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Significance of lipopolysaccharide-binding protein (an acute phase protein) in monitoring critically ill patients

Miroslav Prucha[1], Ivan Herold[2], Roman Zazula[3], Ladislava Dubska[1], Miroslav Dostal[1], Thomas Hildebrand[1] and Josef Hyanek[4]

[1]Staff, Department of Clinical Biochemistry, Hematology and Immunology, Hospital Na Homolce, Czech Republic
[2]Head, Department of Anesthesiology and Intensive Care Medicine, Klaudian's Hospital – Mlada Boleslav, Czech Republic
[3]Head, Department of Anesthesiology and Intensive Care, Thomayer's Hospital, Prague, Czech Republic
[4]Head, Department of Clinical Biochemistry, Hematology and Immunology, Hospital Na Homolce, Czech Republic

Correspondence: Miroslav Prucha, miroslav.prucha@homolka.cz

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Abstract

Introduction The present study was conducted to assess the value of serum concentration of lipopolysaccharide-binding protein (LBP) in patients with systemic inflammatory response syndrome (SIRS), sepsis and septic shock with respect to its ability to differentiate between infectious and noninfectious etiologies in SIRS and to predict prognosis.

Methods This prospective cohort study was conducted in a multidisciplinary intensive care unit. Sixty-eight patients, admitted consecutively to the intensive care unit and who met criteria for SIRS, sepsis or septic shock were included. Serum LBP was measured using an immunochemiluminiscence assay.

Results Serum levels of LBP were significantly increased in patients with SIRS ($n=40$; median 30.6 μg/ml, range 9.2–79.5 μg/ml), sepsis ($n=19$; median 37.1 μg/ml, range 11.8–76.2 μg/ml) and septic shock ($n=9$; median 59.7 μg/ml, range 31.1–105 μg/ml), as compared with levels in the healthy volunteers (5.1 ± 2.2 μg/ml; $P<0.0001$). Serum LBP at study entry was statistically significantly lower in patients with SIRS than in those with septic shock ($P<0.014$); no statistically significant difference existed between patients with SIRS and those with sepsis ($P=0.61$). Specificity and sensitivity of an LBP concentration of 29.8 μg/ml to distinguish between infectious and noninfectious etiologies for SIRS were 50% and 74.2%, respectively. There was no statistically significant difference in LBP concentration between survivors and nonsurvivors in both groups of patients. Furthermore, in septic patients the LBP response appeared to exhibit a decreased magnitude.

Conclusion LBP is a nonspecific marker of the acute phase response and cannot be used as a diagnostic tool for differentiating between infectious and noninfectious etiologies of SIRS.

Keywords acute phase protein, C-reactive protein, lipopolysaccharide-binding protein, procalcitonin, sepsis, systemic inflammatory response syndrome

Introduction

An important group of critically ill patients in intensive care units (ICUs) are those exhibiting a systemic inflammatory response caused by extreme stimulation of the immune system. Etiologic factors include micro-organisms (sepsis) and noninfectious insults such as trauma, burns, major

CRP = C-reactive protein; ICU = intensive care unit; IL = interleukin; LBP = lipopolysaccharide-binding protein; LPS = lipopolysaccharide; SIRS = systemic inflammatory response syndrome.

surgery, ischemia/reperfusion, and pancreatitis (i.e. systemic inflammatory response syndrome [SIRS]). Immunopathogenetic mechanisms play an important role in the course and progression of both sepsis and SIRS. Sepsis is frequently an important factor in the mortality of patients in ICUs.

From a clinical point of view, differentiating between an infectious and a noninfectious etiology in patients with clinical symptoms of sepsis is very difficult. The limiting factor is the lack of specificity in differentiating between underlying causes of inflammation. One of the parameters currently employed to establish whether sepsis is present is C-reactive protein (CRP) [1,2]. During the past few years several new parameters have been introduced, including procalcitonin and lipopolysaccharide-binding protein (LBP) [3,4].

The acute phase proteins used in diagnostic procedures are produced mainly by hepatocytes. Two classes of acute phase proteins may be distinguished on the basis of their synthesis. Class 1, induced by IL-1 in synergy with IL-6, includes CRP and MBP. Class 2, induced by IL-6 alone, includes antiproteases, α_2-macroglobulin, and fibrinogen [5–8].

In 1986, Tobias and coworkers [5] described a new acute phase reactant, namely LBP. It is a 58 kDa protein that is synthesized in the liver, and it potently enhances the sensitivity of monocytes and granulocytes to lipopolysaccharide (LPS) by facilitating binding of LPS to the CD14 cell membrane molecule [9,10]. The mature CD14 protein is a myeloid marker antigen that is expressed on the surface of myeloid cells [11]. CD14 is also found circulating free in plasma, where it is referred to as soluble CD14; the latter form of CD14 mediates LPS activation of CD14-negative cells, such as endothelial and epithelial cells [12]. LBP catalyzes movement of LPS monomers from LPS aggregates to high-density lipoprotein particles [13], leading to neutralization of LPS [12]. LBP takes part in the transport of other phospholipids by acting as a lipid exchange protein. Under physiologic circumstances, LBP binds Gram-negative bacteria via the lipid A part of LPS [14,15], which mediates its binding to the CD14 cellular receptor molecule presented by monocytes and macrophages. This results in the phagocytosis and clearance of these micro-organisms [16,17]. Binding of endotoxin activates monocyte/macrophage system cells via Toll-like receptor-4 [18]. The outcome is the production of proinflammatory cytokines (i.e. IL-1 and tumor necrosis factor-α) [19]. Under normal circumstances serum levels of LPB vary in the range 5–15 μg/ml, but levels increase several fold during the acute phase response.

After the relationship between LPS and sepsis was unraveled, the diagnostic and/or prognostic value of LBP levels in patients with SIRS and sepsis were investigated. Previous studies have shown elevated LBP levels in patients with Gram-negative sepsis [20], and elevated LBP levels in patients with SIRS [21] and in patients with sepsis and septic shock [22].

The primary objective of the present study was to determine whether LBP can distinguish between infectious and noninfectious etiologies of SIRS. Secondary objectives were to assess the relationships between LBP levels and procalcitonin, CRP, and clinical, microbiologic, and prognostic parameters in sepsis.

Methods

Sixty-eight patients (age range 18–68 years, median 48 years; 42 men, 26 women), who fulfilled the diagnostic criteria for SIRS (40 patients), sepsis (19 patients) or septic shock (9 patients) [23], were consecutively enrolled between February 2000 and November 2001.

The diagnostic criteria for SIRS were temperature greater than 38°C or less than 36°C; heart rate greater than 90 beats/minute; respiratory rate greater than 20 breaths/minute or arterial carbon dioxide tension greater than 32 mmHg; and white blood cell count greater than 12×10^9/l or less than 4×10^9/l, or the presence of 10% immature forms.

Sepsis was confirmed by the isolation of an organism considered to be of pathogenic significance from an otherwise sterile site (blood, peritoneal cavity, or lung via bronchial lavage) or by the isolation of an organism of recognized pathogenic potential from an intravascular catheter removed for infection related reasons. All patients were screened on a daily basis for the presence of pathogenic organisms by blood and urine culture and, where indicated, by biopsy or aspiration of potentially infected sites.

Septic shock was defined as sepsis with hypotension resistant to fluid resuscitation and evidence of organ hypoperfusion or dysfunction. Specifically, the criteria for septic shock were hypotension (defined as systolic pressure <90 mmHg or reduced by more than 40 mmHg from baseline) and all of the following criteria: temperature greater than 38°C or less than 36°C; heart rate greater than 90 beats/minute; respiratory rate greater than 30 breaths/min or hyperventilation with arterial carbon dioxide tension under 32 mmHg; white blood cell count greater than 12×10^9/l or less than 4×10^9/l; or the presence of more than 10% immature cells.

Blood samples were obtained from patients within 24 hours of meeting the criteria for SIRS, sepsis, or septic shock. All patients received routine intensive care and resuscitation therapy. Patients with sepsis and septic shock were given antibiotic therapy adjusted in accordance with culture results.

The study was approved by the ethics committees of the participating hospitals, and written consent was obtained from all patients or their relatives.

Clinical and functional investigations

The following data were compiled for each patient: demographic data; Acute Physiology and Chronic Health Evalua-

tion II score; diagnosis of SIRS, sepsis, or septic shock; the presence of Gram-negative or Gram-positive infection; and outcome (mortality).

Laboratory analyses

Blood was obtained in vacutainers (Becton Dickinson, Heidelberg, Germany) containing 15% EDTA for blood counts, and 30 U lithium heparin for bilirubin, CRP, alkaline phosphatase, and other routine biochemical measurements. For LBP and procalcitonin, serum was prepared, following coagulation in vacutainer tubes, by centrifugation at 2000 ***g*** at room temperature for 20 min. The serum levels of LBP were measured by means of a commercial chemiluminiscence method (Immulite DPC; Biermann, Bad Nauhe, Germany). Twenty-three healthy adult volunteers (age range 18–48 years), who exhibited no signs of inflammatory or gastrointestinal disease, served as control individuals. Procalcitonin was measured by immunoluminometric assay (LUMItest PCT; Brahms Diagnostica GmbH, Berlin, Germany). The cutoff value for procalcitonin was 0.5 μg/l. We analyzed the levels from study entry, which was defined as the first 24 hours in which SIRS, sepsis, and septic shock criteria were met. Twenty-three patients were assessed repeatedly (12 patients with sepsis, six patients with SIRS, and five patients with septic shock) at 3- to 5-day intervals for the next 30 days or until death. In the remaining patients, who either died or were transferred to other departments, only the baseline investigations were performed. Altogether 138 measurements were completed. Confirmation of diagnosis was done retrospectively with the knowledge of microbiologic findings. The levels of serum proteins were compared with levels in healthy volunteers, SIRS patients, and patients with sepsis and septic shock; they were also compared between survivors and non-survivors.

Statistical analysis

Normal distribution of data was checked for each variable using the Kolmogorov–Smirnov test. The results are expressed as either a mean and standard deviation, or as a median with range. Significance testing of between group differences was performed using the Student's *t*-test and Mann–Whitney test. Changes in serum concentrations of LBP, procalcitonin, and CRP over time were compared using the Kruskal–Wallis test. To evaluate correlations, Spearman's rank correlation coefficient was used. $P<0.05$ was considered statistically significant.

Results

Sixty-eight patients consecutively admitted to the interdisciplinary ICU were enrolled in the study upon meeting criteria for SIRS, sepsis, or septic shock. The demographic data and clinical parameters of patients are summarized in Table 1. In addition, 23 adult healthy volunteers (age range 18–48 years) served as control individuals.

The observed mortality in patients with SIRS was 15% (6/40), that in patients with sepsis was 57.9% (11/19), and that in patients with septic shock was 89% (8/9). Pneumonia was the leading cause of sepsis (57%), and refractory septic shock and multiple organ dysfunction syndrome were the immediate causes of death. During hospitalization, eight patients with SIRS developed sepsis, and in four patients sepsis changed to septic shock.

Levels of lipopolysaccharide-binding protein at the study entry

The mean serum concentration of LBP in all groups of patients was significantly greater than in control individuals ($P<0.0001$); in ascending order, the levels were 30.6 μg/ml in patients with SIRS, 37.1 μg/ml in those with sepsis, and 59.7 μg/ml in those with septic shock. The difference between levels in patients with SIRS and those with septic shock was statistically significant ($P<0.01$).

The specificity and sensitivity of serum LBP concentration in differentiating between patients with SIRS and those with sepsis/septic shock (with cutoff set at 29.8 μg/ml) were poor, at 50% and 74.2%, respectively. Serum LBP at study entry did not differ between patients with Gram-negative (43.1 ± 21.3 μg/ml) and Gram-positive infections (45.2 ± 19.8 μg/ml).

There was no significant difference between serum LBP in survivors and nonsurvivors in the group of patients with SIRS, or in the group of patients with sepsis and septic shock ($P=0.69$ and $P=0.61$, respectively). There was no correlation between serum LBP and clinical status according to Acute Physiology and Chronic Health Evaluation II (Spearman's rho 0.199; $P=0.278$). LBP serum levels did not differ between patients with positive and those with negative blood cultures (42.1 ± 21.4 μg/ml versus 39.5 ± 18.1 μg/ml). LBP levels were not associated with hepatic dysfunction, as defined by bilirubinemia >50 μmol/l (Spearman's rho = −0.125; $P=0.36$).

The mean serum concentrations of LBP, CRP and procalcitonin are listed in Table 2. There was only a weak correlation between LBP and CRP in the group of patients with sepsis and septic shock, and in survivors (Table 3).

Trends in lipopolysaccharide-binding protein levels during the course of hospitalization

The dynamics of LBP levels in surviving and nonsurviving patients with sepsis were similar. The higher levels seen at the first examination decreased thereafter and were lowest at the last examination, despite the temporary increase seen in some patients who did not survive sepsis (Fig. 1). The difference between the first and last examination was statistically significant (in survivors, median 25.4 μg/ml versus 11.9 μg/ml [$P=0.009$]; in nonsurvivors, median 41.8 μg/ml versus 26.4 μg/ml [$P=0.010$]; Fig. 2). LBP levels at the last examination were significantly different between survivors and nonsurvivors ($P=0.014$).

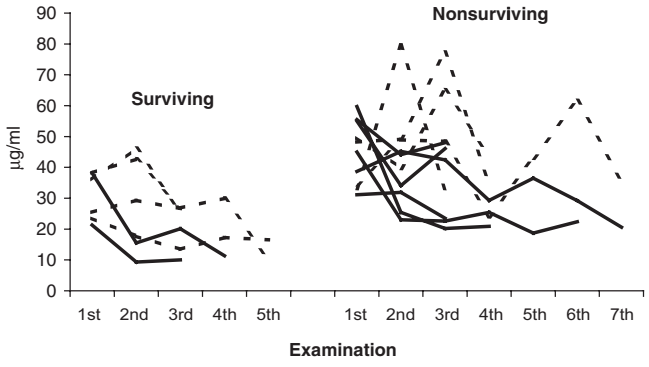
Table 1

Demographic characteristics of patients

Parameter	Value
Age (years; median [range])	
SIRS	49.7 (24–73)
Sepsis and septic shock	45.2 (21–66)
Sex ratio (male:female)	42:26
APACHE II score (median [range])	18.2 (13–28)
Focus (n=28)	
Pneumonia	16
Peritonitis	5
Empyema	1
Mediastinitis	2
Endocarditis	2
Isolated positive blood culture	2
Causative microorganisms	
Gram negative	15
Gram positive	10
Fungus	3
Positive blood cultures (n [%])	11 (39.3)

APACHE = Acute Physiology and Chronic Health Evaluation; SIRS = systemic inflammatory response syndrome.

Figure 1



Time course of lipopolysaccharide-binding protein (LBP) levels in surviving and nonsurviving patients with sepsis and septic shock. Shown are data from patients available for follow up, who were assessed repeatedly at 3- to 5-day intervals for 30 days or until death.

Discussion

The present study showed that serum LBP levels in patients with SIRS, sepsis, or septic shock were higher than those in healthy volunteers. Myc and coworkers [21] reported similar findings. We found no difference in LBP levels at study entry between patients with SIRS of noninfectious etiology and patients with sepsis; neither did we find any difference in LBP levels between surviving and nonsurviving patients with SIRS, or any significant difference in the group of patients with sepsis or septic shock. However, during the follow up of

Table 2

Serum lipopolysacharide-binding protein, procalcitonin, and C-reactive protein at study entry (baseline measurement)

	n	LBP (µg/ml)	PCT (ng/ml)	CRP (mg/l)
SIRS	40	30.6 (9.2–79.5)	0.6 (0.05–2.5)	56.5 (15.2–136.8)
Sepsis	19	37.1 (11.8–76.2)	6.1 (1.4–89.8)	157.1 (41.6–245)
Septic shock	9	59.7 (31.1–105)	25.6 (4.6–85.6)	211.0 (83.3–280)

Data are expressed as median (range). CRP, C-reactive protein; LBP, lipopolysacharide-binding protein; PCT, procalcitonin; SIRS = systemic inflammatory response syndrome.

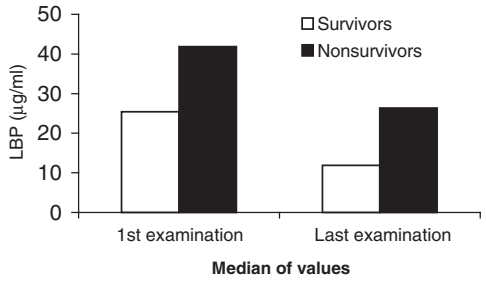
Table 3

Correlations of lipopolysaccharide-binding protein (LBP) with procalcitonin, and of LBP with C-reactive protein at study entry (baseline measurement)

	LBP + PCT		LBP + CRP	
	r	P	r	P
SIRS (noninfectious etiology; n=40)	0.23	0.19	–0.046	0.79
Sepsis + septic shock (infectious etiology; n=28)	0.35	0.046	0.54	0.002
Survivors (n=43)	0.27	0.054	0.22	0.14
Nonsurvivors (n=25)	0.22	0.32	0.58	0.004

Shown are Pearson's correlation coefficients along with corresponding P values. SIRS, systemic inflammatory response syndrome.

Figure 2



Serum lipopolysaccharide-binding protein (LBP) at the first and last examinations in patients with sepsis and septic shock. There was a statistically significant difference between first and last examination in the group of patients who survived ($P=0.009$) and in those who did not ($P=0.010$).

these patients, the nonsurviving septic patients had higher LBP levels than did the surviving patients, which is in accordance with the findings reported by Carroll and coworkers [20] and by Schumann and coworkers [24] but not with those reported by Opal and coworkers [22].

In a surveillance study of several hundred patients, Carroll and coworkers [20] demonstrated a wide range of inflammatory diseases or conditions in which the levels of LBP were elevated (i.e. sepsis, meningococcemia, abdominal infection, and inflammatory bowel disease) and unchanged (i.e. systemic lupus erythematosus, rheumatoid arthritis, and acute graft versus host disease). That study also showed that elevated levels of LBP (>46 µg/ml) at study entry in patients with suspected Gram-negative sepsis were associated with significantly greater mortality. This suggests an association between LBP levels with severity of disease. Severity of disease would be expected to occur in conjunction with increased endotoxin in the systemic circulation. Endotoxemia may originate from regional hypoperfusion and mucosal ischemia, which was suggested to promote translocation of endotoxin to the systemic circulation [25]. In the present study we did not perform measurements of endotoxin and so we are unable to assess its correlation with LBP levels.

Opal and coworkers [22] also did not find any such correlation, but they reported significantly lower serum LBP levels in nonsurvivors than in survivors within 24 hours of onset of sepsis. They hypothesized that synthesis of LBP fails in the presence of rapidly progressive septic shock. Carroll and coworkers [26] reported data from additional clinical trials suggesting that LBP is elevated in patients with hemorrhagic trauma or cystic fibrosis, as well as in patients with partial hepatectomy, and concluded that these patients were systemically exposed to bacteria and endotoxin. In the present study we did not find any relationship between LBP and hepatic function, as indicated by bilirubinemia.

Key messages

- LBP is a nonspecific marker of the acute phase response
- LBP is not a suitable parameter for differentiating between infectious and noninfectious etiologies of SIRS

Similar to Froon and coworkers [27], we observed no difference between LBP levels in patients with Gram-negative and those with Gram-positive infections.

The dynamics of LBP levels in surviving and nonsurviving patients with sepsis were interesting. In both groups of patients, the higher LBP levels seen at the first examination decreased thereafter and were lowest at the last examination. This cannot be explained by hepatic failure because in the survivors hepatic function recovered, but the phenomenon could be due to anergy or tolerance to a long-lasting insult, in this case endotoxin or infection.

We found initial LBP levels to have low specificity and sensitivity in distinguishing between sepsis and SIRS. This conclusion is consistent with earlier reports that LBP is a marker of overall inflammation (i.e. SIRS or multiple organ dysfunction syndrome) [28]. It is possible that patients with sepsis were erroneously classified as having SIRS because of limitations in currently used diagnostic methods. LBP levels have been shown to increase in hemorrhagic colitis and hemolytic uremic syndrome [29]. We found no correlation between LBP and procalcitonin or CRP in any diagnostic group of patients, and neither were the LBP serum levels correlated with illness severity scores.

Conclusion

In conclusion, LBP is a nonspecific marker of the acute phase response and cannot be used as a diagnostic tool for differentiating between infectious and noninfectious etiologies of SIRS. This conclusion is supported by our observation of similar LBP serum levels in patients with SIRS and in those with sepsis. The dynamics of LBP levels (followed in 17 patients) suggest that the LBP levels in septic patients decrease over the course or at the end of the disease. However, the course of LBP levels in individual patients is variable.

Competing interests

None declared.

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