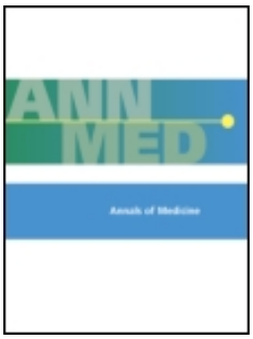

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Markers of inflammation in sepsis

Annika Takala[1,5], Irmeli Nupponen[2,5], Marja-Leena Kylänpää-Bäck[3,5] and Heikki Repo[4,5]

Pathophysiology of sepsis is characterised by a whole body inflammatory reaction and concurrent activation of the host's anti-inflammatory mechanisms. The balance between pro- and anti-inflammatory reactions is critical for the outcome of the patient. Strongly activated phagocytes and high levels of proinflammatory cytokines occur in patients who are at risk of developing circulatory shock and multiple organ dysfunction. Extensive anti-inflammatory reaction, which is characterised by the presence of high levels of circulating anti-inflammatory cytokines and impaired innate and adaptive immune functions, renders critically ill patients prone to secondary infections. Evaluation of the immune-inflammatory status on admission to the hospital may be helpful in the early identification of patients who are bound to develop organ dysfunction. Such patients could possibly benefit from a mode of therapy aimed at modifying the course of inflammatory response. The use of inflammatory markers may also improve diagnosis of severe infection. The present review summarises the studies on markers of inflammation and immune suppression used, first, as predictors of organ dysfunction in patients with systemic inflammation, and, second, as indicators of infection in adults and neonates.

Keywords: acute pancreatitis; CD11b; cytokine; innate immunity; organ dysfunction; sepsis; systemic inflammation

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Introduction

Despite the development of modern intensive care and new antimicrobial agents, mortality of the patients with septic shock remains high, 50–90% (1, 2). The poor outcome is considered to be a consequence of an overactive systemic inflammatory response elicited by the invading micro-organisms. Indeed, evidence has accumulated to show that systemic inflammation contributes to the development of multiple organ dysfunction (reviewed in ref. 3), the major cause of mortality in patients with septic shock (1).

The severity of systemic inflammation is affected by genetic factors, which govern the patient's immune-inflammatory response to invading microbes (4). Although infection is the most frequent trigger of systemic inflammation, it may be elicited by a variety of non-infectious insults such as a whole body trauma, haemorrhagic shock, acute pancreatitis and autoimmune disorders.

Systemic inflammation is a consequence of activation of the innate immune system. It is characterised by intravascular release of pro-inflammatory cytokines and other vasoactive mediators, and concurrent activation of innate immune cells, such as neutrophils and monocytes, within the circulation (Figure 1). The phlogistic mediators can cause circulatory collapse and vascular panendothelial injury, which increases microvascular permeability (5). In addition to the pro-inflammatory reactions, also the host's anti-inflammatory mechanisms are activated and aimed at counteracting the inflammatory response.

In critically ill patients, the reversal of the pro-inflammatory response leads not so infrequently into a state of immune suppression. Accordingly, monocytes are unable to generate pro-inflammatory cytokines in response to bacterial cell wall structures (6) suggesting a defect in innate immunity. Furthermore, a decrease in monocyte surface density of class II human leukocyte antigens (HLA-DR) (7), a sign of adaptive immune defect, can be detected. Such patients are susceptible to secondary infections, which contribute to the development of late organ dysfunction.

In acutely ill patients, the evaluation of the quality and intensity of systemic inflammation may aid to identify the patients at risk of organ dysfunction. Such

From the Departments of [1]Anesthesia and Intensive Care Medicine, [3]Surgery and [4]Medicine, Helsinki University Central Hospital, Helsinki, Finland; [2]Hospital of Children and Adolescent, Helsinki University Central Hospital, Helsinki, Finland; [5]Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Helsinki, Finland.

Correspondence: Annika Takala, MD, Department of Anesthesia and Intensive Care Medicine, Helsinki University Central Hospital, P.O. Box 340, FI-00029 Hus, Finland. Fax: +358-9-57135500; E-mail: annika.takala@helsinki.fi

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patients might benefit from therapies which alter the course of systemic inflammation. On the other hand, in patients with emerged immune suppression, the institution of immune suppressive therapy would be detrimental. The markers might also aid the physician to suspect the presence of a severe infection and institute antimicrobial chemotherapy early enough to prevent the development of the whole body inflammatory reaction.

Since acutely ill patients present varying stages of systemic inflammation and immune suppression, evaluation of the immune-inflammatory status is necessary. No single marker is sufficient for achieving this, and most probably a set of markers of inflammation and immune suppression is needed. The individual tests should be simple enough to be carried out in the hospital laboratory as a 24 hour service. A variety of candidate markers, which can be used as routine tests, are currently available and are summarised in this review. The humoral markers include interleukin(IL)-6, IL-8, IL-10, soluble IL-2 receptor (sIL-2R) and procalcitonin, all of which can be assayed by commercially-available automatic counters. The cellular markers include neutrophil and monocyte surface density of CD11b/CD18, a β_2-integrin, and monocyte surface density of HLA-DR

Key messages

- Systemic inflammation may contribute to development of early organ dysfunction in septic shock and acute pancreatitis but not in haemorrhagic shock.
- Overactive anti-inflammatory response may lead to immune suppression, which increases risk of secondary infections and late organ dysfunction.
- Markers of systemic inflammation improve early diagnosis of severe infection.

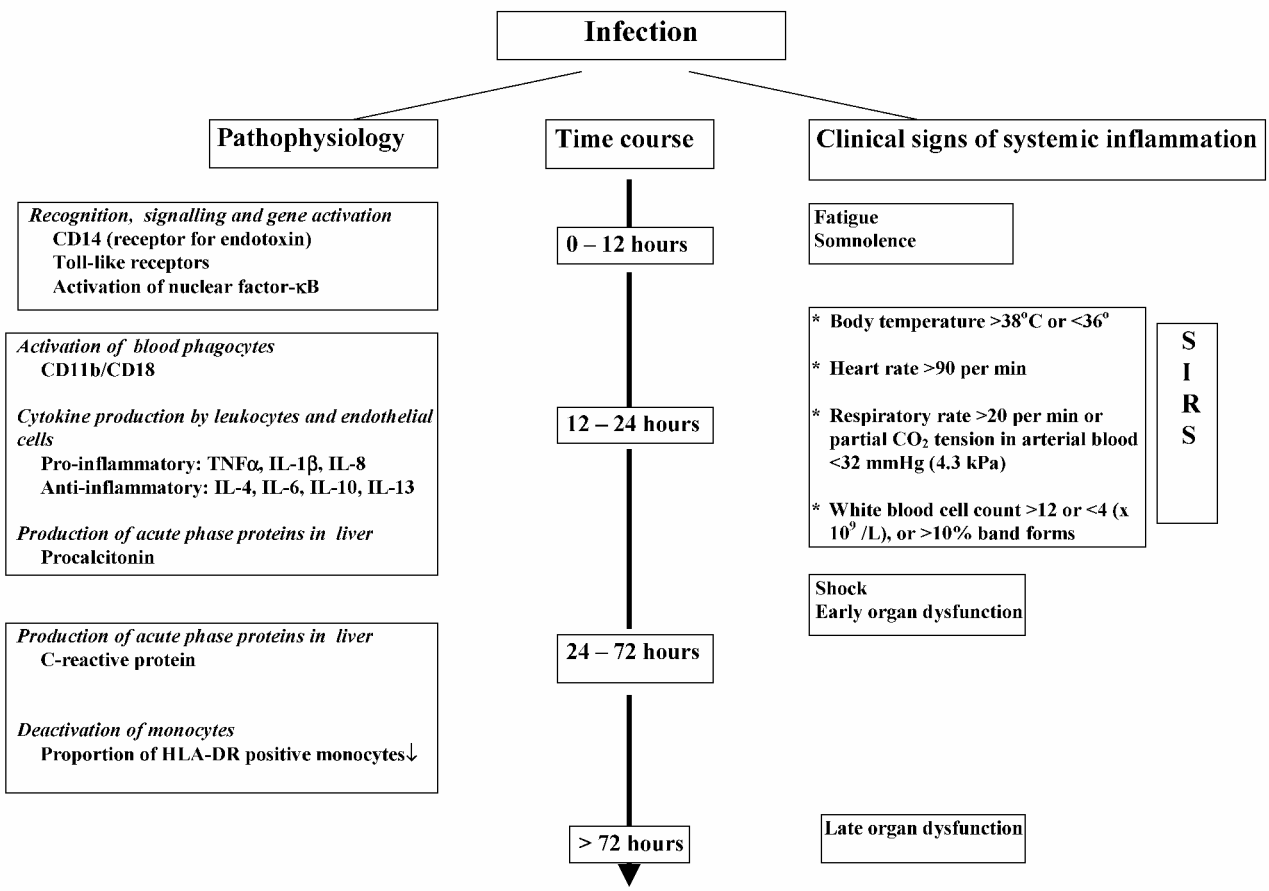

Figure 1. Time course of inflammation markers and concurrent clinical signs in patients with severe infection. Mononuclear phagocytes recognise microbial structures using CD14 receptors. Signalling into intracellular compartments occurs via Toll-like receptors, resulting in activation of nuclear factor-kappaB, which initiates transcription of pro- and anti-inflammatory genes. Next, the release of pro- and anti-inflammatory cytokines into the circulation occurs. Circulating neutrophils and monocytes become activated expressing increased cell surface density of CD11b/CD18 molecules. Blood procalcitonin levels increase. C-reactive protein levels start to increase. The number of HLA-DR molecules on monocytes to diminishes, denoting the development of immune suppression. The concurrent clinical events are shown on the right panel. The time table should be considered as a rough estimate. See also the corresponding part of the text.

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antigens, all of which can be determined by flow cytometry.

Systemic inflammation

Clinical aspects

In 1991 the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine suggested the use of definitions of systemic inflammatory response syndrome (SIRS) in order to uniform the patient populations recruited for research projects (8). Acute abnormalities for body temperature, respiratory rate, heart beat and white blood cell counts constitute the sensitive but very unspecific criteria of SIRS (Figure 1). The clinical definition of sepsis is SIRS caused by infection. It was acknowledged that SIRS can be present in numerous other conditions such as acute pancreatitis, trauma, burn injuries or autoimmune diseases. Furthermore, the use of SIRS criteria was suggested to improve the bed-side detection of sepsis in an individual patient. Among severely ill patients, however, SIRS is a very common finding and fails to serve as a marker of sepsis or predictor of organ dysfunction. Furthermore, when evaluating acutely ill patients admitted to a university hospital medical emergency department, the sensitive criteria include patients who virtually lack systemic inflammation (9). There are several scoring systems, other than SIRS, such as Acute Physiology and Health Evaluation Score II (APACHE II) (10), Sepsis-related Organ Failure Assessment (SOFA) (11), and Multiple Organ Dysfunction Score (MODS) (12), which have been used to predict and describe the development of organ dysfunction in critically ill patients. However, the scoring systems are not well suited for clinical medicine because they comprise a variety of laboratory and clinical variables, require follow-up periods from hours to tens of hours and are sensitive to the treatment of the patient.

Time course of inflammation markers and clinical findings

Mononuclear phagocytes bind microbial structures, such as endotoxins (lipopolysaccharides), by the cell surface receptor CD14 whereas neighbouring receptors, which are members of the Toll-like receptor family, serve as signalling elements (13). In addition to endotoxins, CD14 and Toll-like receptors may interact with other exogenous and endogenous ligands, including respiratory syncytial virus, heat-shock proteins and fibrinogen (14). The signalling results in activation of nuclear factor kappaB, a transcription factor, which promotes synthesis and release of a variety of pro- and anti-inflammatory cytokines. These events occur during early hours of microbial invasion and may be associated with minor clinical symptoms, such as somnolence and fatigue (Figure 1). At this stage, the symptoms are mild and few patients, if any, seek for medical services, and, thus, evaluation of markers of systemic inflammation is not possible. Subsequently, pro-inflammatory cytokines induce fever and contribute to the changes in heart rate, respiratory rate and white blood cell count, i.e., to the development of SIRS. At this stage, patients usually seek for medical help. Some patients develop circulatory shock, occasionally irreversible and fatal. If the patient survives, vital organ dysfunction may develop during subsequent days. Later on, levels of C-reactive protein (CRP), an acute phase reactant, increase and immune suppression develops, which renders the patient susceptible to secondary infections, late onset organ dysfunction and death (Figure 1). Thus, among these patients, defining immune-inflammatory status on admission and subsequent monitoring of it might provide a means to predict the development of organ dysfunction and aid in decision making whether to use immune suppressive treatment or immune stimulatory treatment.

Soluble markers

The two cytokines associated with the early pathophysiological events of septic shock are tumour necrosis factor α (TNFα) and IL-1, both of which can be assayed by the automatic counter (Immulite®). However, the use of TNFα and/or IL-1β as a marker of systemic inflammation and predictor of outcome is hampered by several reasons. TNFα is not necessarily detectable in patients on admission because it has a median half-life as short as 17 minutes. Furthermore, TNFα is sensitive to sampling handling procedures. Thus, the levels determined by immunoreactive methods may not be perfect estimates of the actual biological activity. IL-1β is found only occasionally in plasma of sepsis patients (15, 16). Since TNFα and IL-1 stimulate the synthesis of other proinflammatory cytokines, such as IL-6 and IL-8, the latter have been used as estimates of TNFα and IL-1 activities.

IL-6, IL-8 and IL-10 are all produced in large amounts by activated mononuclear phagocytes. IL-6 induces the acute phase protein synthesis in the liver (17). It has both pro- and anti-inflammatory properties (18). IL-8 attracts neutrophils and guides their migration towards the site of tissue injury (19). IL-10 is an important immune regulatory cytokine which inhibits macrophage production of TNFα, IL-1, IL-6 and IL-8 (18).

IL-2 is the most powerful growth factor for T-cells. IL-2 acts on a high-affinity receptor consisting of three subunits. One of them, the alpha subunit, is not detectable on resting T cells but is rapidly induced in

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antigen-stimulated T cells. The sIL-2R is a truncated portion of the IL-2 receptor alpha chain (20), also known as CD25 or Tac antigen. Increased levels of it are consider to serve as an activation marker of T cells (21).

The occurrence of calcitonin-like immunoreactivity in the blood of patients with various extrathyroid diseases (22) led to the finding that procalcitonin, a precursor of calcitonin hormone, is an early marker of bacterial infection (23). The exact site of procalcitonin production in patients with systemic inflammation is unknown. Procalcitonin mRNA is expressed in monocytes, and the expression increases in response to bacterial lipopolysaccharides (endotoxins) and pro-inflammatory cytokines (24). In addition, human TNFα and IL-2 administered to cancer patients increased procalcitonin serum levels, and, studied *ex vivo*, stimulated human liver slices to produce procalcitonin (25). The latter study gives credence to the view that procalcitonin is an acute phase reactant whose peak levels occur markedly earlier than do those of CRP.

Cellular markers

The CD11b/CD18 heterodimer is an integrin-type glycoprotein receptor, which is constitutively expressed at a low level on the surface of neutrophils and monocytes. It mediates irreversible adhesion and transmigration of phagocytes from the circulation into tissues. Additional CD11b/CD18 molecules are stored in the cytoplasmic granules. Upon phagocyte activation, they are quickly mobilised and transferred to the cell surface. The phagocyte activation can be induced by mediators of systemic inflammation, such as TNFα. This, and the fact that de novo protein synthesis is not needed, makes CD11b/CD18 a promising early marker of systemic inflammation (reviewed in ref. 26).

The cell surface expression of HLA-DR molecules is associated with monocyte ability to present antigens to T-cells. Exogenous IL-10 decreases monocyte HLA-DR expression (27), resulting in a decrease in the proportion of HLA-DR positive monocytes. If the proportion of HLA-DR expressing monocytes falls below 30%, the patient is considered to be anergic (28).

The sample volume needed for a whole blood flow cytometric determinations of CD11b/CD18 and HLA-DR is as small as 25 to 50 μl, less than 10% of the volume needed for the measurement of the soluble markers using the current automatic counters. The use of cellular markers in evaluation of the innate immune status is favourable if the sample volume is critical.

Prediction of organ dysfunction

Sepsis

Despite extensive research, at present there is no single marker that would reliably identify at early stage of disease individual patients with sepsis who are bound to develop organ dysfunction. Inadequate perfusion supply to tissues is a risk factor for the development of organ dysfunction. Accordingly, the development of circulatory shock is the major epidemiological predictor for mortality among patients with sepsis (2).

We recently studied the course of systemic inflammation in patients with blood-culture positive sepsis during the first week after admission and evaluated the presence of organ dysfunction at day seven (29). It is of note that none of the patients without cardiovascular shock developed organ dysfunction. The patients bound to develop organ dysfunction exhibited stronger inflammatory responses than did the patients who recovered without complications. In the initial sample, the strongly enhanced levels of CD11b/CD18 expression and circulating IL-6, IL-8, and sIL-2R, but not CRP, were associated with subsequent development of organ dysfunction. As to the individual markers, however, a considerable overlap was seen between the organ dysfunction and no-dysfunction groups (15, 29). We therefore developed a composite score on the basis of the individual markers, presence of shock and counts of monocytes and platelets in blood. Unlike individual markers, the composite score did identify already on admission to the hospital the patients bound to develop organ dysfunction (29).

In our study (29), eight of the nine patients with community-acquired septic shock developed organ dysfunction. In three patients with comparable clinical severity of disease, the causative agent was *Neisseria meningitidis* (Table I). In two patients who developed organ dysfunction, the profile of inflammation markers exhibited more enhanced systemic inflammation compared to the third patient without organ dysfunction. If confirmed in larger studies, the findings suggest that the markers used may identify septic shock patients who recover without organ dysfunction.

The levels of procalcitonin increase with the severity of sepsis (23, 30, 31) and the levels at an early stage of sepsis have been shown to be higher in non-survivors than those in patients who survive (32), but not in all studies (30, 31). The possibility that procalcitonin improves the marker profile predicting organ dysfunction warrants further studies.

Pro- and anti-inflammatory responses co-occur in the early phase of severe sepsis (33). In non-survivors of sepsis, the proportion of HLA-DR positive mono-

Table 1. The profile of systemic inflammation in three patients with septic shock triggered by *Neisseria meningitidis*. The profile was determined within 48 hours after sampling for blood culture. The data derive from ref. 29.

Patient	*Neisseria meningitidis*	APACHE II score	Serum IL-6 (normal <5 ng/L)	Serum IL-8 (normal <5 ng/L)	CD11b (normal 25-77 RFU[1])	Platelet count $\times 10^9$/L (normal >150)	Organ dysfunction at day seven
1.	Group C	15	2 500	92	328	18	Yes
2.	Group B	20	3 600	569	271	100	Yes
3.	Group C	21	200	6	126	162	No

[1] RFU = relative fluorescence unit.

cytes tended to persist low (<40%), suggesting that also immune suppression markers may serve as a predictor of outcome of sepsis. This is also supported by previous studies indicating that the risk of death is the highest in febrile patients with high IL-10 concentration related to low TNFα level (34). In patients with major trauma, surgery, or burn injuries, monocyte HLA-DR expression diminishes soon after the insult (33, 35). The clinical recovery is accompanied by the recovery of HLA-DR expression (33). However, the patients who show persistently low HLA-DR density, are prone to secondary infections (36, 37), which may further depress monocyte HLA-DR expression. In sepsis patients, the presence of anergy, defined by a low (<30%) proportion of HLA-DR positive monocytes, is predictive for death, and treatment with interferon-γ alleviated anergy and appeared to improve survival (28). The use of immune stimulation, however, may be a double-edged sword. Indeed, immune suppression in these patients seems to be confined to the blood while hyperinflammatory reaction persists in other body compartments, such as the lungs (reviewed in refs. 38, 39), where immune stimulation might enhance tissue destruction.

Acute pancreatitis

The clinical manifestations in patients with severe acute pancreatitis are indistinguishable from those in patients with severe infection. Like in sepsis, the major cause of mortality and morbidity in patients with acute pancreatitis is organ dysfunction (12, 40), the most common form of which is acute respiratory distress syndrome (ARDS).

The natural course of severe acute pancreatitis is considered biphasic. In the first phase, pro-inflammatory mediators are produced locally and released into the circulation. Accordingly, we found that the severity of systemic inflammation, as defined by the inflammation markers, is related to the development of acute lung injury (41) supporting the idea that systemic inflammation plays a role in the development of organ dysfunction as well in acute pancreatitis as in sepsis. The second phase occurs approximately after the second week of the onset and is typified by the presence of immune suppression and secondary infections (42, 43). Despite intensive search, no clinical or biochemical marker has been found to date, which would be helpful in clinical practice by predicting at presentation the course of acute pancreatitis.

We recently found that in patients with acute pancreatitis the procalcitonin levels predict already on admission the development of organ dysfunction (44). To our surprise, many of the patients developed organ dysfunction within 24 hours after admission, which agrees with the recent finding that organ dysfunction due to acute pancreatitis emerges early (45). The findings strongly suggest that the risk of organ dysfunction needs to be evaluated immediately on admission and that the severity marker need to respond rapidly to the disease process. Against this background it is evident that rapid markers are superior to those which increase along time, such as CRP. In accordance, CRP is not helpful as a predictor of the disease severity on admission, yet, it is helpful in the follow-up of the course of the disease (46, 47). As to the rapid markers other than procalcitonin, CD11b densities on blood neutrophils and monocytes are related to the development of organ dysfunction (48) and serum levels of IL-6 (49) and IL-8 (50) to severity of acute pancreatitis.

Immune suppression (51) and elevated serum levels of anti-inflammatory cytokines IL-6 (49) and IL-10 (52) are detected at an early phase of acute pancreatitis. We found that severe immune suppression, as defined by low monocyte HLA-DR expression, seemed to develop concurrently with ongoing systemic inflammation, as determined by enhanced phagocyte CD11b expression (48). Similar time course of developing immune suppression was recently found also in patients with sepsis (33). The findings raise an important question whether immune suppressive therapy started at this stage is harmful because it may strengthen the patient's anti-inflammatory reaction and contribute to the development of undue deep immune suppression.

Taken together, systemic inflammation and immune suppression both play a role in the development of organ dysfunction in patients with acute

pancreatitis. In terms of systemic inflammatory reaction, acute pancreatitis and sepsis are very similar, if not identical. Like in sepsis, the use of a marker combination is most probably superior to any single marker in predicting organ dysfunction in acute pancreatitis. A reliable marker profile is needed because clinicobiochemical scoring systems are difficult to use at emergency departments (53), and the patients at risk for organ dysfunction benefit from early monitoring and support at intensive care units (54). In the future, determining the immune-inflammatory status on admission appears mandatory when evaluating the effects of novel drugs aimed at depressing the early, pro-inflammatory phase, or inducing immune stimulation in patients who have developed immune suppression.

Haemorrhagic shock

In patients with trauma, an individual risk factor for the development of organ dysfunction is the high number of packed red blood cell units transfused within the first twelve hours after trauma (55). Haemorrhagic shock and massive transfusion may be followed by the deterioration of lung function by an indirect mechanism. The animal models suggest that haemorrhagic shock and global ischaemia trigger strong systemic inflammation (56), and that inhibiting it, for instance by interfering leukocyte-endothelial interactions is beneficial (57). In humans, however, the mechanisms are less clear. Of note, in trauma patients, neutrophil CD11b density is strongly enhanced but not related to the development of organ dysfunction (41, 58). Secondly, the lack of relationship between the levels of IL-6, IL-8 or CD11b and lung injury was detected in patients with massive transfusion (41). These findings suggest that systemic inflammation may not contribute substantially to the development of organ dysfunction in patients with haemorrhagic shock. In accordance with this suggestion, patients with trauma or haemorrhagic shock did not benefit from therapies that modulate the course of the systemic inflammation such as CD11/CD18 blockade (reviewed in ref. 59). To summarise, several lines of evidence suggest that systemic inflammation plays a role in the development of organ dysfunction in septic shock and severe acute pancreatitis but not in haemorrhagic shock.

Early detection of infection

Newborn infants

In the newborn infants, especially in those born prematurely, the rapid diagnosis of bacterial sepsis is crucial for survival. The clinical symptoms and markers presently used are less sensitive and specific than in older children or adults. Thus, it is imperative that empiric broad-spectrum antimicrobial chemotherapy is instituted immediately when infection is suspected. The determination of CRP is of limited value when diagnosing sepsis because of its poor sensitivity and specificity (69). Numerous markers have been reported to detect early onset neonatal sepsis. Among the most promising variables are the soluble inflammatory mediators, such as IL-6 and IL-8 (70, 71). We recently demonstrated that the expression of CD11b on neutrophils serves as a sepsis marker in newborns (72). It shows reasonably high sensitivity and specificity, and a strong correlation with IL-8 concentration (Figure 2). The use of CD11b/CD18 appears favourable because the sample volume (25 μl) needed is small enough to permit daily sampling for follow-up of preterm infants. CD11b may aid to reduce the courses of antimicrobial drugs in the newborns, a possibility which warrants prospective studies with cost-benefit analysis.

Adult patients

In a febrile adult admitted to a hospital medical emergency department, the history, clinical examination and routine laboratory tests may reveal a focus of infection. However, infection may be cryptic and particularly in elderly patients does not necessarily cause fever. In such a case, the clinical criteria of SIRS and CRP test may aid to decide whether the patient has systemic inflammation. If systemic inflammation is present, empiric antimicrobial chemotherapy needs to be started, and then the diagnostic workup may be safely continued. However, CRP levels increase slowly (Figure 1) and may not be elevated at an early stage of infection while IL-6 level and CD11b density are high (9, 60). Procalcitonin, CD11b/CD18, IL-6, sIL-2R, IL-8 and IL-10 all may serve as an early marker of infection, but high levels occur also in patients with SIRS trigged by a non-infectious disorder (9, 61). Thus, none of these markers is specific for infection. Still, evidence has accumulated to show that for instance procalcitonin concentrations remain low in patients with non-bacterial infection or non-infectious disorders (23).

At present it appears that markers of systemic inflammation may be helpful in special clinical settings. Thus, procalcitonin seems to distinguish between sepsis and local infection or systemic inflammation triggered by a non-infectious disease (62), between sterile and infected pancreatic necrosis (63), and between infection and acute rejection in patients with solid organ transplantation (64), although caution is needed (65). Patients who have counteracted systemic inflammation by developing anergy are susceptible to secondary infections, which

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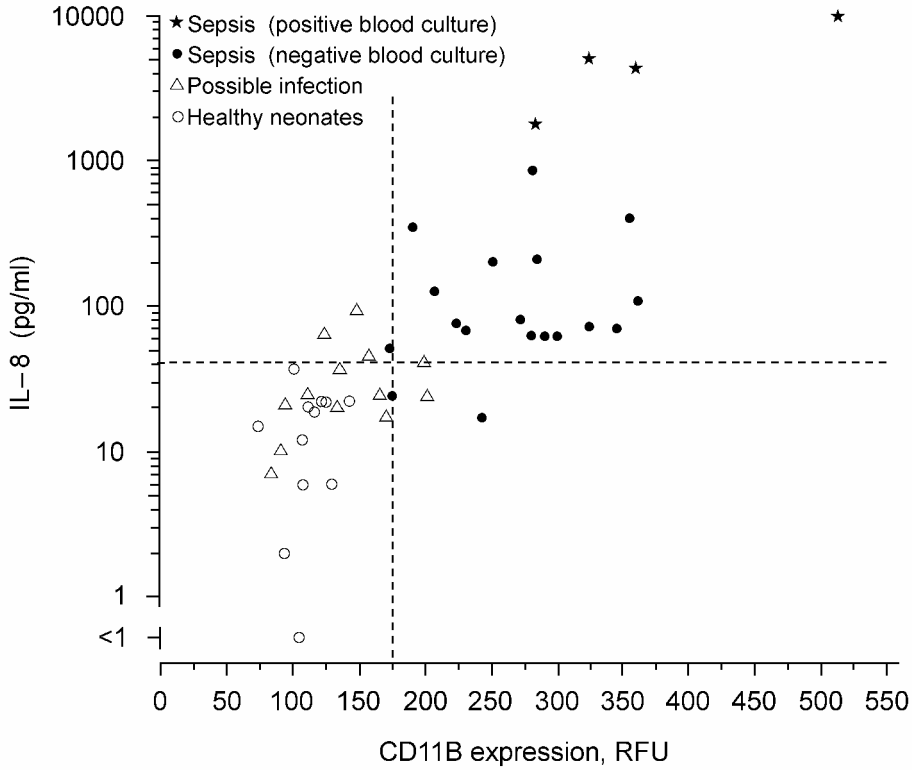

Figure 2. Correlation between neutrophil CD11b expression and plasma IL-8 concentration in newborns. Dotted lines denote median values for the whole study population. RFU indicates relative fluorescence units. R = 0.82, [95% confidence interval 0.70±9.90]. Reproduced from ref. 72 (by permission).

are difficult to detect at an early stage. In the whole blood assay, the patients' phagocytes show poor innate responses to bacterial lipopolysaccharides (28). Accordingly, the pro-inflammatory cytokine levels did not increase in ARDS patients with nosocomial blood stream infections (66). Also the procalcitonin may not be a perfect marker in detecting secondary infections in intensive care patients (67, 68). Taken together, the results above indicate that markers of systemic inflammation may be helpful in the diagnosis of cryptic community-acquired infections but not necessarily in anergic patients who fail to elicit innate responses during nosocomial infections. The results also suggest that evaluation of the immune-inflammatory status of the patients at risk for secondary infections is meaningful in clinical medicine.

Future directions

Although the markers of inflammation are indirect and unspecific indicators of infection, the recent studies of CD11b as a marker of severe infection in newborns are promising. Indeed, the CD11b test may aid to limit the use of antimicrobial drugs in neonates in a cost-effective manner, a possibility which needs to be explored in prospective studies. In the search for predictors of organ dysfunction, DNA microarray technology provides new possibilities. In the future, the analysis of patterns of activated genes, using DNA chips, in patients with sepsis, acute pancreatitis and haemorrhagic shock in relation to the development of organ dysfunction is important. Because the gene activation pattern does not necessarily correlate to the release and biological activity of the respective gene products, such as cytokines, assays which permit analysis of complex mixtures of proteins in serum are needed. This may be achieved in the future by using peptide chips and a large panel of antibodies, i.e., an immune assay on microarrays (reviewed in ref. 73)

Concluding remarks

Systemic inflammation, and anti-inflammatory reaction induced by it, co-occur and contribute to the development of organ dysfunction in patients with septic shock and severe acute pancreatitis. Therefore, instead of a single marker, a set of markers of inflammation and immune suppression is needed to evaluate a patient's immune inflammatory status. Such a marker set may also identify early the patients at risk for organ dysfunction. In anergic patients, immune suppression seems to be confined to the blood compartment whereas hyperinflammatory reaction persists in tissues. Whether these patients

should be treated with immune stimulatory drugs is uncertain. Immune stimulation might be beneficial in the blood compartment but could increase inflammatory reactions and injury in the tissue compartments. Anergic patients fail to elicit innate responses, in other words increase IL-6 and CRP levels and develop fever, thus interfering with the use of acute phase reactants in the diagnostics of secondary infections.

Recently, evidence has accumulated to show that systemic inflammation does not contribute to the development of organ dysfunction in patients with haemorrhagic shock. Such patients may not benefit from therapies aimed at altering the course of systemic inflammation to prevent or alleviate organ dysfunction. The markers of systemic inflammation are not specific for infection. Still, they appear to serve as a reasonably reliable sepsis markers in neonates, most probably because non-infectious causes of systemic inflammation in neonates are not so frequent. In the future, studies on genomics and proteomics may provide novel tools for predicting organ dysfunction and detecting infection at its early stage.

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