Is there an optimal serum marker for the diagnosis of sepsis?

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Introduction

Severe sepsis and septic shock are major health care problems in the United States. Between the years 1979 and 2000, there was an annual increase in the incidence of sepsis of 8.7% per year, from 82.7 cases per 100,000 population in 1979 to 240.4 cases per 100,000 population in the year 2000 (1). Despite the improvement in mortality rates over the last decades (28% between 1979 and 1984 to 18% between 1995 and 2000), the increasing incidence of sepsis has resulted in nearly a tripling of the number of hospital deaths related to sepsis [from 43,579 deaths (21.9 per 100,000 population) in 1979 to 120,491 deaths (43.9 per 100,000 population) in 2000] (1). In fact, septicemia is the 10th leading cause of death in the United States, responsible for 1.4% of deaths (2). The estimated overall average length of stay and cost per each severe sepsis case were 19.6 days and $22,100 respectively, and the annual total costs associated with the care of patients who have sepsis have been estimated to be near $16.7 billion dollars (3).

Clinically, sepsis has been divided into phases, early and late, by fluctuations in specific host responses in order to facilitate further targeted therapies (4). The early stage of sepsis, defined as the first 6 hours, is highlighted by an early diagnosis of severe sepsis or septic shock and institution of antibiotic and early goal-directed therapy, both of which have demonstrated to decrease in-hospital and overall mortality (5-7). These facts stress the importance of an early diagnosis which may be missed in patients that do not present with the typical features of sepsis.

A case of a subject transferred to our medical center from an outside institution who presented with atypical features of sepsis is presented, and a discussion of potential serum markers of sepsis that may aid in its diagnosis follows. Such markers would make early diagnosis and treatment institution, with subsequent improvements in mortality, much easier than the classic clinical recognition.

Case Presentation

A 52 year-old man presented to an outside hospital with three days of worsening dyspnea which was worse at night and with minimal exertion. According to the referring hospital documentation the patient did not have fevers or sputum production. His past medical history was positive for chronic kidney disease (CKD) stage V (Patient had an AV fistula placed 5 months prior to admission in preparation for hemodialysis), systolic congestive heart failure (ejection fraction prior to admission of 15%), type 2 diabetes mellitus on insulin, hypertension, hypothyroidism and coronary artery disease. His home medications were aspirin, carvedilol, ferrous sulfate, hydralazine, insulin, levothyroxine and pravastatin.

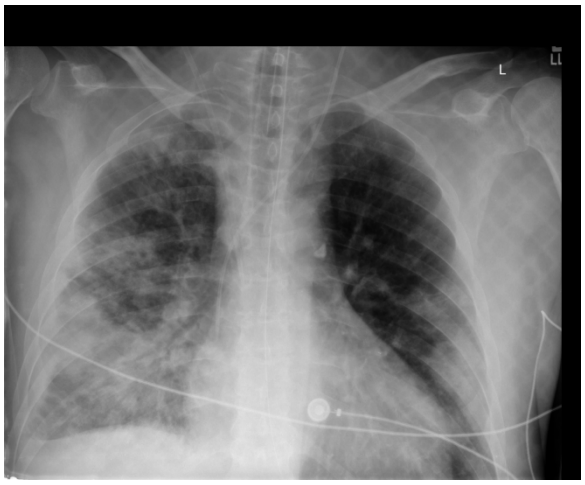

Figure 1- CXR upon transfer

His physical examination was positive for hypoxemia, crackles in posterior lung bases and peripheral pitting edema, and he was afebrile. His chest radiograph was suggestive of pulmonary edema and bilateral pleural effusions (**figure 1**). Initial labs from the outside hospital are shown in **Table 1**, demonstrating a normal leukocyte count, hyperkalemia, azotemia and an elevated brain natriuretic peptide (BNP). The initial diagnostic impression of the referring physician was that the patient had progression of his CKD to the point of needing hemodialysis, with secondary congestive heart failure. He was referred to our medical center due to hypoxemic respiratory failure requiring intubation and the need for institution of hemodialysis.

On arrival to our hospital, he was found to have fever (T: 100.3 F), tachypnea, and bandemia of 39 %. Treatment for septic shock was started at that point including antibiotics, IV fluids and vasopressors; antibiotics were given within one hour of arrival to our hospital, but ten hours after initial presentation to the referring facility. Hemodialysis was attempted to treat his hyperkalemia,but due to severe hypotension this was not completed. Blood cultures drawn in our institution grew Klebsiella pneumoniae within 4 hours. Shock, lactic acidosis and hypotension progressed and patient expired on day 2 of admission.

	Outside Facility	Admission
WBC	7.2 K/uL	6.4 K/uL
Neutrophils	86%	36%
Bands	3%	39%
Hemoglobin	10.8 g/dL	9.3 g/dL
Sodium	132 mmol/L	132 mmol/L
Potassium	5.4 mmol/L	5.7 mmol/L
Bicarbonate	16.9 mmol/L	19 mmol/L
BUN	92 mg/dL	101 mg/dL
Creatinine	8.4 mg/dL	9.1 mg/dL
Glucose	187 mg/dL	164 mg/dL
Troponin	<0.05 ng/mL	N/A
BNP	1160 pg/mL	N/A
Anion gap	21	12
Lactate		2.3

Table 1- Lab results

Discussion

A case of a patient with septic shock who presented with atypical features is presented. Due to his atypical presentation appropriate management for this condition was delayed. As mentioned above, for every hour in delay of adequate resuscitation and antibiotic treatment in sepsis the mortality increases (5-7). The following questions arise within the present case: a) is there is a reproducible test helpful for early detection of sepsis? and b) is there an objective measure to assess the appropriateness of current antibiotic therapy in sepsis?

Habarth et al. assessed the diagnostic value of procalcitonin (PCT), interleukin (IL)-6, IL-8, and standard measurements in identifying critically ill patients with sepsis (8). Prospective cytokine measurements in 78 consecutive patients admitted to an intensive care unit (ICU) with systemic inflammatory response syndrome (SIRS) and suspected infection were obtained. Cytokine measurements were performed within

12 hours of admission and daily during the entire ICU stay. PCT yielded the highest discriminative value for sepsis, with an area under the receiver operating characteristic curves (AUC) of 0.92 (CI, 0.85 to 1.0). At a cutoff of 1.1 ng/ml, PCT yielded a sensitivity of 97% and a specificity of 78% to differentiate patients with SIRS from those with sepsis. Median PCT concentrations on admission (ng/ml) were 0.6 for SIRS; 3.5 for sepsis; 6.2 for severe sepsis; and 21.3 for septic shock ($p< 0.001$). According to the authors, elevated PCT could be an indicator of sepsis in newly admitted, critically ill patients capable of complementing clinical signs and routine laboratory parameters suggestive of severe infection.

Several meta-analyses support the use of PCT as a diagnostic tool in sepsis. Simon et al. demonstrated that PCT was more sensitive (88%) and specific (81%) than CRP in differentiating bacterial from non-infective causes of inflammation. Also, the sensitivity of PCT to differentiate bacterial from viral infections was 92%. This study was criticized because of the heterogeneity of the studied population and the fact that these patients were not always in the critical care unit (10).

Another meta-analysis focusing on a more homogeneous population of adult septic patients in the ICU setting was published in 2006 by Uzzan et al (8). For PCT, the OR for diagnosis of infection in SIRS was 15.7, while CRP OR was only 5.4. The authors concluded that PCT represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock, and that PCT is superior to CRP for this purpose. They also suggest that PCT should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units.

Muller et al prospectively evaluated 925 patients admitted with community acquired pneumonia and evaluated the accuracy of PCT predicting the occurrence of bacteremia (9). Out of the 925 patients, only 73 (7.9%) had true bacteremia. With an area under the curve of 0.82, PCT had higher diagnostic accuracy for predicting positive blood cultures than CRP, WBC count and other clinical and laboratory predictors. Overall, a PCT cutoff of 0.1 m g/L identifies 99% of the positive blood cultures with a specificity of 13%. Similarly, 0.25 m g/L and 0.5 m g/L cutoffs would identify 96% and 88%, respectively, of positive blood cultures (with a specificity of 40% and 55% respectively). Authors concluded that "initial PCT level accurately predicted blood culture positivity in patients with CAP".

PCT is not a flawless test. Increased serum ProCT levels often indicate systemic infection or sepsis, but similar levels can be encountered in several noninfectious inflammatory conditions (10). Nonspecific elevations of PCT levels in the absence of a bacterial infection can also be seen in situations of massive stress (severe trauma or surgery). Conversely, falsely low PCT levels, typically seen during the early course or localisedstate of an infection, often show an increase in the follow-up measurements(11).

Can PCT levels be used to follow the appropriateness of antibiotic therapy and response to therapy in the critically ill? (12). Charles et aldemonstrated that appropriate first-line empirical antibiotic therapy was associated with a significantly greater decrease in PCT between days 2 and 3 ($P < 0.01$), while patients with inappropriate antibiotics had a greater rise between days 1 and 2 ($P = 0.20$). Finally, PCT kinetics between days 2 and 3 were also found to be significantly different, since a

decrease ≥ 30% was expected in the survivors and was found to be an independent predictor of survival (odds ratio = 2.94; P = 0.02). Further studies are ongoing, but it seems as though PCT levels may be able to be followed to assess response to therapy in sepsis.

Conclusion

Diagnosis and management of sepsis remains a challenge. A high index of suspicion and aggressive treatment of this condition remain as the mainstay of management. Available evidence to support any test that may help in the diagnosis of sepsis is limited due to a number of factors including the heterogeneity of the included subjects in studies, the different definitions of sepsis utilized (SIRS, bacteremia, positive blood cultures), and the different outcomes studied.

PCT is a promising test that could potentially help in the early diagnosis of sepsis. A careful review of the literature reveals that in our patient, an early positive PCT could have helped in starting appropriate antimicrobial therapy and fluid resuscitation, with a probable better outcome. More evidence is needed in order to apply the use of this test widely as a tool for the diagnosis of sepsis and response to its therapy.

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