Utility of Procalcitonin as a Biomarker for Sepsis in Children

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Abstract

Sepsis is a complex process defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. It is associated with significant morbidity and mortality in both adults and children, and emphasis has been placed on its early recognition and prompt provision of antimicrobials. Owing to limitations of current diagnostic tests (i.e. poor sensitivity, delayed results), significant research has been conducted to identify sepsis biomarkers. Ideally, a biomarker could reliably and rapidly distinguish bacterial infection from other, non-infectious causes of systemic inflammatory illness. In doing so, a sepsis biomarker could be used for earlier identification of sepsis, risk stratification/prognostication, and/or guidance of antibiotic decisions. In this Minireview, we review one of the most commonly clinically used sepsis biomarkers, procalcitonin, and its roles in sepsis management in these three areas. We highlight key findings in the adult literature, but focus the bulk of this review on pediatric sepsis. The challenges and limitations of procalcitonin measurement in sepsis are also discussed.
Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection (1), and remains a major cause of morbidity and mortality worldwide. Recent estimates indicate close to 50 million incident cases of sepsis worldwide each year, with nearly half of these cases in infants, children, and adolescents (2). In the US, more than 1.7 million adults in the United States develop sepsis each year with an associated mortality of approximately 20% (3), while pediatric sepsis is associated with a mortality between 8-10% (4). Organ dysfunction can progress rapidly to shock and death if the underlying cause is un- or undertreated. Thus, educational efforts have focused on early sepsis recognition with goals to initiate supportive therapies and antibiotics as quickly as possible. However, because sepsis is a complex, heterogeneous process rather than a singular entity, accurate early diagnosis and risk stratification is challenging.

Despite the high morbidity and mortality associated with sepsis, it is unnecessary and unsafe to treat every patient that could have sepsis with antibiotics. Instead, clinicians need to use clinical judgement to determine the appropriateness of antibiotics in each individual patient. Due the complexity of sepsis, however, clinicians need both a high index of suspicion and diagnostic tools that can help differentiate sepsis from other inflammatory processes. While sepsis is most often associated with bacterial infections, it can result from any type of infectious process. In most studies of patients with suspected sepsis, bacterial infections are identified in only about 50% of cases (5). Unfortunately, microbial cultures, the current gold standard for diagnosing bacterial infections, are not 100% sensitive and cannot always be readily obtained. Additionally, collecting adequate cultures from focal sites of infection (i.e. lung, intra-abdominal cavity, etc.) is often not feasible, particularly during initial evaluation and for deep or tissue-based infections. Furthermore, results of microbial cultures are not immediately available, even when positive, limiting their utility in informing early decisions about initial sepsis management. Finally,
cessation of antibiotic therapy once an infection is appropriately treated is important in sepsis management, leading to potential reductions in need for prolonged intravenous access and decreasing the development of antimicrobial resistance.

As a result of the limitations of currently available diagnostic tests, extensive research has been performed to identify surrogate tests (e.g. biomarkers) that can accurately and rapidly distinguish those individuals with bacterial infections from other causes of critical illness and stratify patients by risk of adverse outcomes. In doing so, an ideal sepsis biomarker could improve the care of patients with sepsis in three primary areas: 1) early diagnosis, 2) risk stratification, and 3) antibiotic stewardship. The goals of using a sepsis biomarker for these three indications are summarized in Figure 1. While not necessarily exclusive of one another, these areas represent the primary settings for which biomarkers are studied and used clinically in sepsis.

This aim of this review is to summarize the current literature relating to one of the most commonly utilized sepsis biomarkers, procalcitonin (PCT). We will provide brief background on why PCT is a sepsis biomarker and highlight its utility in sepsis in the context of these three areas. Because PCT has been the focus of several reviews in the adult literature (6-9), this Minireview will specifically highlight PCT data in children, when possible. In doing so, we seek to provide a concise yet thorough review of the utility of PCT as a biomarker for sepsis in pediatric sepsis.

What is Procalcitonin?

Procalcitonin is a precursor of the hormone calcitonin that is produced by C cells in the thyroid gland and, to a lesser extent, other neuroendocrine cells throughout the body.(10) PCT is expressed in the central nervous system very early in fetal development (11), but the function of...
PCT itself is unclear; it is converted in the thyroid to calcitonin, a hormone involved in calcium homeostasis. Because PCT is nearly exclusively produced in the thyroid under normal physiologic conditions, it is typically undetectable in the serum in healthy patients. But, in the setting of bacterial infection, pro-inflammatory cytokines (TNF-α, IL-1-β, IL-6) trigger CALC-1 expression, the gene responsible for PCT production, in numerous cells throughout the body (10). In primates injected with LPS, mRNA expression was detected in several tissues including liver, lung, kidney, brain, intestine, skin, spleen, adrenals, and pancreas (12). But, since most cells are unable to convert PCT to calcitonin, PCT enters the circulation and blood levels rise while calcitonin levels are unchanged. Additionally, because PCT is produced by tissues in the setting of bacterial infection, in addition to immune cells, it should be reliably produced in both immune competent and immune compromised patients. Importantly, cytokines more selectively produced in response to viral infection, such as interferon-γ, attenuate CALC-1 upregulation such that viral infections tend not to induce the same degree of blood PCT elevation. As a result, PCT is more specific to bacterial than viral infections and offers a potentially attractive biomarker to differentiate patients with bacterial causes of infection from other etiologies.

Although viral infections are less likely to cause elevations in PCT, several other inflammatory conditions aside from bacterial infections can lead to increased blood PCT concentrations (13). Nonbacterial infections, such as severe fungal infections and malaria, surgery, burns, and bowel wall ischemia can all cause a rise in PCT, as can some paraneoplastic syndromes and cancers (10). Meanwhile, clearance of PCT levels from blood may be prolonged among patients with severe kidney disease, even though PCT does not require renal elimination to be cleared from blood(14). In this study (14), the authors suggested that the delayed PCT clearance may actually be due to prolonged production of PCT in patients with severe renal dysfunction, as a result of ongoing inflammation, rather than decreased elimination.
Because there is a normal physiologic increase in PCT immediately after birth, neonates have detectable PCT that peaks around 24 hours of life and declines over the subsequent 2 days (15). Thus, different cut offs are necessary for diagnosis of infection in the immediate post-partum period. Meanwhile, gestational age influences PCT values and the normal physiological rise that takes place following birth is blunted, leading to delayed normalization in preterm infant (16). This has led to the development of different age-specific reference intervals for PCT among preterm infants (17). Beyond the neonatal period, however, PCT should not be detectable in the blood under normal conditions and, thus, the adult reference range should apply to children. However, the performance of PCT likely differs between adults and children because of age-related differences in the epidemiology, microbiology, and immune response in sepsis, as well as maturational variability in comorbid conditions that affects production and clearance of PCT directly and indirectly through cytokines. Consequently, it is likely that one should interpret a given rise in PCT differently in a child, young adult, or geriatric patient (18).

Procalcitonin in the Diagnosis of Sepsis

Since PCT was originally found to be elevated in patients with staphylococcal toxic shock syndrome (19), numerous studies have investigated the utility of PCT as a biomarker to differentiate bacterial infection and sepsis from non-bacterial causes of critical illness that cause systemic inflammation. One of the earliest studies to evaluate PCT as a biomarker for bacterial infection was performed in hospitalized children with suspected infections (20). In this study, 19 infants and children with severe bacterial infections had high PCT compared to those with no infection and those with localized bacterial infection or viral infections. Proof of principle for the concept of PCT as a biomarker of bacterial infection was then provided by demonstrating that endotoxin injection into healthy volunteers produces a rise in PCT (21). The kinetics revealed
that PCT peaks at 6 hours after endotoxin injection and remains elevated through 24 hours, making it a promising early biomarker to differentiate bacterial from nonbacterial infections prior to the results of microbiologic cultures (21). Further, while several other processes that cause inflammation may cause transient rises in PCT, these elevations are generally somewhat lower than those in seen in bacterial infections, and are typically only sustained over the course of days when concomitant infection is present (13).

Multiple studies in adults have confirmed that PCT is a sensitive and specific biomarker for severe bacterial infections, providing insights into clinical situations in which PCT is most useful. A prospective study of 101 medical intensive care unit (ICU) patients with systemic inflammatory response syndrome (SIRS) and anticipated length of stay ≥24 hours showed that PCT was higher in patients with sepsis and positive cultures, with 89% sensitivity and 94% specificity for sepsis using a PCT cutoff of 1 ng/mL (22), PCT outperformed C-reactive protein (CRP), IL-6, and lactate as a diagnostic biomarker for sepsis in this study (22). Meta-analyses have subsequently confirmed these findings. One meta-analysis of 30 studies comprising 3,244 emergency department or ICU patients with SIRS calculated a pooled sensitivity of 77% and pooled specificity of 79% with an area under the receiver operating characteristic curve (AUC) of 0.85 (95% confidence interval [CI] 0.81 - 0.88) for PCT to differentiate sepsis from non-infectious SIRS (23). In this meta-analysis, PCT performed better in surgical compared to medical patients. A more recent meta-analysis of 58 studies comprising 16,514 patients with suspected infection or sepsis calculated a pooled sensitivity and specificity to detect bacteremia of 76% (95% CI 72 – 80) and 69% (95% CI 64 – 72), respectively, at a cut-off of 0.5 ng/mL (AUC of 0.79) (24). In this meta-analysis, PCT performed best in ICU patients (AUC 0.89) and worst in immunocompromised/neutropenic patients (AUC 0.71) (24). Meanwhile, Wu et al. performed a meta-analysis of PCT to detect bacterial infections in patients with autoimmune diseases and calculated a summary AUC of 0.91 (95% CI 0.88 – 0.93), better than CRP (AUC
0.81, 95% CI 0.78 – 0.93), providing evidence that PCT may even be useful in patients with
known systemic inflammatory conditions that are frequently treated with immunosuppressive
therapies (25).

Similar to adults, many studies have investigated the use of PCT in children in various clinical
settings. PCT can help differentiate serious bacterial infections in children with fever and central
venous catheters or neutropenia (26, 27), distinguish bacterial from viral/aseptic meningitis (28,
29), and identify the presence of meningococcal disease in febrile children with rashes (30).
PCT is particularly well studied, though, in critically ill children in the pediatric ICU (PICU). In a
prospective study of 80 children in a PICU with suspected sepsis, PCT had higher diagnostic
performance for severe infections than CRP or leukocyte count (31). Among 78 PICU patients
with sepsis, PCT was elevated in those with bacterial sepsis but not in those with fungal, viral,
or culture-negative sepsis, and PCT was persistently elevated over time in children with multiple
organ dysfunction syndrome and nonsurvivors (32).

A prospective cohort study of 64 PICU patients with SIRS also showed that PCT can identify
those with bacterial infections better than CRP as a single biomarker, although the performance
of PCT alone was only moderate (AUC 0.71) (33). However, measuring both PCT and CRP
improved diagnostic accuracy: the posttest probability of bacterial infection was 74% when PCT
and CRP were both indicative of infection, and was only 3% when both were negative (33).

Using data from this study (33), Figure 2 visually demonstrates how the combination of PCT
and CRP improved the post-test probabilities of bacterial infection in children with SIRS
compared to use of either test alone. Similarly, in a prospective study of 85 PICU patients with
SIRS and suspected infection, measurement of multiple biomarkers accurately identified
critically ill children with low risk of bacterial infection: a combination of CRP < 4 mg/dL together
with PCT < 1.75 ng/mL had a negative predictive value of 0.9 (95% CI 0.79 – 1.0) (34).
Other studies in the PICU population have also demonstrated utility of PCT to exclude bacterial infections, which is useful to guide treatment decisions and limit unnecessary antibiotic use. A retrospective study of 646 PICU patients with PCT measured within 48 hours of admission showed that PCT peaked within 24 hours of PICU admission, outperformed leukocyte count, and had better performance to "rule out" rather than "rule in" infection, with a negative likelihood ratio (LR-) of 0.3 (35). In a detailed analysis of false negative results, the authors found that PCT was less helpful to distinguish bacterial infections with localized central nervous system, soft tissue, bone, and severe lower respiratory tract infections (35).

Because PCT has a good negative likelihood ratio, PCT can identify lower risk patients who have are very unlikely to have bacterial infections. Sensitivity and specificity are metrics that describe a test's utility as a screening test in a population, but are less useful when interpreting an individual patient's test results. Likelihood ratios, which are interpreted in the context of pretest probability, are more useful clinically. In adult patients with suspected sepsis, using a PCT cut-off of 0.5 ng/mL, the negative LR (LR-) reported in a meta-analysis of 19 studies (3,012 patients) was 0.27 (5). Thus, among the population of all patients with suspected sepsis, if 50% have bacterial infections (pre-test probability of infection = 0.50), a LR- of 0.27 means that an individual with a PCT below 0.5 ng/mL would still have approximately a 20% chance of having an infection (post-test probability). As a result, a low PCT value drawn at onset of suspected sepsis would be insufficient to withhold antibiotics if no additional information was considered. In clinical practice, however, the actual pretest probability of bacterial infection varies from patient to patient and clinicians always have additional data available aside from the PCT. Using other information (CRP, clinical judgement, etc.) can alter the pretest probability and allow interpretation of a low PCT to be highly reflective of absence of infection.
Several gaps remain in understanding the utility of PCT as a rapid biomarker to detect serious bacterial infections in critically ill children. While there are some data supporting its use in patients with neutropenia (36), it is not well studied in other types of immunocompromising conditions and specifically in immunocompromised critically ill children. PCT may miss patients with localized, yet still clinically relevant, infections (30, 35, 37). Finally, PCT has variable utility in patients with fungal infections, and, when elevated, the PCT levels are typically lower than in bacterial infections (32, 38, 39). Therefore, the precise utility of PCT in children at high-risk for non-bacterial causes of sepsis remains unclear.

Risk Stratification

Multiple studies have demonstrated that PCT exhibits a “dose-response” gradient that tracks with overall severity of bacterial infection in both adults (40), as well as in children (41, 42). In general, localized bacterial infections (e.g., lower urinary tract infection) tend to induce a minimal rise in circulating PCT, while there is a progressive increase in PCT levels in more invasive bacterial infections that cause SIRS (e.g., pyelonephritis with bacteremia) and with clinical progression to sepsis and septic shock. A similar rise in PCT may even be apparent among critically ill children with increasing severity of viral infections (35). Furthermore, among hospitalized patients, non-survivors tend to have higher PCT levels compared to survivors (43, 44). These observations led, in part, to the US Food and Drug Administration’s initial approval of PCT in 2008 (45), “For use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.”

An important challenge to the application of PCT as a biomarker of illness severity at the bedside, however, is the lack of clear discrimination across individual patients. For example, among 646 children treated in a PICU, patients with bacterial septic shock exhibited higher...
median PCT than patients with bacterial infection without shock (7.16 vs. 1.51 ng/mL, respectively) (35). However, the interquartile ranges overlapped considerably in the 2-4 ng/mL range (2.21-42.28 ng/mL with shock and 0.41-4.04 ng/mL without shock) (35). Similarly, Van der Kaay et al. found that median PCT levels at PICU admission were significantly higher in children with meningococcal disease who had septic shock than in children with sepsis without shock (270 vs. 64 ng/mL, p<0.01), but with notable overlap in the ranges for each group (septic shock, 6-672 vs. sepsis, 21-284 ng/mL) (46). These studies highlight the large “gray zone” of PCT, in which results are indeterminate when used to distinguish septic shock from sepsis.

The discriminatory prognostic value of PCT may be even less pronounced among patients with similar categories of illness severity. For example, in meta-analysis of all hospitalized adults with infection and SIRS, the weighted mean difference of initial PCT values between survivors and non-survivors was -6.02 ng/mL (95% CI -10.01 to -2.03, p=0.003) (47). But, this difference was no longer significant when the analysis was limited to patients with the highest clinical illness severity of severe sepsis or septic shock (pooled mean difference, -1.71 95% CI -10.16 to 6.73, p=0.69). In a study of 75 children with septic shock, Hatherill et al. reported a higher median PCT in non-survivors compared to survivors (273 versus 82 ng/mL, p=0.03), but the ranges were nearly identical (non-survivors 5.1-736 versus survivors 3.3-760 ng/mL) (48). Thus, the prognostic capacity of a single elevated PCT measurement may be limited. On the other hand, a very low or normal PCT (<0.5-1 ng/mL) may more reliably indicate a reassuring prognosis, with a negative predictive value for adverse outcomes (e.g., death) that approaches 100% in several pediatric studies (44, 46, 48).

Serial testing of PCT likely provides more accurate prognostic information than a single test. For example, Hatherill et al. demonstrated that the absence of a decline in PCT after 24 hours of treatment for pediatric septic shock was associated increased mortality (44% versus 9%, 12
Biomarker data from REsearching severe Sepsis and Organ dysfunction in children: A gLobal perspective (RESOLVE), a phase III trial of drotrecogin alfa (activated) in pediatric severe sepsis, demonstrated a greater decline in PCT values over the first 6 days of septic illness among 324 survivors compared to 63 non-survivors (49). Similarly, in a small study of pediatric severe sepsis/septic shock performed in India, Poddar et al. reported a 76% reduction in PCT among 14 survivors compared to an increase in 200% for 6 non-survivors (p=0.006) (50). Serial testing is especially necessary in pediatric conditions in which an initial PCT may be elevated due to the underlying insult, such as after trauma, burn injuries, and cardiac surgery. For example, in a single center study of 33 children following open heart surgery, persistent elevation of PCT through post-operative day 4 was associated with severity of organ failure and mortality (51).

While additional pediatric data are needed, a threshold decrease of at least 80% from initial PCT measurement has been tested in adults with severe sepsis and septic shock in the Multicenter Procalcitonin Monitoring Sepsis (MOSES) study (52). Among 646 patients who were alive and in the hospital on day 4, there was a significantly higher risk of death if PCT did not decline by at least 80% from baseline to day 4 after adjustment for initial illness severity and other clinical variables associated with adverse outcome (aHR 1.97, 95% CI, 1.18–3.30, p <0.01). Ultimately, while PCT is useful to distinguish illness severity across groups of patients, the additional informative data provided by a single elevated PCT at the bedside beyond other clinical distinguishing factors (e.g., SIRS versus shock) is not yet clear. In particular, for predicting risk of mortality among patients, a clinician must incorporate the precipitating cause of illness, the clinical milieu, and other clinical information (i.e. other test results, underlying conditions, etc.) when estimating illness severity or prognosis for an individual patient. In this setting, serial measurement of PCT likely yields more accurate predictive validity than initial values.
Antimicrobial stewardship

Among adult patients meeting current definition of sepsis, bacterial infections are identified in approximately 50% of cases (5). In children, according to a nationally representative administrative dataset (53), bacterial or fungal pathogens were identified in only 43% of sepsis cases. Despite important limitations in current methodologies for identifying pathogens, it follows that not all patients with suspected sepsis will benefit from antibiotic treatment. Knowing that inappropriate antibiotic use contributes to the development of antimicrobial resistance and leads to increased adverse events and hospital costs, an important clinical use of any sepsis biomarker is its ability to guide antibiotic decisions. Antimicrobial stewardship focuses on the judicious use of antibiotics, and biomarkers such as PCT can help aid clinicians regarding who needs antibiotics and for how long. As a result, there are three avenues relating to antibiotic stewardship for which PCT has been predominantly studied: 1) antibiotic initiation, 2) escalation of antibiotics (i.e. broadening antibiotic spectrum), and 3) antibiotic cessation.

Antibiotic initiation

To facilitate early identification of sepsis and timely treatment, clinicians seek a biomarker that optimizes sensitivity. Several meta-analyses summarize the test characteristics of PCT and other biomarkers for the diagnosis of sepsis in critically ill adult patients (5, 54, 55). In a recent meta-analysis of 19 observational studies involving 3,012 adult patients (5), the pooled sensitivity for the diagnosis of sepsis, according to the Sepsis-3 definition (1), was 0.80 (95% CI 0.75-0.84). Based on this pooled test performance, if clinicians were to rely solely on PCT values to initiate antibiotics in patients with suspected sepsis, 1 in 5 patients with sepsis would go untreated. As described earlier, these data suggest that PCT is a helpful biomarker for identifying patients with sepsis, but inadequate to serve as a stand-alone test to guide decisions about antibiotic initiation in acutely ill patients with clinical features of septic shock for whom a
low threshold for empiric antibiotics is appropriate. In the current quest to ensure early initiation of antibiotics in patients with sepsis, PCT does not yet play an effective role.

Similar data exist for neonates with early- and late-onset sepsis. In a 2018 meta-analysis of 28 studies that included 2,661 neonates with suspected sepsis, PCT had a pooled sensitivity of 0.85 (95% CI 0.79-0.89) for distinguishing sepsis from non-sepsis (56). The diagnostic accuracy of PCT for neonatal sepsis improved when results were combined with CRP values: a pooled sensitivity of 0.91 (95% CI 0.84-0.95) (56). As it does in adults, PCT has insufficient accuracy in itself for the diagnosis of neonatal sepsis. When combined with other biomarkers, however, such as CRP, PCT is more helpful in identifying patients who would most benefit from antibiotics.

Even fewer data exist for older children. To our knowledge, no meta-analyses have examined the test performance of PCT for sepsis exclusively in older children. Thus, data are limited to single-center observational studies. While in theory PCT should perform similarly among children as in adults since PCT values are not age-dependent, it is unlikely that PCT performs sufficiently to serve as an independent sepsis screening test for antibiotic initiation in ill-appearing children.

**Escalation of antibiotics**

Because patients whose PCT fails to decline on serial measurement have increased mortality (48, 49), it is postulated that persistently elevated concentrations over time may signal the presence of an inadequately treated infection. Under this pretense, serial measurement could help identify patients who would benefit from escalation of antibiotics (i.e. broader spectrum therapy) to ensure adequate antimicrobial coverage of potential pathogens. The goal of utilizing
PCT in this respect is to facilitate the early identification of an inadequate response to initial antibiotic therapy in patients with infection rather than early identification of infection itself.

There has only been one RCT studying the utility of PCT in this context and none involving children (57). In the PASS trial, conducted across 9 ICUs in Denmark, investigators asked whether the availability of PCT results and an obligatory guideline for antimicrobial escalation would result in provision of appropriate antibiotic therapy earlier in infected critically ill patients and improve survival (57). The investigators randomized 1,200 patients upon ICU admission to standard-of-care or a PCT-guided drug escalation arm and collected PCT daily. The standard of care arm was not informed of PCT results while in the PCT arm clinicians were instructed to escalate antibiotics if the PCT was >1 ng/mL and not decreasing by at least 10% from the previous day. Additional diagnostic testing was also directed in the PCT arm to identify uncontrolled sources of infection. De-escalation was permitted when PCT was less than 1 ng/mL for 3 consecutive days. By design, subjects in the PCT arm received significantly more (2,925 vs 1,893 days, p<.001) and broader antibiotics than patients in the standard of care arm. However, among patients with microbiologically confirmed infections, the time to appropriate therapy was similar in the two groups: 0.2 days (PCT group) vs 0.4 days (standard of care; p = .61). And, there was no difference in 28-day survival (HR 0.98, 95% CI 0.83-1.16), even across a number of pre-specified sub-group analyses such as gender, age, APACHE II score, severity of infection, and prior surgery. Meanwhile, the PCT arm had worse secondary outcomes including more ICU days on mechanical ventilation, days with renal failure, and days in the ICU. The authors concluded that escalation of antibiotics based on PCT results did not improve survival while leading to administration of more and broader antibiotics, longer hospital stays, and negative effects on organ function.
To our knowledge, there are no pediatric studies that have utilized PCT in this manner. Because the PASS study had a very specific algorithm for how antibiotics were to be escalated and interventions followed, the outcomes were heavily dependent upon the specifics of the algorithm. It is possible that a different algorithm, one that escalates breadth of coverage based on different criteria or that broadens to different antimicrobial agents, would have less deleterious outcomes. However, mandatory escalation of therapy in the setting of rising or persistently elevated PCT values does not appear to be an effective therapeutic strategy.

De-escalation/antibiotic cessation

Data are supportive of PCT use in ICU settings to inform decisions around safe cessation antibiotics. In a patient-level meta-analysis of RCTs evaluating PCT-guided treatment on mortality among adults with acute respiratory tract infections, the use of a PCT algorithm was associated with decreased overall mortality among adults in an ICU (odds ratio 0.88; 95% CI 0.77-1.00) (58). Similarly, a Cochrane review of PCT to initiate or discontinue antibiotics for acute respiratory tract infections found decreased 30-day mortality (odds ratio 0.88, 95% CI 0.77-1.00) among ICU trials (59). As reported above in the Diagnosis section, PCT has a good negative predictive value, particularly when combined with other clinical data, such as CRP. Therefore, low PCT values drawn at suspected sepsis onset can support early antibiotic cessation when other data similarly suggests that infection is absent. Because PCT decreases by 50% every 1-2 days in the absence of active infection (i.e. when infection is adequately treated) (21), serial PCT measurement can also be useful to guide antibiotic duration in patients with documented or proven infections. Meta-analyses of RCTs of PCT-based antibiotic cessation have found that implementation of an algorithm that specifies stopping antibiotics when PCT is low (usually <0.5 ng/mL), or when concentrations have decreased by ≥80% from peak values, leads to a significant reduction in antibiotic duration compared to standard of care without an increase in mortality (6, 7). Two recent meta-analyses both concluded that use of a
PCT-based cessation algorithm led to 1.3 fewer days of antibiotics in critically ill adults (6, 7).

PCT-guided cessation was also associated with decreased short-term mortality compared with standard care groups (RR 0.82; 95% CI 0.70 – 0.96; p = 0.01) (6). While there was significant heterogeneity across included studies, and variable levels of adherence to PCT-defined algorithms in the included trials, implementation of a PCT-based cessation guideline appears to be an effective strategy to decrease antibiotic usage in critically ill adults. This has led to publication of an international consensus document supporting measurement of PCT every 24-48 hours with recommendations to discontinue antibiotics when PCT is < 0.5 ng/mL or has dropped by 80% from peak values (60).

Fewer RCTs have been conducted in children. The NeoPIns study was a large RCT across 18 hospitals among neonates with suspected early-onset sepsis (61). This trial stratified more than 1,700 infants based on their risk for early onset sepsis and randomized subjects to standard of care or PCT-guided discontinuation. Based on the specific algorithm implemented, only those with unlikely or possible infection were eligible for PCT-based discontinuation, as those with probable or proven infections were treated with a standard regimen of 7-21 days of antibiotics. Similar to adult studies, the duration of antibiotics was reduced in the PCT group (intention to treat: 55.1 vs 65.0 hours, p<0.0001) without an increase in adverse outcomes. Although the difference in antibiotic duration was only 10 hours, this is a substantial and important reduction in overall use (15% shorter) in neonates.

To our knowledge, there are no published RCTs comparing PCT-based discontinuation to standard of care in older pediatric patients. However, there are observational studies available (62). One study evaluated the impact of an algorithm on antibiotic use in critically ill children with SIRS (62). The algorithm stated to stop antibiotics at 24-48 hours if PCT drawn at SIRS onset was <1 ng/mL and CRP < 4 mg/dL, microbiologic cultures were negative, and there were no
focal signs of infection present on evaluation. Although antibiotic use was not decreased among all patients with SIRS (p = 0.76), implementation of this algorithm was associated with a significant reduction in days of therapy in the subset of patients who had both CRP and PCT below the defined cut-points: 129.9/1000 days vs 301.2/1000 days (IRR 0.43, 95% CI 0.26-0.71) (62). While observational, this study demonstrates the potential utility of PCT to allow for safe antibiotic de-escalation in pediatric patients at low risk for bacterial infection.

Conclusions

Procalcitonin has become a biomarker used frequently in sepsis due to its relative specificity for bacterial over viral infections compared to other biomarkers available for clinical use. Despite its superior test performance over more traditional biomarkers such as CRP and white blood cell count, PCT is not sufficiently sensitive nor specific to serve as a stand-alone test for the diagnosis of sepsis. Given the diverse nature of sepsis, and PCT’s moderate performance as a sepsis biomarker, clinicians should be careful not to be overly reliant on the results of any single PCT measurement. Similarly, while an elevated PCT concentration at the time of initial sepsis evaluation portends a worse outcome in patients with severe sepsis or septic shock, serial measurement provides more reliable prognostic information, as values decline more readily in survivors/responders to treatment. Figure 3 summarizes the performance of PCT with respect to each of the clinical scenarios highlighted in this review.

With an understanding of its limitations and prognostic ability, PCT can help guide safe antibiotic cessation decisions in children initially suspected to have a bacterial infection but who clinically improve without confirmation of a true infection. In low-risk patients, where additional information or clinical assessment makes bacterial infection unlikely, a very low PCT can provide further evidence that stopping antibiotics early is safe in both critically ill adult and...
pediatric patients. Meanwhile, in higher risk patients, including those with documented infections, serial measurement can provide data to guide duration of therapy, leading to a reduction in overall antibiotic use compared to standard of care practices (i.e. arbitrary 7-14-day course). In adults, an 80% decline in PCT from peak concentrations, or to values <0.5 ng/mL, has been supported as a means to reduce antibiotic duration (60). Confirmation that these targets are safe and effective in pediatric patients will need to be verified.

Finally, while biomarker-based algorithms employ a cut-point to assist with interpretation of PCT results, clinicians must remember that results should not be accepted in absolute terms (i.e. above the cut-point is diagnostic of sepsis while below rules it out). Cut-points have been identified as inflection points that best influence the likelihood that bacterial infection is present or absent. But, because PCT is not a diagnostic test, it should only be used to supplement not replace clinical judgement.
REFERENCES


Figure Legend(s):

Figure 1. General goals and challenges for use of sepsis biomarkers at onset and during illness.

Figure 2. Example of how measurement of PCT and CRP in combination strengthens the performance of biomarkers in pediatric SIRS. Data in figure derived from Simon et al. (33). In this study of 69 children with SIRS, 24 had bacterial infection (pre-test probability 39%). A: Use of PCT alone had positive likelihood ratio (LR+) of 2.65, increasing post-test probability to 60%, and a negative likelihood ratio (LR-) of 0.43, decreasing post-test probability to 22%. B: Use of CRP alone had a LR+ of 1.63 (post-test probability of 50%) and LR- of 0.10 (post-test probability of 6%). C: Combination of PCT and CRP had LR+ of 4.32 (post-test probability of 74%) and LR- of 0.043 (post-test probability of 3%). Discordant CRP and PCT results (not shown) had LR of 0.27 to 0.70 (post-test probability of 15-30%).

Figure 3. Performance of PCT and data supporting its use at sepsis onset and during illness. Green shading denotes the presence of good evidence to support use of PCT in that scenario. Yellow shading denotes the presence of weak evidence to support use of PCT in that scenario. Red shading denotes presence of evidence against use of PCT in that scenario.
<table>
<thead>
<tr>
<th>Time frame</th>
<th>Result</th>
<th>Sepsis identification (SI)</th>
<th>Risk stratification (RS)</th>
<th>Antimicrobial stewardship (AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sepsis onset</strong></td>
<td><strong>Biomarker abnormal</strong></td>
<td>Accurately and rapidly identifies patient with sepsis</td>
<td>Informs prognostication, leading to implementation of interventions that improve survival/outcomes</td>
<td>Promotes appropriate initiation of targeted antibiotics</td>
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<td></td>
<td><strong>Biomarker normal</strong></td>
<td>Accurately rules out infection as cause of illness</td>
<td>Identifies patients at low risk for disease progression/poor outcomes</td>
<td>Facilitates withholding unneeded antibiotics</td>
</tr>
</tbody>
</table>

**Challenges to Use**

- Need knowledge of test performance in numerous clinical scenarios and patient populations to accurately define factors contributing to false negative and false positive results (SI, AS)
- Kinetics of biomarker have to align with clinical onset of infection to support early measurement (SI, RS, AS)
- Results need to be available quickly to inform early decisions (SI, RS, AS)
- Clinical utility requires that timely and impactful interventions exist and are accessible (RS)
- Cost of test needs to support routine use (SI, RS, AS)

<table>
<thead>
<tr>
<th>Time frame</th>
<th>Result</th>
<th>Sepsis identification (SI)</th>
<th>Risk stratification (RS)</th>
<th>Antimicrobial stewardship (AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During illness</strong></td>
<td><strong>Biomarker abnormal or worsening</strong></td>
<td>Confirms diagnosis of sepsis; may suggest untreated source of infection</td>
<td>Informs prognostication, leading to implementation of interventions that improve survival/outcomes</td>
<td>Supports continued administration of antibiotics</td>
</tr>
<tr>
<td></td>
<td><strong>Biomarker normal or normalizing</strong></td>
<td>Confirms absence of infection</td>
<td>Identifies patients at low risk for disease progression</td>
<td>Promotes safe, early discontinuation or de-escalation of antibiotics</td>
</tr>
</tbody>
</table>

**Challenges to Use**

- Need knowledge of test performance over time in numerous clinical scenarios and patient populations to accurately define factors contributing to false positive and false negative results (SI, RS, AS)
- Kinetics of biomarker have to align with resolution of infection to promote serial measurement (SI, AS)
- Measurement must improve knowledge of patient status compared to standard clinical care (RS, AS)
- Requires education to ensure adherence to biomarker-guided antibiotic prescribing (AS)
- May not be practical or cost effective, particularly in resource-limited settings (SI, RS, AS)
<table>
<thead>
<tr>
<th>Time frame</th>
<th>Result</th>
<th>Sepsis identification (SI)</th>
<th>Risk stratification (RS)</th>
<th>Antimicrobial stewardship (AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis onset</td>
<td>PCT normal</td>
<td>Accurately rules out infection as cause of illness</td>
<td>Identifies patients at low risk for disease progression/poor outcomes</td>
<td>Facilitates withholding unneeded antibiotics</td>
</tr>
<tr>
<td>PCT abnormal</td>
<td></td>
<td>Accurately and rapidly identifies patient with sepsis</td>
<td>Informs prognostication, leading to implementation of interventions that improve survival out comes</td>
<td>Promotes appropriate initiation of targeted antibiotics</td>
</tr>
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**Examples of Data Supporting Its Use**

**SI and AS:** A meta-analysis of 30 studies and 3,244 patients calculated a pooled sensitivity of 77% and pooled specificity of 79% with an area under the receiver operating characteristic curve (AUC) of 0.85 (95% confidence interval [CI] 0.81 - 0.88) to differentiate sepsis from non-infectious SIRS in adults (23). In a meta-analysis of 19 observational studies involving 3,012 adult patients (5), the pooled sensitivity for the diagnosis of sepsis based on Sepsis-3 definition was 0.80 (95% CI 0.75-0.84). In a 2018 meta-analysis of 29 neonatal studies that included 2,691 neonates with suspected sepsis, PCT had a pooled sensitivity of 0.85 (95% CI 0.79-0.93) for distinguishing sepsis from non-sepsis (56). Our opinion: PCT has modest performance for the diagnosis of sepsis. Its performance as a stand-alone test is insufficient to guide decisions about initiation of antibiotics in patients with suspected sepsis.

**RS:** In a meta-analysis of hospitalized adults with infection and SIRS, the weighted mean difference of initial PCT values between survivors and non-survivors was -6.02 ng/mL (95% CI -10.01 to -2.03, p=0.003) (47). A very low or normal PCT (<0.5-1 ng/mL) has a negative predictive value for adverse outcomes (e.g., death) that approaches 100% across several pediatric studies (44, 46, 48). Our opinion: High PCT portends worse outcomes among adults with SIRS. A very low PCT at SIRS onset is associated with a low risk for poor outcomes in children.

**SI and AS:** Two meta-analyses published in 2019 concluded that use of a PCT-based escalation algorithm led to 1.3 fewer days of antibiotics in critically ill adults (6, 7). In a large, multi-center RCT among neonates with suspected early-onset sepsis, duration of antibiotics was reduced in the PCT-guided discontinuation group compared to subjects receiving standard of care (intention to treat: 55.1 vs 65.0 hours, p=0.001) without an increase in adverse outcomes (61). In an RCT comparing PCT-based escalation of care to standard practice (67), the time to appropriate therapy was similar in the two groups and there was no difference in 28-day survival (HR 0.98, 95% CI 0.83-1.16), while the PCT arm had worse secondary outcomes including more ICU days on mechanical ventilation, days with renal failure, and days in the ICU.

Our opinion: Data support the use of serial measurement of PCT to guide decisions about antibiotic cessation among adults with sepsis. Serial measurement should not be used to guide decisions about expanding breadth of antibiotic coverage.

**RS:** In a study of 846 patients who were alive and in the hospital on day 4 (52), there was a significantly higher risk of death if PCT did not decline by at least 80% from baseline to day 4 after adjustment for initial illness severity and other clinical variables associated with adverse outcome (aHR 1.07, 95% CI, 1.18–3.30, p <0.01). In a study of 75 children with septic shock, Hatherill et al. demonstrated that the absence of a decline in PCT after 24 hours of treatment for was associated increased mortality (44% versus 9%, p=0.02) (46). In a phase III trial of drotrecogin alfa (activated) in pediatric severe sepsis, there was a greater decline in PCT values over the first 6 days of septic illness among 324 survivors compared to 63 non-survivors (48).

Our opinion: Persistently high PCT portends worse outcomes among adults and children with sepsis and septic shock.