Are There Useful New Markers of Sepsis?

M. MEISNER, K. REINHART

Severe infections and sepsis are common causes of morbidity and mortality in intensive care units. Clinical and laboratory signs of systemic inflammation such as changes in body temperature, leukocytosis, and tachycardia are frequently used for the diagnosis of infection or sepsis [1]. However, these signs and symptoms are neither specific nor sensitive for infection or sepsis. Various other and non-microbial infection related aetiologies of systemic inflammation may induce these symptoms. For example, patients suffering from pancreatitis, major trauma or burns present with a similar inflammatory response even in the absence of infectious complications. On the other hand, bacteriological evidence of infection, though definitive and specific, may not develop concurrently with clinical signs of sepsis.

Early diagnosis of sepsis with better markers would allow early treatment, imperative in reducing mortality and morbidity. Markers may be helpful in conducting trials with immunomodulatory therapeutics. Markers of sepsis capable of predicting the immune status of the septic patient may help target the population most likely to benefit from such therapeutics. An ideal method or marker of infection should be cheap, easy to measure, be highly specific and sensitive, allowing early diagnosis of sepsis, and should correlate with the severity of infection and help gauge the efficacy of therapeutic measures. Although numerous parameters and methods have been proposed, none fulfils all the requirements.

A common feature of the presently used parameters is that they are related to the systemic inflammatory response secondary to infection. Humoral and cellular elements of the immune response are activated during the immune response and induce numerous mediators and inflammatory-related molecules e.g. cytokines, chemokines, acute phase proteins and various other metabolites. Some of these parameters are increased to a various degree in patients with sepsis and infection as compared to patients without systemic inflammation or infection. Recent studies intend to evaluate to what degree these parameters reflect the activation of the systemic inflammatory response in patients with or without microbial infection. Among other parameters, C-reactive protein (CRP), interleukin 6 (IL-6) and procalcitonin were focused on for their possible clinical use for the diagnosis of sepsis, severe sepsis and septic shock.

A. E. Baue et al. (eds.), *Sepsis and Organ Dysfunction*

Procalcitonin

Procalcitonin is the 13-kDa propeptide of calcitonin which is normally produced in the C-cells of the thyroid glands. In healthy individuals, procalcitonin levels are very low (< 0.1 ng/ml). In patients with sepsis, however, procalcitonin levels increase dramatically, sometimes to more than several hundred ng/ml [3, 8]. The site of procalcitonin production during sepsis and its biological function is unknown. In a recent experimental study, inhibiting procalcitonin action during sepsis improved survival whereas treating animals with procalcitonin decreased survival [27]. The basic biology of procalcitonin during sepsis deserves further investigation.

A number of studies support procalcitonin as a marker of severe infections and of sepsis. Patients with procalcitonin levels below or equal to 0.5 ng/ml are unlikely to have severe sepsis or septic shock. Increases in procalcitonin levels may indicate the presence of infection; however, the cutoff point may differ depending on the setting. In the intensive care setting, only levels above 1.5 ng/dl may identify sepsis [10]. A localized focus of bacterial infection, failing to induce systemic inflammation, does not usually induce increased procalcitonin concentrations.

Procalcitonin levels reflect the severity of the inflammatory/infectious response. Infections accompanied by severe systemic reactions and signs of organ dysfunction or poor peripheral perfusion more profoundly increase procalcitonin levels than infections with only moderate systemic response. Therefore, therapies effective in controlling sepsis and reducing severity of disease may lead to reductions in procalcitonin levels [17]. In pediatric patients, procalcitonin levels fell after successful antibiotic treatment [3].

Procalcitonin values are of prognostic significance in patients with bacterial sepsis [29]. In critically ill patients, outcome was best predicted with procalcitonin as compared with TNF-α, IL-6, and C-reactive protein [23, 29]. Importantly, commonly used signs of infection such as body temperature and leukocyte count were poor predictors of outcome. Procalcitonin may also be helpful in the differentiation between bacterial and viral infections. In neonates and children, those with bacterial meningitis had significantly higher levels of procalcitonin than those with viral meningitis [7]. Preliminary results suggest that procalcitonin may help differentiate an infectious from a non-infectious cause of the acute respiratory distress syndrome (ARDS) in adults [5], and systemic fungal or bacterial infections from episodes of graft rejection [12, 19, 20]. Procalcitonin can also be induced in immunocompromized patients [2, 19, 20]. Also, in patients with necrotizing pancreatitis, procalcitonin was the best predictor of infection of the pancreatic necrosis as compared to C-reactive protein and IL-8. The predictive power of procalcitonin was almost equal to that of fine needle biopsy, the gold standard [31]. However, these studies are based on small numbers of patients and need to be reproduced in a larger patient population.

Procalcitonin may not or may only slightly increase when infection remains confined to a tissue or organ with no systemic manifestations. In patients with severe infection, appropriate therapy may lead to very low levels of procalcitonin which may not indicate eradication of the infection. In these patients, antibiotics or other therapeutic interventions may be indicated despite normal or low procalcitonin levels.

Procalcitonin concentrations exceeding 10 ng/ml almost exclusively occur in patients with severe sepsis or septic shock. However, procalcitonin levels may increase (median 1-2 ng/ml, occasionally values up to 10 ng/ml) during non-infectious inflammation such as major trauma, major surgery, birth stress, or therapies with TNF-α or OKT3. In these situations, further increases or decreases in procalcitonin level may be more informative than the absolute value. Procalcitonin levels also increase during cardiogenic shock; however, the levels are considerably lower than those during septic shock [10].

C-reactive protein

C-reactive protein is an acute phase protein released by the liver after onset of inflammation or tissue damage. During infections, C-reactive protein has both pro- and anti-inflammatory effects. C-reactive protein may recognize and adhere to pathogens and to damaged cells and mediate their elimination through interaction with inflammatory cells and mediators. However, C-reactive protein also prevents adhesion of neutrophils to endothelial cells, inhibits superoxide production, and increases IL-1 receptor antagonist production. Although IL-6 is the main stimulus for the induction of C-reactive protein, other cytokines also play a role in its production [6]. C-reactive protein is a frequently used clinical marker to assess the presence and severity of an inflammatory response. Some studies support C-reactive protein as a marker of infection or of sepsis [15]. C-reactive protein has been found to differentiate patients with pneumonia from those with endotracheal infections [9], to aid the diagnosis of appendicitis [14], to assess severity of sepsis [30] or to differentiate bacterial and viral infections [36]. Other studies, however, point to important properties of C-reactive protein which limit its usefulness as a marker of severe infection and sepsis. First, plasma levels of C-reactive protein increase up to 24 hours later than those of other markers such as cytokines or procalcitonin [6, 25]. Second, plasma concentrations of C-reactive protein may increase during minor infections and do not adequately reflect severity of infection, nor differentiate between survivors and non-survivors of sepsis [23, 37]. Third, plasma levels remain elevated for up to several days even when infection is eliminated [23]. Lastly, C-reactive protein is also elevated during inflammatory states of non-infectious etiologies, e.g. autoimmune and rheumatic disorders [11, 34], myocardial infarction, malignant tumors, or postoperatively [24]. Probably because of these reasons, the predic-

tive values of C-reactive protein in various patient populations can be poor for the diagnosis of sepsis [13] and less so when assessing severity of sepsis.

Cytokines

Cytokines are peptides that regulate the amplitude and duration of the host inflammatory response [13]. Cytokines are released from various cells (blood and endothelial cells, macrophages, etc.) in response to infectious stimuli and bind to specific receptors of other cells, changing their behavior and defining their role in the inflammatory response.

Mean serum levels of cytokines are increased in septic as compared to non-septic patients. Persistently high or increasing levels of cytokines are mostly found in non-survivors, whereas low and decreasing levels are found in survivors of sepsis. Despite the important role cytokines play in the pathogenesis of sepsis, they do not fulfill many requirements of a good marker. First, some cytokines are only released sporadically during severe infections and may bind to receptor antagonists, and therefore have a very short circulating half life. Second, cytokines are induced by numerous diseases other than sepsis or infection. Third, assays to determine plasma cytokine levels are mostly expensive and time consuming. Lastly, cytokine levels may vary or may be undetectable depending on the assay used.

TNF-α, IL-1, IL-6, IL-8, and IL-10 are cytokines often associated with the presence of sepsis. Cytokines such as TNF-α, IL-1β, and IL-10 are not always detectable in patients with sepsis. Because of this, they do not correlate well with the clinical course of the patients [38] and are therefore not very helpful as markers of infection despite their major role in the pathogenesis of sepsis.

Among cytokines, only IL-6 and IL-8 are most closely related to the severity and outcome of patients with sepsis [38, 18] and high levels of IL-6 have been proposed as an additional inclusion criterion for an immune modulatory sepsis trial with antibodies directed against TNF-α [32]. In neutropenic patients, IL-8 and IL-6, but not C-reactive protein, were significantly different between microbiologically documented infections and unexplained fevers [13]. In neonates, increased plasma levels of both IL-6 and IL-8 can predict early onset of sepsis with a high sensitivity and specificity [4]. During sepsis, high plasma levels of IL-6 and IL-8 suggest an increased risk of complications and poor outcome [13]. However, in patients with pancreatitis, increased IL-8 plasma levels do not indicate infection of pancreatic necrosis with high sensitivity [31]. Furthermore, IL-6 and IL-8 can also be induced to a variable degree after major surgery [35], after major trauma [26], during acute exacerbations of autoimmune disorders [33, 21], during viral infections and after transplant rejection [16, 22].

In summary, among cytokines, only IL-6 and IL-8 may have limited utility as a marker of the presence, severity and outcome of sepsis. However, clinical

use of these expensive parameters is questionable, and whether IL-6 can be used as a very early predictor of infection or of sepsis deserves further investigation.

Conclusion

Early diagnosis of infection in critically ill patients is important to prevent complications of microbial infection. Patient history and physical examination with or without routine laboratory parameters frequently suffice to establish the diagnosis of sepsis. However, in some patients these same symptoms and parameters may also occur during systemic inflammation of non-infectious etiology. Furthermore, defining the severity of sepsis on clinical data alone may be difficult. Recently cytokines (specially IL-6 and IL-8), C-reactive protein, and procalcitonin have been proposed as markers of sepsis and infection. All these parameters have some merit depending on the clinical circumstances. C-reactive protein and procalcitonin are parameters with a different profile during various degrees of systemic inflammation and sepsis. Procalcitonin is superior for the diagnosis and especially for the follow-up of patients with a bacterial focus complicated by symptoms of severe sepsis and septic shock. Especially during the more severe stages of systemic inflammation, plasma procalcitonin concentrations correlate better with the severity of inflammation than other parameters. Also, procalcitonin concentrations rapidly decline after successful elimination of the infectious focus and with the disappearance of the inflammatory response. Procalcitonin can also be used to assess the efficacy of therapeutic measures in controlling the source of sepsis. Furthermore, it is a very good predictor of increased TNF-α and IL-6 levels in septic patients [28]. This suggests that procalcitonin may reflect the immune status of septic patients and may be helpful in recruiting patients in immunomodulatory trials. C-reactive protein is a more sensitive parameter for the diagnosis of infection, but is less specific for the diagnosis of sepsis and bacterial infection. Various etiologies other than microbial infection, such as autoimmune disorders, tissue trauma or viral infections, easily induce this acute phase protein. C-reactive protein is induced at high concentrations already during less severe stages of the systemic inflammatory response; this means that C-reactive protein is not very useful for the discrimination between the different stages of severity, e.g., between severe sepsis and septic shock. Also the increase and especially the decrease of C-reactive protein plasma levels is delayed by 24-48 hours as compared to procalcitonin. Although cytokines such as IL-6 and IL-8 correlate to some degree with the severity of sepsis and patient outcome, they have not yet been adequately evaluated for diagnosis and clinical decision-making at the bedside. For the diagnosis of bacterial infection without signs of systemic inflammation, procalcitonin is not superior to C-reactive protein. However, in patients with severe sepsis and septic shock procalcitonin seems to be a useful parameter to improve diagnosis and therapy monitoring in these severely ill patients.

References

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864-87
2. Al-Nawas B, Shah PM (1996) Procalcitonin in patients with and without immunosuppression and sepsis. Infection 24:434-436
3. Assicot M, Gendrel D, Carsin H et al (1993) High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 341:515-518
4. Berner R, Niemeyer CM, Leititis JU et al (1998) Plasma levels and gene expression of granulocyte colony-stimulating factor, tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6, IL-8, and soluble intercellular adhesion molecule-1 in neonatal early onset sepsis. Pediatr Res 44:469-477
5. Brunkhorst FM, Forycki ZF, Wagner J (1995) Discrimination of infectious and non-infectious etiologies of the adult respiratory distress syndrome (ARDS) with procalcitonin immunoreactivity. Clin Intens Care 6:3-3
6. Brunkhorst FM, Heinz U, Forycki ZF (1998) Kinetics of procalcitonin in iatrogenic sepsis. Intensive Care Med 24:888-889
7. Chiesa C, Panero A, Rossi N et al (1998) Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. Clin Infect Dis 26:664-672
8. Dandona P, Nix D, Wilson MF et al (1994) Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 79:1605-1608
9. Dev D, Wallace E, Sankaran R et al (1998) Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. Respir Med 92:664-667
10. De Werra I, Jaccard C, Corradin SB et al (1997) Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentrations: comparisons in patients with septic shock, cardiogenic shock, and bacterial pneumonia. Crit Care Med 25:607-613
11. Eberhard OK, Haubitz M, Brunkhorst FM et al (1997) Usefulness of procalcitonin for differentiation between activity of systemic autoimmune disease (systemic lupus erythematosus/systemic antineutrophil cytoplasmatic antibody-associated vasculitis) and invasive bacterial infection. Arthritis Rheum 40:1250-1256
12. Eberhard OK, Langefeld I, Kuse E et al (1998) Procalcitonin in the early phase after renal transplantation - will it add to diagnostic accuracy? Clin Transpl 12:206-211
13. Engel A, Mack E, Kern P, Kern WV (1998) An analysis of IL-8, IL-6 and CRP serum concentrations to predict fever, gram-negative bacteremia and complicated infection in neutropenic cancer patients. Infection 26:213-221
14. Eriksson S, Granstrom L, Olander B, Wretlind B (1995) Sensitivity of interleukin-6 and C-reactive protein concentrations in the diagnosis of acute appendicitis. Eur J Surg 161:41-45
15. Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340:448-454
16. Gendrel D, Raymond J, Assicot M et al (1998) Procalcitonin, C-reactive protein and interleukin 6 in bacterial and viral meningitis in children. Presse Med 27:1135-1139
17. Gramm H-J, Dollinger P, Beier W (1995) Procalcitonin - ein neuer Marker der inflammatorischen Wirtsantwort. Longitudinalstudien bei Patienten mit Sepsis und Peritonitis. Chir Gastroenterol 11[Suppl 2]:51-54
18. Hamano K, Gohra H, Noda H et al (1998) Increased serum interleukin-8: correlation with poor prognosis in patients with postoperative multiple organ failure. Word J Surg 22:1077-1081
19. Hammer S, Meisner F, Dirschedl P et al (1998) Procalcitonin: a new marker for diagnosis of acute rejection and bacterial infection in patients after heart and lung transplantation. Transpl Immunol 6:235-241
20. Kuse ER, Langefeld I, Jaeger K, Külpmann WR (1999) Procalcitonin in fever of unkown origin (FUO) following liver transplantation - a parameter to differentiate acute rejection from infection. Crit Care Med (in press)

21. Kutukculer N, Caglayan S, Aydogdu F (1998) Study of pro-inflammatory (TNF-alpha, IL-1alpha, IL-6) and T-cell-derived (IL-2, IL-4) cytokines in plasma and synovial fluid of patients with juvenile chronic arthritis: correlations with clinical and laboratory parameters. Clin Rheumatol 17:288-292
22. Malaguarnera M, Di Fazio I, Romeo MA et al (1997) Elevation of interleukin 6 levels in patients with chronic hepatitis due to hepatitis C virus. J Gastroenterol 32:211-215
23. Meisner M, Tschaikowsky K, Palmaers T, Schmidt J (1999) Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. Crit Care 3:45-50
24. Meisner M, Tschaikowsky K, Hutzler A et al (1998) Postoperative plasma concentrations of procalcitonin after different types of surgery. Intensive Care Med 24:680-684
25. Monneret G, Labaune JM, Isaac C et al (1997) Procalcitonin and C-reactive protein levels in neonatal infections. Acta Paediatr 86:209-212
26. Nast-Kolb D, Waydhas C, Gippner-Steppert C et al (1997) Indicators of the posttraumatic inflammatory response correlate with organ failure in patients with multiple injuries. J Trauma 42:446-454
27. Nylen ES, Whang KT, Snider RH et al (1998) Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. Crit Care Med 26: 1001-1006
28. Oberhoffer M, Karzai W, Meier-Hellmann A et al (1999) Sensitivity and specifity of various markers of inflammation for the prediction of tumor necrosis factor and interleukin-6 in patients with sepsis. Crit Care Med (in press)
29. Oberhoffer M, Vogelsang H, Russwurm S et al (1999) Outcome prediction by traditional and new markers of inflammation in patients with sepsis. Clin Chem Lab Med 37:363-368
30. Povoa P, Almeida E, Moreira P et al (1998) C-reactive protein as an indicator of sepsis. Intensive Care Med 24:1052-1056
31. Rau B, Steinbach G, Gansauge F et al (1997) The role of procalcitonin and interleukin-8 in the prediction of infected necrosis in acute pancreatitis. Gut 41:832-840
32. Reinhart K, Wiegand-Lohnert C, Grimminger F et al (1996) Assessment of the safety and efficacy of the monoclonal anti-tumor necrosis factor antibody-fragment, MAK 195F, in patients with sepsis and septic shock: a multicenter, randomized, placebo-controlled, dose-ranging study. Crit Care Med 24:733-742
33. Robak T, Gladalska A, Stepien H, Robak E (1998) Serum levels of interleukin-6 type cytokines and soluble interleukin-6 receptor in patients with rheumatoid arthritis. Mediators Inflamm 7:347-353
34. Schwenger V, Sis J, Breitbart A, Andrassy K (1998) CRP levels in autoimmune disease can be specified by measurement of procalcitonin. Infection 26:274-276
35. Shenkin A, Fraser WD, Series J et al (1989) The serum interleukin 6 response to elective surgery. Lymphokine Res 8:123-127
36. Shaw AC (1991) Serum C-reactive protein and neopterin concentrations in patients with viral or bacterial infection. J Clin Pathol 44:596-599
37. Ugarte H, Silva E, Mercan D (1999) Procalcitonin used as a marker of infection in the intensive care unit. Crit Care Med 27:498-504
38. Wakefield CH, Barclay GR, Fearon KC et al (1998) Proinflammatory mediator activity, endogenous antagonists and the systemic inflammatory response in intra-abdominal sepsis. Scottish Sepsis Intervention Group. Br J Surg 85:818-825