been the subject of much research for quite some time. However, research with children is limited. When paired with additional diagnostic indicators, such as C-reactive protein (CRP), IL-6 blood levels are even greater in children diagnosed with sepsis compared to kids with noninfectious systemic inflammation alone (43,44).(43)In addition, IL-6 levels are a good predictor of severe sepsis when used in clinical practice, and higher levels are related with more severe instances in children with sepsis (45).

Researchers have found that IL-6 is an excellent indicator of bacteremia and clinical sepsis in children who have been diagnosed with cancer and who are experiencing febrile neutropenia.(17, 16)

But IL-6 testing is currently underutilized in clinical practice for a number of reasons, including its expensive price tag, restricted availability, and an absence of strong research supporting its usage, particularly in children.

Type 8 interleukin

One pro-inflammatory cytokine that may indicate whether critically sick infants will survive is interleukin-8 (IL-8). IL-8 can activate neutrophils and facilitate chemotaxis; it also has potential as a biomarker for risk classification. Children who did not survive 28 days after septic shock were shown to have greater levels of IL-8, according to a genome expression study(46) of pediatric patients with septic shock. According to a study published by the same original author(47), infants with septic shock have a 95% chance of survival if their IL-8 serum levels are less than or equal to 220pg/mL, as determined in the first 24 hours of hospitalization. Thus, IL-8 could be utilized to weed out intervention clinical trials that do not involve patients at low risk.

In children diagnosed with cancer who also experience febrile neutropenia, IL-8 may serve as a risk stratifier. Recent research using prospective cohorts demonstrated that low IL-8 serum levels were a strong predictor of a low risk of bacteremia (98% negative predictive value and 90% sensitivity). To validate these findings, additional research is required.In a similar vein, a higher risk of severity was associated with IL-8 levels above 300pg/mL, elevated C-reactive protein levels, and age more than 12 years in pediatric patients with cancer and febrile neutropenia (48).(49)

However, additional research involving adults is warranted because a study of adult patients revealed that IL-8 does not seem to be an effective biomarker of stratification in this population.[18] Interleukin 50

The pro-inflammatory cytokine interleukin-18 (IL-18), which is secreted by activated macrophages, has a role in the activation of cellular immunity. Inflammatory diseases, such as rheumatoid arthritis, sepsis, and newborn infections, are characterized by elevated IL-18 levels.Research on adult populations has demonstrated that septic individuals with high levels of IL-18 have a bad prognosis (51–53).(53) Additional research is needed in this area because there is a dearth of published publications on the use of IL-18 as a diagnostic or risk stratification biomarker, particularly in children.

Serum concentrations of the aforementioned interleukins vary substantially; nonetheless, evaluation of these levels is still not utilized frequently in the majority of pediatric and adult intensive care units; rather, it is utilized almost exclusively in research. To fully grasp the potential of interleukins as biomarkers in pediatric sepsis and their use, additional research is required, particularly multicenter trials. Potentially more serious than a previously healthy patient's febrile neutropenia from a severe bacterial infection, IL-6 and IL-8 show promise in the classification of pediatric patients.

Gelatinase from human neutrophils

One potential biomarker of acute kidney injury is human neutrophil gelatinase, also known as serum neutrophil gelatinase-associated lipocalin, or NGAL. A prospective cohort study(54) with 140 children ranging in age from 1 month to 21 years old and acute kidney failure graded using the pRIFLE (Pediatric modified Risk Injury, Failure, Loss, End-stage Kidney Disease) criteria confirmed urinary NGAL as an early

biomarker of acute kidney injury. Urinary NGAL concentrations rose two days prior to serum creatinine levels in this investigation, coinciding with a worsening of acute kidney damage as measured by the pRIFLE score. In critically sick pediatric patients, that study opens up new possibilities for the early detection and prevention of acute renal damage.(55)

In contrast, when it comes to pediatric patients experiencing septic shock, serum NGAL has not been proven to be a reliable indicator of acute renal impairment. In these patients, Wheeler et al. demonstrated that serum NGAL is a sensitive but non-specific predictor of acute renal injury; hence, additional research is needed to confirm this.(56) Urinary NGAL remains unchanged by sepsis, lending credence to its function as a predictor of acute kidney injury, according to an observational cohort study conducted in critically unwell infants. If a patient has sepsis, serum NGAL cannot tell you if they have acute renal injury or not.Plasma NGAL appears to have great sensitivity as a diagnostic predictor of acute kidney injury in adults, according to a recent investigation in sepsis patients (57).(58) NGAL could, in clinical practice, determine the earlier introduction of renal protective measures, such as the replacement of nephrotoxic antibiotics, initiation of water restriction, and even the initiation of hemodialysis or hemofiltration, thus contributing to improved prognosis in critically ill patients with sepsis and renal dysfunction. Urine is already validated as an early predictor of acute kidney injury, and serum is still considered nonspecific in this prediction. There is a lack of strong research on the utility of NGAL as a biomarker in this patient population.

Adrenomedullin, also known as protorenomedullin

In response to physiological stress, several tissues release the peptide adrenomedullin (ADM), which acts as a vasoregulatory, antibacterial, and anti-inflammatory. This novel biomarker shows promise, but it is difficult to assess because of how quickly it is digested in the blood. Because of its greater stability and ease of measurement, proadrenomedullin (proADM or the related midregional-proADM [MR-proADM]) has attracted greater interest as a biomarker. There are two reasons why ADM levels rise in sepsis: first, the calcitonin gene is involved in ADM synthesis, which increases during severe infections; and second, bacterial endotoxins and pro-inflammatory cytokines promote an upregulation of ADM gene expression in several tissues.Additionally, elevated blood levels of proADM during infection may be at least partially explained by impaired renal metabolism (59).59 and 60Serum MR-proADM levels were substantially higher in critically ill children (95 patients) who needed mechanical ventilation and inotropes, according to an observational study. With a stronger positive predictive value for prognosis (in-hospital mortality) than PCT and CRP, this biomarker showed a correlation with severity and might be utilized as a risk and prognostic stratifier.(61) A recent study evaluated the utility of ADM in cancer patients with febrile neutropenia as an indicator of infection. Compared to individuals with clinical illness alone or fever of unknown origin, febrile neutropenic patients with microbiologically proven infection had greater serum ADM levels. Among the three biomarkers examined, ADM had the strongest association with severity prediction compared to CRP and PCT.(62) Severe community-acquired pneumonia and sepsis are two of the many adult illnesses for which ADM has been the subject of substantial research.64, 63

For ADM to be better understood as a diagnostic marker, risk factor, and prognostic indicator in clinical practice, more investigations in children are required to assess its efficacy as a biomarker of sepsis and overall infection.

Use of biomarkers in risk stratification in pediatric sepsis

Although difficult, biomarkers show promise in risk classification of sepsis in pediatric patients. At this time, there is no foolproof way to utilize a single biomarker to forecast a patient's precise result. It is exceedingly improbable that a singular biomarker might be employed to detect and categorize all sepsis cases in pediatric patients, taking into account the intricate immunological response of every host and the genetic variety of populations.

There may be a need for a risk stratification technique that incorporates various biomarkers. The adult population has already made use of a number of biomarker models. The Pediatric Sepsis Biomarker Risk Model (PERSEVERE) was published by Wong et al. and is a multibiomarker model for risk classification in

pediatric septic shock. In the first twenty-four hours following hospital admission, 220 American children were assessed for twelve biomarkers.(65)The findings informed the development and validation of a risk model for the estimation of mortality in children afflicted with septic shock. This model makes use of five biomarkers: CCL3, IL-8, HSPA1B, GZMB, and MMP8. Individual decision-making, clinical trial selection (to exclude patients with a low risk of death and include patients with a high risk of death), patient stratification, and attempts to enhance the quality of treatment for septic shock are all areas that could benefit from this model.A multicenter cohort of 182 infants with septic shock from several pediatric intensive care units in the US was used to validate the PERSEVERE model (66). Statistical tests were used to determine if the multiple biomarker model accurately predicted the 28-day mortality risk in these patients, who had the five biomarkers evaluated within 24 hours of the clinical start of septic shock. Consistent with percentages published in the literature on pediatric sepsis mortality, the study cohort mortality rate was 13.3%. With a 34% positive predictive value and a 97% negative predictive value, PERSEVERE had an accuracy rate of 83% for mortality prediction and a specificity rate of 75%.(66)This study provides more evidence that biomarkers can be used to predict outcomes in pediatric patients and provide credence to their prognostic significance. Still up in the air, though, is the question of whether or not biomarkers can improve treatment adherence and outcomes for juvenile septic shock patients.

A panel of biomarkers including bicarbonate, angiopoietin-2, and angiopoietin-1 was found to be a more accurate predictor of severity in pediatric septic patients compared to utilizing each biomarker alone, according to a recent study.(67) There is hope for better patient selection for clinical trials, more accurate severity stratification, and more accurate mortality prediction in children with sepsis when several indicators are used concurrently for risk stratification. Additional research with individuals of this age should be made possible by these encouraging findings.

CONCLUSION

Although there should always be a correlation between biomarker use and clinical evaluation, their use in pediatric sepsis is encouraging. Sepsis diagnosis and prognosis may be improved by combining many biomarkers, as opposed to using just one. This is because multiple biomarkers have the potential to boost sensitivity and specificity. Clinical practice has recognized the importance of biomarkers like C-reactive protein and procalcitonin. C-reactive protein, in particular, has demonstrated its usefulness in dynamically assessing the response to antibiotic treatment. While measuring procalcitonin levels can help doctors decide whether to start or stop antibiotic treatment for patients with serious infections, there are some limitations to this method, such as the possibility of false negatives, the impact of renal dysfunction on serum levels, and the fact that clinical trials often exclude certain patients.

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