A novel marker procalcitonin may help stem the antibiotic overuse in emergency setting

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Abstract

The day the wonder drugs, antibiotics, were available for cure to humans; dramatic rise of average life expectancy has been recorded compared to past. However, disease-causing microbes that have developed resistance to antibiotics are an increasing public health problem. Recently, superbug emergence was reported in some countries including India. One of the reasons quoted was misuse of antibiotics. Clinical signs and symptoms of infection often do not point towards the etiology. The dilemma occurs as diagnosis of sepsis is difficult because of nonspecificity of clinical signs and symptoms, and frequent overlapping of symptoms with other noninfectious causes of systemic inflammation. Key for improving survival rates lies in early diagnosis and treatment. Serum procalcitonin (PCT) levels measuring in sick patients during infection may be valuable in diagnosing the conditions, and its changing levels have some prognostic value too.

Key words: Biomarkers, procalcitonin, resistance, sepsis, systemic inflammatory response syndrome

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Introduction

As the reports of emergence of multidrug resistant bacteria are increasing, the increase in the mortality and morbidity due to bacterial infections can be a reason of worry for physicians in the near future. One of the major reasons documented for such resistance is blind usage of antibiotics, very commonly committed omission mistake by physicians, healthcare providers, and even the common man by misusing access to over the counter (OTC) drugs. The subtherapeutic doses or overdosing of antibiotics; and mutations in structure or genome of microbes are other important contributors. Though untreated bacterial infections may cause serious complications, treating viral illnesses or noninfective causes of inflammation with antibiotics is not only ineffective but also adds to cost, increases the number of adverse drug reactions, and contributes to the development of resistance.

The diagnosis of bacterial infection in the critically ill patient remains notoriously difficult, particularly in the presence of other noninfectious conditions that can generate an inflammatory response (e.g., trauma, major surgery, and burns). This difficulty and the delay in diagnosis can lead to occurrence of severe sepsis in the patient. Cases of severe sepsis are expected to rise in the future for several reasons, including: Increasing numbers of immunocompromised patients due to spread of acquired immunodeficiency syndrome (AIDS) like fast spreading diseases; wider use of invasive procedures; more resistant microorganisms; and an aging population.¹

Etiology of sepsis in most cases is associated with bacterial or fungal infection; as such, culture and drug sensitivity testing often is considered the gold standard for diagnosis of infection. But culture report becomes available only after 48-72 h. This long lag period of culture result and its unconvincing low sensitivity and specificity may be fatal for many patients.
Rational use of antibiotic is not only to ensure the right indication, dose, and duration; in an attempt to limit resistance, but also to demarcate the causality of the disease with the help of markers which are sensitive as well as specific and hence making a wise decision to initiate or withhold the antibiotic and combat with the emerging problem of resistance.

Sepsis and the Related Conditions

Sepsis is a systemic inflammatory response in the presence of a confirmed or suspected infection. As described by the American College of Chest Physicians and the Society of Critical Care Medicine, the broad term sepsis encompasses several degrees of disease severity, defined as systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock.[3] SIRS is a systemic inflammatory response to a variety of clinical insults. The response is manifested by two or more of the following conditions: (a) Temperature >38°C or <36°C, (b) heart rate >90 beats per min; (c) respiratory rate >20 breaths per min or PaCO₂ <32 mmHg; and (d) white blood cell count (WBC) >12,000/µL, <4,000/µL, or >10% immature (band) forms. SIRS is manifested by two or more of the conditions detailed previously.

Severe sepsis is acute organ dysfunction secondary to infection and septic shock may present as severe sepsis plus hypotension not reversed with fluid resuscitation. Hypoperfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status [Table 1].

Markers: Can They Help?

Shortcomings in both culture tests and available blood tests have driven the research more oriented towards other sensitive and specific markers. Since the signs and symptoms of severe infections can be ambiguous, biomarkers provide a more reliable tool in ascertaining the presence of a relevant bacterial infection, its severity and treatment response. Even the United States Food and Drug Administration (USFDA) has advocated the development new biomarkers, both for routine diagnostic and drug development purposes, under it's Critical Path Initiative program.[1] The need of hour is to provide evidence and need based antibiotic therapy to patients because of emerging issues of resistance. Therefore, a marker specific for bacterial infection will be helpful.

The markers which point towards infection have long been utilized by the physicians as a diagnostic tool, to know the extent and severity of the infection. Well-known examples of markers used to interpret bacterial infection are WBC count and C-reactive protein (CRP). Others are tumor necrosis factor (TNF)-alpha, interleukin-6 (IL-6), and IL-8. Recently, Mondal et al., proposed a battery of tests for specific diagnosis of neonatal sepsis. These included four tests namely microerythrocyte sedimentation rate, immature to total neutrophil count, morphological changes in neutrophils, and CRP.[4]

CRP is an acute-phase reactant, belonging to the pentraxin family of proteins, so called because they form a cyclic pentamer composed of five identical nonglycosylated subunits, noncovalently bound, and organized in a very stable discoid-like structure. The serum concentration of CRP in the normal human population has a median of 0.8 mg/l (interquartile range: 0.3-1.7 mg/l).[5] Elevations in serum CRP levels are seen with both acute systemic gram positive and gram negative bacterial infections, as well as systemic fungal infections, even in immunodeficient patients. By contrast, CRP concentrations tend to be lower in most acute viral infections.[6] Nevertheless, this rule is not absolute and uncomplicated infections with adenovirus, measles, mumps, and influenza are sometimes associated with high CRP levels. Systemic viral infections caused by cytomegalovirus and Herpes simplex also induce marked changes in CRP concentrations.

In addition to infection, there are several other conditions that commonly lead to substantial changes in CRP concentrations. These include trauma, surgery, burns, tissue necrosis, immunologically-mediated inflammatory diseases, crystal-induced inflammatory diseases, and advance cancer.[7] Accordingly, it has been advocated that serial CRP measurement, rather than a single determination at the time of admission, is a more valuable instrument in the diagnosis of sepsis and infection as well as in monitoring the response to therapy.

Newer Focuses

Elsing et al., reported that new biomarkers such as lipopolysaccharide binding protein (LBP) and IL-6 have the potential to determine the severity and outcome of infectious diseases. Comparing established markers of infection

| Table 1: Consensus definition of systemic inflammatory response syndrome/sepsis by the American College of chest physicians and the Society of critical care Medicine |
| Condition | Criteria |
|---|---|
| SIRS | Two or more of the following criteria  
Temperature <36°C or >38°C  
Heart rate >90 Respiratory rate >20 or PaCO₂ <32  
White blood count >12,000; <4,000; or >10% immature forms |
| Sepsis | Documented infection together with two or more above mentioned SIRS criteria |
| Severe sepsis | Sepsis associated with organ dysfunction |
| Septic shock | Sepsis with refractory hypotension or hypoperfusion abnormalities in spite of adequate fluid resuscitation |

SIRS=Systemic inflammatory response syndrome
Due to short PCT has is very As such, the release of PCT into the circulation in large concentrations in various disease states is not accompanied by significant elevations in calcitonin levels.

Procalcitonin (PCT) is another recently focused biomarker; and in recent years it has established its role as a candidate marker for the diagnosis of systemic inflammation, infection, and sepsis; both in children and adults. It has been demonstrated to be clinically useful in a range of different patient populations and has proved to be valid in assisting the clinician in identifying patients who do not need antibiotic treatment. It has been reported to support early diagnosis and clinical decision making which could direct an effective therapy at the right time and avoid unnecessary spending for critically ill patients.

**Physioacitonin**

Physiochemical characteristics

PCT was first identified from a medullary thyroid carcinoma cell line. It is a 116 amino acid with molecular weight of 13 kDa. It is encoded by CALC-1 gene on the short arm of chromosome 11, and is produced in the C-cells of the thyroid gland as a pro-hormone of calcitonin. Normally, PCT is cleaved in the thyroid to calcitonin. Consequently, the serum concentrations of PCT are <0.1 ng/mL in healthy humans. Structurally, the PCT peptide is comprised of three parts: Situated in the center of the peptide is calcitonin, at the amino terminal end is amino procalcitonin, and at the carboxy terminal end is calcitonin carboxy terminal peptide-1.

Regulation of PCT

Regulation of thyroid and inflammatory PCT are fundamentally different. C-cells of thyroid gland react to elevated calcium levels as well as to a number of other stimuli, such as glucocorticoids, calcitonin gene-related peptide (CGRP), glucagon, gastrin, and α-adrenergic stimulation to increase calcitonin release. Somatostatin and vitamin D suppress calcitonin production. Neither hypercalcemia nor any other of above listed stimuli leads to release of PCT during inflammation. The production of PCT during inflammation is linked to the bacterial endotoxins and inflammatory cytokines.

Why is calcitonin not considered?

In healthy individuals, production of PCT and subsequently calcitonin is restricted to the thyroid C-cells. Bacterial infections selectively induce an increase in the concentration of PCT; because both endotoxins released from the bacterial cell wall as well as the host responses to infection activate the production of PCT mainly in parenchymal tissues. This results in accumulation of PCT, because unlike neuroendocrine cells, parenchymal cells lack the ability to cleave PCT into its mature form, calcitonin. As such, the release of PCT into the circulation in large concentrations in various disease states is not accompanied by significant elevations in calcitonin levels.

Elevated PCT levels

Elevated levels of PCT in the absence of an infection are observed in severe trauma and post cardiopulmonary bypass. PCT levels may also be elevated during the first 24 h of life. Patients with C-cell carcinoma of the thyroid and small cell lung cancer have also been reported to have elevated serum PCT concentrations.

Patients with verified bacterial infections have higher PCT concentrations than those with nonbacterial (including viral) infections. The increase in the PCT concentration following stimulation with endotoxins from *Escherichia coli* is very large (up to >10,000 times) and fast. It can be detected in serum within 2-6 h after stimulation of healthy individuals, maintaining a high level plateau for the next 24 h, and can be detected for up to 7 days.

**PCT versus CRP**

The half-life of PCT is 25-35 h, which is not altered significantly by renal failure or by continuous hemodialysis; therefore serum concentrations of PCT can be used for diagnostic purposes even in patients with impaired renal function. Due to short half-life as compared to CRP, concentrations normalize fairly quickly with the patient’s recovery. In comparison, CRP takes 12-24 h to rise and remains elevated for up to 3-7 days. Because PCT concentrations increase earlier and normalize more rapidly than CRP, PCT has the potential advantage of earlier disease diagnosis, as well as better monitoring of disease progression.

In critically ill children, the PCT concentration at the time of admission has been adjudged a better diagnostic marker of infection than CRP or leukocyte count. A PCT concentration of 2 ng/mL has been considered as a cut-off value in differentiating severe bacterial disease in infants and children. PCT has shown more specificity and better diagnostic efficiency compared to CRP for diagnosis of bacterial sepsis. In patient with trauma developing infectious complications, PCT values have been shown to mark the septic events more promptly compared to CRP.

**PCT measurements**

PCT is measured in the serum using an immunolumimetric assay. The USFDA has cleared several assays for determination of PCT in human serum and plasma like PCT-Q (for rapid
Subsequently it was shown that in contrast

None

Though these devices utilize different technologies and instruments to obtain results, they have a similar indication for use; which is to aid in the assessment of risk progression to severe sepsis and septic shock in critically ill patients on the first day of admission to intensive care unit (ICU). The devices are intended to be used in conjunction with other laboratory findings and clinical assessments to determine whether an infection is bacterial or viral; thus potentially avoiding unnecessary use of antibiotics.

The assay employs two antigen specific monoclonal antibodies, one directed at the calcitonin region which carries the luminescence label and the other at the katacalcin region. It is rapid and sensitive laboratory-based assay, providing results in 20 min. The detection limit for the assay is 0.1 ng/mL and the coefficient of variation between 1-1,000 ng/mL is 5-10%. The assay is also free of interference from the antibiotics, sedatives, and vasoactive agents that are commonly used in ICU. PCT is present at very low concentrations, usually <0.05 ng/mL and may be undetectable by some assays in healthy individuals.[23]

PCT levels of >2.0 ng/mL on the first day of ICU admission represent a high risk for progression to severe sepsis and/or septic shock; while levels <0.5 ng/mL represent a low risk, though do not entirely exclude an infection because localized infections (without systemic signs) may also be associated with such low levels; and levels <0.3 ng/mL are below the detection limit of the test and represent a healthy condition. PCT levels between 0.5 and 2.0 ng/mL should be analyzed critically taking into account the specific clinical background and conditions(s) of the individual patient. Clinicians should always interpret the PCT results in conjunction with other laboratory findings and clinical signs of the patient.[24]

ROLE OF PCT IN VARIOUS INFECTIVE/ PATHOLOGICAL CONDITIONS

PCT as a marker of infection

Much of the original prospective work on PCT as a diagnostic marker for infection was performed on pediatric populations. Levels of PCT in children with severe bacterial infections were demonstrated to be very high compared to those who had absent, localized, or viral infections; in a study conducted by Assicot et al. These raised PCT levels were shown to decrease with antibiotic therapy.[25] Subsequently it was shown that in neonates, PCT was a more accurate marker of bacterial infection than CRP.[26]

Following the initial work by Assicot’s group, other published data supported the notion that serum PCT levels were dramatically elevated in patients with bacterial and malarial infections.[27] The data in fungal sepsis are less convincing. Two clinical trials demonstrated a predictive role for PCT as a marker of fungal sepsis in transplant recipients.[20] In contrast to bacterial and parasitic infections, only modest elevations of PCT are seen in viral infections. Consequently, serum PCT levels have been proposed as a marker to differentiate between viral and bacterial sepsis, particularly in patients with meningitis.[21] However, its utility in distinguishing between bacterial and viral pneumonias is less convincing.[22] It is really difficult to differentiate between acute pyelonephritis and urinary tract infection (UTI) without renal parenchymal involvement among children, because of common clinical findings and nonspecific laboratory parameters. It has been reported that PCT may help in differentiating pyelonephritis from lower UTI, thus altering management algorithm.[11]

PCT as a marker of infection in oncology, transplantation, and Kawasaki disease

Serum PCT levels have been proved to be useful diagnostic tool in patients with solid tumors (as a marker of bacteremia), in patients with liver transplantation (to distinguish between infection and rejection), in patients undergoing regular hemodialysis (to identify infective complications), and in burn patients (to diagnose superinfection).[23-36]

The serum PCT levels were more useful compared to WBC count or CRP in differentiating the Kawasaki disease patients from the patients with autoimmune diseases. The optimal cut-off value of 3.0 ng/mL of PCT has been shown to increase the prediction rate of coronary aneurysms also.[27]

PCT as a marker of SIRS

SIRS is a frequently encountered clinical entity in the medical and surgical ICU, and is a feature of a wide variety of infectious and noninfectious insults. About, 25-49% of patients with SIRS have a clinical infection; and among all the patients developing sepsis, only 10-40% patients present with bacteremia.[28] None the less, it is important to differentiate noninfectious SIRS from infectious SIRS for two reasons: Early diagnosis and appropriate treatment of sepsis has been shown to reduce mortality; and inappropriate use of antibiotics which carries problems of cost and emerging antibiotic resistance with it may be minimized. Elevated levels of PCT typically points towards infectious SIRS.

Patients with the highest serum PCT levels typically have systemic bacterial infections or multiorgan failure. PCT level of <0.5 ng/mL are considered normal, whereas levels >10 ng/mL is considered significantly elevated. Serum concentrations between 2 and 10 ng/mL are considered suggestive of sepsis, whereas PCT concentrations between 0.5 and 2 ng/mL indicate the possibility of sepsis, without excluding other
causes of elevated PCT levels like inhalation injury, trauma, surgery, pancreatitis, heat stroke, and some cancers. Typically, PCT ranges between 2 and 3 ng/mL in these settings; however, the concentration in severe cases may rise up to 20 ng/mL.\(^{[39]}\)

**Trial/study results**

In a study conducted in the pediatric emergency department setting in 328 children aged 1-36 months with fever and no identified source of infection, 54 (16\%) children were diagnosed with systemic bacterial infection (SBI): 48 UTIs, four pneumonias, one meningitis, and one bacteremia. The area under the curve (AUC) for PCT (0.82; 95\% confidence interval (CI): 0.77-0.86), CRP (0.88; 95\% CI: 0.84-0.91), and WBC (0.81; 95\% CI: 0.76-0.85). The study data demonstrated that CRP, PCT, and WBC had almost similar diagnostic properties and were superior to clinical evaluation in predicting SBI in children aged 1-36 months.\(^{[39]}\)

PCT was validated as the best biological marker in a European multicenter case cohort study conducted to distinguish between bacterial and aseptic meningitis in children in the setting of six pediatric emergency or ICUs, analyzing 198 patients of which 96 had bacterial meningitis. At 0.5 ng/mL threshold, PCT level had 99\% sensitivity (95\% CI: 97-100\%) and 83\% specificity (95\% CI: 76-90\%) for distinguishing between bacterial and aseptic meningitis.\(^{[9]}\)

A meta-analysis evaluated the comparative accuracy of determination of PCT and CRP levels for the diagnosis of bacterial infection; compared to CRP levels, PCT levels were more sensitive (88\%, 95\% CI: 80-93\% vs 75\%, 95\% CI: 62-84\%) and more specific (81\%, 95\% CI: 67-90\% vs 67\%, 95\% CI: 56-77\%) for differentiating bacteria from noninfective causes of inflammation.\(^{[10]}\)

Schuetz et al., proposed an algorithm for PCT-guided antibiotic therapy in critically ill patients [Figure 1]. This algorithm advocates definite use of antibiotics if PCT levels are >0.5 \(\mu\)g/L and to withhold any antibiotics if PCT levels are <0.25 \(\mu\)g/L. If antibiotics have been withheld, reevaluation of the clinical status and measurement of serum PCT levels has been mandated after 6-24 h. It has been advocated to overrule the algorithm in patients with immediately life-threatening disease.\(^{[40]}\)

Another meta-analysis favored the implementation of PCT-based algorithm as it concluded that this may reduce antibiotic exposure in critically ill, septic patients without compromising clinical outcomes.\(^{[41]}\) Nobre et al., similarly

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**Figure 1:** Procalcitonin-based algorithm as a guide of antibiotic usage

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advocated that a protocol based on serial PCT measurements allow reducing duration of the antibiotic treatment and exposure in patients with severe sepsis and septic shock without apparent harm.[42]

In another study conducted to assess the usefulness of serum PCT as a marker of sepsis in critically ill patients, using the semiquantitative, rapid immune-chromatographic kit, in tertiary care hospital, moderate sensitivity (86%) and high specificity (95%) of the PCT assay at a cut-off ≥2 ng/mL was reported.[43] The assay could be performed and reported rapidly and provided valuable information before availability of culture results.

These cut-offs are merely guides however, and there are reports of patients having sepsis with low serum concentrations of PCT. Similarly, it is not mandatory that every sick patient with elevated PCT has sepsis. As mentioned previously, elevations of PCT are seen in many clinical settings, so a sound clinical judgment is necessary when evaluating an infection in patients. A sustained elevation or marked increase of PCT may indicate the advent of infection or sepsis; therefore, serial measurements may be more useful to identify trends in serum concentrations.[44]

**Conclusion**

Clearly, a validated tool to predict benefits from antibiotic prescribing by assisting clinical assessment and differentiating mild from serious infection of presumed bacterial etiology is highly warranted. To date, biomarkers seem to be powerful tools for reducing antibiotic prescriptions by ruling out serious infection. PCT being one of them is emerging as a strong predictive marker. It is important to acknowledge that a low PCT concentration does not mean ‘no treatment’ or ‘no hospital admission’, but indicates a low probability of benefit from antibacterial drugs. So such markers and many more in future may lead to a more rational, more judicious use of antibiotics, and help fighting the emerging problem of the day viz. antibiotic resistance which simply could be combated by prevention strategy. Improvement in the allocation of healthcare resources can also be one of the impacts of introducing biomarker-guided treatment algorithms.

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