Heparin-Binding Protein: An Early Marker of Circulatory Failure in Sepsis

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Background. The early detection of circulatory failure in patients with sepsis is important for successful treatment. Heparin-binding protein (HBP), released from activated neutrophils, is a potent inducer of vascular leakage. In this study, we investigated whether plasma levels of HBP could be used as an early diagnostic marker for severe sepsis with hypotension.

Methods. A prospective study of 233 febrile adult patients with a suspected infection was conducted. Patients were classified into 5 groups on the basis of systemic inflammatory response syndrome criteria, organ failure, and the final diagnosis. Blood samples obtained at enrollment were analyzed for the concentrations of HBP, procalcitonin, interleukin-6, lactate, C-reactive protein, and the number of white blood cells.

Results. Twenty-six patients were diagnosed with severe sepsis and septic shock, 44 patients had severe sepsis without septic shock, 100 patients had sepsis, 43 patients had an infection without sepsis, and 20 patients had an inflammatory response caused by a noninfectious disease. A plasma HBP level \( \geq 15 \) ng/mL was a better indicator of severe sepsis (with or without septic shock) than any other laboratory parameter investigated (sensitivity, 87.1%; specificity, 95.1%; positive predictive value, 88.4%; negative predictive value, 94.5%). Thirty-two of the 70 patients with severe sepsis were sampled for up to 12 h before signs of circulatory failure appeared, and in 29 of these patients, HBP plasma concentrations were already elevated.

Conclusion. In febrile patients, high plasma levels of HBP help to identify patients with an imminent risk of developing sepsis with circulatory failure.

In sepsis, the molecular mechanisms inducing capillary endothelial leakage are of key importance. The extravasation of plasma and white blood cells (WBCs) to the focus of infection are critical steps in the inflammatory process [1]. However, severe sepsis is characterized by an uncontrolled increase of vascular permeability, leading to hypotension, disturbed microcirculation, hypoxia, and organ dysfunction. The heparin binding protein (HBP; also known as azurocidin and CAP37) is an inflammatory mediator with the ability to induce vascular leakage [2]. The protein is contained within the secretory and azurophilic granulae of human neutrophils [3] and is secreted upon stimulation of the leukocytic \( \beta 2 \) integrins. HBP induces cytoskeletal rearrangements of endothelial cells, which leads to breakage of cell barriers and an increase of the macromolecular efflux [2]. It has been shown that HBP is released upon neutrophil adhesion to endothelial cells and, thus, functions in a paracrine fashion. However, HBP is also secreted when neutrophils are activated by circulating protein complexes formed by streptococcal M protein and fibrinogen, a virulence mechanism that was shown to induce severe organ damage in vivo [4, 5].

The mortality associated with sepsis is still substantial despite the increasing awareness of the diagnosis and recent advancements in treatment strategies [6–8]. An important task for the clinician is to recognize sepsis before it progresses into a more severe state with signs of circulatory failure. It has recently been shown that in patients with septic shock, mortality was correlated to the time between the fall in systolic blood pressure and the start of antibiotic treatment [9]. The diagnosis of sepsis is sometimes difficult and relies mainly on clinical parameters and standard laboratory tests. Thus, a reliable molecular tool identifying patients who are at risk of developing severe sepsis among patients...
METHODS

Study population. Two hundred thirty-three febrile adult patients with clinically suspected infection were enrolled in a prospective nonconsecutive convenience sample study at the Clinic for Infectious Diseases at Lund University Hospital (Lund, Sweden). The inclusion criteria were a body temperature of \( \geq 38^\circ \text{C} \) and a suspected infection as judged by the attending physician. Exclusion criteria were antibiotic treatment for \( >24 \) h, neutropenia because of hematological malignancy, immunosuppressive therapy, and age \( <18 \) years. The project protocol was approved by the ethics committee of Lund University Hospital, and informed consent was obtained from all patients or their close relatives.

From March 2006 through April 2007, 216 patients were enrolled. After an interim analysis, to increase the number of patients with more severe disease, the following inclusion criteria were added: \( \geq 3 \) signs of the systemic inflammatory response syndrome (SIRS; body temperature, \( \geq 38^\circ \text{C} \); WBC count, \( >12 \times 10^9 \) cells/L or \( <4 \times 10^9 \) cells/L; pulse rate, \( >90 \) beats/min; and respiratory rate, \( >20 \) breaths/min [15]) or a significant hypotension (systolic blood pressure, \( <90 \) mmHg or a decrease of \( >40 \) mmHg from baseline). Therefore, a total of 248 patients were included in the study through April 2008, and on the basis of the exclusion criteria, 233 patients were evaluable. At enrollment, body temperature, pulse and respiratory rates, and WBC counts were recorded. In hospitalized patients, the systolic blood pressure, pulse rate, and respiratory rate were measured at least every hour for the next 12 h. Also, age, sex, and in-hospital mortality were recorded. The final diagnoses of the patients were made by attending physicians who were unaware of the study results, with use of standard microbiological tests and radiological procedures.

On the basis of the presence of SIRS criteria, the presence or absence of organ failure, and the final diagnosis, the patients were categorized into various groups according to the criteria proposed by the American College of Chest Physicians/Society of Critical Care Medicine [15]. Severe sepsis was defined as an infectious disease, at least 2 SIRS criteria, and the presence or development of hypotension and/or organ failure within 24 h after the collection of the blood samples. Septic shock was defined as severe sepsis in addition to hypotension requiring vasopressor support or a persistent hypotension for \( >1 \) h despite adequate fluid resuscitation. The patients were divided into the following groups: (1) severe sepsis with septic shock; (2) severe sepsis without septic shock; (3) sepsis, including an infectious disease, at least 2 SIRS criteria, and no presence or development of organ failure; (4) infection without SIRS; and (5) SIRS without infection, including a noninfectious disease and at least 2 SIRS criteria.

Analysis of HBP, other plasma proteins, and lactate levels. Blood samples for the analyses of plasma proteins and lactate levels were collected at enrollment in 5 mL plastic vacutainer tubes containing 0.5 mL of 0.129 mol/L sodium citrate. In 27 patients, serial blood samples were collected for up to 96 h. Tubes were immediately centrifuged at 2000 \( g \) for 10 min, and separate aliquots of the plasma supernatants were stored at \( -70^\circ \text{C} \) until analysis. The concentration of HBP was determined by enzyme-linked immunosorbent assay [3]. Briefly, microtiter plates (Nunc) were coated with a mouse monoclonal antibody directed against human HBP (2F23A) at a concentration of 1.0 \( \mu \text{g/mL} \) in coating buffer (0.05 mol/L NaHCO\(_3\), pH 9.6). Plates were washed with phosphate-buffered saline plus 0.05% Tween and blocked with 2% bovine serum albumin (Sigma) in phosphate-buffered saline plus 0.05% Tween. Patient plasma samples were diluted 1:40 in incubation buffer, were added to the wells in duplicate, and were incubated for 30 min at 37°C. Each plate also contained calibration samples of known concentration of recombinant human HBP (0–600 ng/mL) [16]. After washing, plates were incubated with a polyclonal rabbit antiserum (diluted 1:7000) against human HBP [17]. Bound antibodies were detected by incubation with peroxidase-conjugated antibody against rabbit immunoglobulin G (diluted 1:3000) (Bio-Rad). Plates were developed and the optical density at 420 nm was determined as described elsewhere [3]. The level of HBP in each patient sample was determined by calculating the mean optical densities of the duplicates, which were correlated to the results from the standard curve. The day-to-day variation of the assay had a coefficient of variance of \( <5\% \). Interleukin (IL)–6 was measured in plasma (diluted 1:40 in phosphate-buffered saline) by a quantitative sandwich enzyme-linked immunosorbent assay (Quantikine; R&D Systems) according to the manufacturer’s instructions (detection limit, \( <0.0007 \) ng/mL). Analyses of procalcitonin levels were performed with an enzyme-linked fluorescent immunoassay (Biome’rieux) according to the recommendations of the manufacturer (detection limit, 0.05 ng/mL). C-reactive protein and lactate analyses were performed on a Roche Hitachi Mod-
### Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe sepsis with septic shock (n = 26)</th>
<th>Severe sepsis without septic shock (n = 44)</th>
<th>Sepsis (n = 100)</th>
<th>Infection without SIRS (n = 43)</th>
<th>SIRS without infection (n = 20)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>65 (32–90)</td>
<td>64 (18–91)</td>
<td>57 (20–90)</td>
<td>44 (18–92)</td>
<td>74 (33–90)</td>
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<tr>
<td>Sex, % male</td>
<td>50</td>
<td>55</td>
<td>45</td>
<td>35</td>
<td>90</td>
<td>.31</td>
</tr>
<tr>
<td>SIRS, mean score at entry</td>
<td>3.4</td>
<td>3.1</td>
<td>2.6</td>
<td>1.0</td>
<td>2.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>5 (19)</td>
<td>2 (4.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>&lt;.01</td>
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<tr>
<td>Final diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>URTI</td>
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<td>0 (0)</td>
<td>19 (19)</td>
<td>18 (41)</td>
<td>0 (0)</td>
<td>.21</td>
</tr>
<tr>
<td>LRTI</td>
<td>6 (23)</td>
<td>14 (32)</td>
<td>38 (38)</td>
<td>6 (14)</td>
<td>0 (0)</td>
<td>.20</td>
</tr>
<tr>
<td>UTI</td>
<td>10 (38)</td>
<td>9 (20)</td>
<td>20 (20)</td>
<td>8 (19)</td>
<td>0 (0)</td>
<td>.28</td>
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<tr>
<td>SSTI</td>
<td>4 (15)</td>
<td>11 (24)</td>
<td>14 (14)</td>
<td>5 (12)</td>
<td>0 (0)</td>
<td>.21</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>3 (12)</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;.01</td>
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<td>Gastroenteritis</td>
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<td>2 (5)</td>
<td>6 (6)</td>
<td>5 (12)</td>
<td>0 (0)</td>
<td>.34</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (12)</td>
<td>6 (14)</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>No infection</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>20 (100)</td>
<td></td>
</tr>
<tr>
<td>Etiological agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>11 (42)</td>
<td>12 (27)</td>
<td>11 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td>8 (31)</td>
<td>11 (25)</td>
<td>18 (18)</td>
<td>11 (26)</td>
<td>0 (0)</td>
<td>.16</td>
</tr>
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<td>Virus</td>
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<td>23 (23)</td>
<td>24 (56)</td>
<td>0 (0)</td>
<td>.07</td>
</tr>
<tr>
<td>Other microorganism&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0 (0)</td>
<td>4 (9)</td>
<td>10 (10)</td>
<td>4 (9)</td>
<td>0 (0)</td>
<td>.20</td>
</tr>
<tr>
<td>Culture-negative infection&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7 (27)</td>
<td>17 (39)</td>
<td>38 (38)</td>
<td>4 (9)</td>
<td>0 (0)</td>
<td>.62</td>
</tr>
<tr>
<td>No infection</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>20 (100)</td>
<td></td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>16 (62)</td>
<td>13 (30)</td>
<td>13 (13)</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. LRTI, lower respiratory tract infection; SIRS, systemic inflammatory response syndrome; SSTI, skin and soft-tissue infection; URTI, upper respiratory tract infection; UTI, urinary tract infection.

<sup>a</sup> P values are given for the comparison between the 2 severe sepsis groups (n = 70) and the sepsis group (n = 100) with use of the Mann-Whitney nonparametric analysis.

<sup>b</sup> Including septicemia, viral meningitis and encephalitis, malaria, and Dengue fever.

<sup>c</sup> Including *Mycoplasma pneumoniae*, *Plasmodium falciparum*, and *Pneumocystis jirovecii*.

<sup>d</sup> Including chest radiography–positive pneumonia and SSTIs.

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**RESULTS**

**Characteristics of the patients.** Two hundred thirty-three patients met the inclusion criteria. Twenty-six patients were diagnosed with severe sepsis with septic shock, 44 patients with severe sepsis without septic shock, 100 patients with sepsis, 43 patients with infection without SIRS, and 20 patients with SIRS without infection. All patients with severe sepsis (with or without septic shock) were hospitalized, as were 75% of the patients in the sepsis group, 33% of the patients with infection without SIRS, and 83% of the patients with SIRS without infection. Forty-one (93%) of 44 patients with severe sepsis without septic shock experienced nonpersistence hypotension. Fifteen of the patients with severe sepsis with septic shock were treated in the intensive care unit with vasopressor agents, and 8 received mechanical ventilation.

Patient demographic characteristics and diagnoses are presented in Table 1. Pneumonia and urinary tract infections were most common. These diagnoses were also overrepresented in the severe sepsis (with or without septic shock) and the sepsis groups. Infected patients without symptoms of SIRS mostly experienced upper respiratory infections with documented or suspected viral etiology. However, patients within this group also experienced invasive infection, such as pneumonia or bac-
Figure 1. Plasma levels of the 6 biomarkers measured at hospital admission in 233 patients with fever and a suspected infection. Each dot represents the concentration in an individual plasma sample of heparin-binding protein (HBP) (A), procalcitonin (B), interleukin (IL)-6 (C), lactate (D), C-reactive protein (CRP) (E), and white blood cells (WBCs) (F). The 5 patient groups are described in the Methods. Bars represent the median of the values. The suggested cut-off value for HBP is marked at 15 ng/mL. In panel A, the dots at 120 ng/mL represent higher values in the severe sepsis with septic shock group (494, 269, 290, and 182 ng/mL) and in the severe sepsis without septic shock group (298 and 179 ng/mL). In panel B, the dots at 120 ng/mL represent higher values in the severe sepsis with septic shock group (200, 200, 200, 190, and 133 ng/mL). SIRS, systemic inflammatory response syndrome.

teremia. Notably, 20% of the patients meeting the criteria for sepsis with use of the SIRS score received a diagnosis of a viral infection. Among the 20 patients who experienced a noninfectious disease, the diagnoses were systemic vasculitis (n = 4), cardiac failure (n = 3), gastrointestinal bleeding (n = 3), pulmonary embolism (n = 2), relative corticosteroid deficiency due to hypopituitarism (n = 2), dehydration (n = 2), acute pancreatitis (n = 2), deep vein thrombosis (n = 1), and urinary retention (n = 1). Eleven of these patients developed significant hypotension.
The overall mortality rate was 3.4%. In the severe sepsis group, the mortality rate was 10%, and 19% of the patients with septic shock died.

**Plasma levels of HBP, IL-6, procalcitonin, lactate, CRP, and WBC.** At enrollment, HBP levels were significantly higher in both of the severe sepsis groups, compared with the other 3 patient groups ($P<.001$) (Figure 1A). Twenty-four (92.3%) of 26 patients in the severe sepsis with septic shock group and 37 (84.1%) of 44 patients with severe sepsis without septic shock exceeded an HBP cut-off level of $\geq 15$ ng/mL. In the other patient groups, 7 of 100 patients with sepsis, 0 of 43 patients with infection without SIRS, and 1 of 20 patients with SIRS without infection had a plasma HBP level $\geq 15$ ng/mL.

The plasma concentrations of some previously studied markers of severe infection, procalcitonin, IL-6, lactate, and CRP, were also determined and compared between patient groups. The levels of these markers were generally also significantly higher ($P<.05$) in the 2 severe sepsis groups. However, there were considerable overlaps between various groups, and there were no significant differences in lactate levels when comparing the severe sepsis group with the SIRS without infection group (Figure 1B–1E). No significant differences were recorded when the WBC counts in the different patient groups were compared (Figure 1F).

Assuming a 30% prevalence of severe sepsis, as in the present study, a cut-off level for HBP of $\geq 15$ ng/mL showed a sensitivity in diagnosing severe sepsis of 87.1%, a specificity of 95.1%, a positive predictive value (PPV) of 88.4%, and a negative predictive value (NPV) of 94.5% (Table 2). These values exceeded those for the other tested markers. Receiver-operating characteristic curves demonstrated that HBP was the best predictor of severe sepsis, with an area under the curve value of 0.95 (Figure 2). All combinations of HBP with procalcitonin, IL-6, lactate, and CRP levels resulted in increased NPVs but substantially reduced PPVs (data not shown). In the severe sepsis group, Gram-positive and gram-negative bacterial etiology was verified in 23 and 19 patients, respectively. When comparing HBP levels in these patients, no significant difference ($P = .31$) was detected.

**HBP:WBC ratio.** HBP is released by neutrophils, and it was of interest to correlate HBP levels with the WBC counts. In the severe sepsis groups (with or without septic shock), there was a correlation between plasma HBP levels and WBC ($r = 0.68$). To identify severe sepsis patients with a relatively low HBP level due to transient leukopenia, a HBP:WBC ratio (calculated by dividing HBP levels in ng/mL by WBC counts in cells/L $\times 10^9$) was calculated for each patient. One additional patient in each of the 2 severe sepsis groups were considered to have positive results with a HBP:WBC cut-off ratio of $\geq 2.0$. The combined use of plasma HBP level and HBP:WBC ratio thus identified 25 of 26 patients in the severe sepsis with septic shock group and 38 of 44 patients with severe sepsis without septic shock. No correlation between plasma HBP levels and WBC counts was found in the remaining patient groups ($r = -0.14$ to 0.36), and no additional patients in these groups were considered to have positive results when the HBP:WBC cut-off ratio of $\geq 2.0$ was used.

**HBP as an early diagnostic and prognostic marker.** Thirty-two of the 70 patients that were classified as having severe sepsis were enrolled before fulfilling the criteria for this diagnosis. Thus, plasma samples from these patients were collected up to 12 h before the onset of significant hypotension. In 29 of these patients, the HBP levels were already elevated, demonstrating that plasma concentrations of HBP may be increased several hours before the circulatory failure is evident (Figure 3). Levels of other biomarkers were also increased in these patients. Using the cut-off levels in Table 2, procalcitonin levels were increased in 23 patients, IL-6 in 25 patients, and lactate in 9 patients. The CRP was $>100$ mg/mL in 29 patients; however, the specificity for this marker is low.

Twenty of the patients with severe sepsis were monitored with serial plasma sample collection during the course of disease. The 18 patients that survived had HBP levels that de-
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Figure 2. Receiver-operating characteristics curves of heparin-binding protein (HBP), procalcitonin, interleukin (IL)-6, lactate, C-reactive protein (CRP), and white blood cell (WBC) levels in plasma, differentiating between the presence and absence of severe sepsis with or without septic shock. Areas under the receiver-operating characteristics curves were 0.949 (95% confidence interval [CI], 0.917–0.982) for HBP, 0.85 (95% CI, 0.799–0.95) for procalcitonin, 0.799 (95% CI, 0.736–0.863) for IL-6, 0.79 (95% CI, 0.73–0.85) for lactate, 0.685 (95% CI, 0.611–0.759) for CRP, and 0.516 (95% CI, 0.429–0.603) for WBC.

Figure 3. Heparin-binding protein (HBP) levels are increased before the onset of circulatory failure. Thirty-two of the patients in the severe sepsis groups were enrolled before significant hypotension was evident. Each dot represents 1 patient. The HBP levels and times from plasma sampling to the development of hypotension are indicated.

Increased rapidly when the clinical signs improved and the blood pressures were normalized (data not shown).

DISCUSSION

On the basis of previous in vitro and animal data in which neutrophil-released HBP was shown to induce vascular leakage [2, 4], we hypothesized that plasma HBP levels might correlate with the severity of infection and, in particular, with the development of circulatory failure. The results of the present study show a close correlation between increased HBP plasma levels and the development of hypotension, organ failure, and septic shock. Twenty-four (92.3%) of the 26 patients with septic shock had increased plasma HBP levels at enrollment. Of the remaining 44 patients with severe sepsis, 37 (84.1%) had elevated levels. In contrast, among 100 patients with nonsevere sepsis, only 7 patients had an increased HBP level. Moreover, all 43 patients with less severe infections without SIRS, presented with HBP below the cut-off level, although some of these patients received a diagnosis of pneumonia or bacteremia. The data suggest that the finding of a normal HBP plasma level in a febrile patient with suspected infection would, with high probability (negative predictive value of 94.5%), rule out the risk of developing severe sepsis. HBP is secreted by neutrophils, and it remains to be investigated whether HBP is a reliable biomarker for severe sepsis in patients with, for example, drug-induced neutropenia.

However, some patients with severe sepsis develop a transient neutropenia, and in these patients, it seems that the use of a HBP:WBC ratio could further increase the diagnostic sensitivity of HBP measurement.

Some of the enrolled patients in the study later received a diagnosis of a noninfectious disease. Interestingly, of these 20 patients, 11 developed circulatory failure caused by various noninfectious clinical conditions. In contrast to patients with severe infection, all but 1 of the patients with nonseptic hypotension had low HBP levels. These data support the proposed hypothesis in which HBP has a specific pathogenic role in the circulatory failure observed in patients with severe sepsis.

Several other investigators, in particular intensivists, have stressed that early institution of adequate antibiotic therapy and intravenous fluid resuscitation has a great impact on the mortality in patients with septic shock [9, 18]. For every hour that proper treatment is delayed, the mortality increases 7.5% [9]. Importantly, in the present study, an increased plasma HBP level preceded the clinical development of circulatory failure by several hours in many patients. Twenty-nine of 32 patients in the severe sepsis groups (n = 70) showed elevated HBP plasma levels up to 12 h before circulatory failure was evident. An obvious implication of these findings is that the detection of an increased plasma HBP level in a febrile patient should immediately alert the clinician to intensify fluid resuscitation and start proper antibiotic treatment. However, HBP is clearly not a marker for bacterial infection per se, because several patients with bacteremia and other invasive bacterial infections showed normal HBP levels.

The present study has several strengths. The study sample was large and involved a broad range of clinical presentations and diagnoses. The included subjects with fever and a suspected...
infection reflect a spectrum of patients that is likely to be encountered if HBP would be used as a test for severe sepsis in the future. However, several limitations deserve consideration. Patients receiving immunosuppressive therapy or those with neutropenia due to hematological malignancy were excluded from this study. Further investigations are necessary to evaluate the use of HBP measurements in these patient groups. The study is a single-center nonconsecutive study, and selection bias may have led to a nonrepresentative population. The calculations of predictive values are based on an estimated 30% prevalence of severe sepsis (with or without septic shock). If plasma HBP determinations were to be used in a population with a significantly lower prevalence of severe sepsis, for example, as a screening test for all febrile patients at an outpatient clinic, positive predictive values would decrease. On the other hand, negative predictive values would increase significantly. Although independent clinicians determined the diagnosis for each patient, the use of clinical criteria and microbiological evidence did not ascertain the exact cause of symptoms in all patients. This may have led to misclassifications in some cases. The relatively low overall mortality rate probably reflects that a large number of patients with less severe disease were included. However, in a recent study, also performed in an emergency department [19], the mortality rate of 12% among patients with severe sepsis was in concordance with the 10% mortality in the present study.

Compared with the other markers investigated, HBP was found to be the best predictor of vascular failure. Given the direct effect of HBP on endothelial permeability, this is perhaps to be expected. Our results suggest that prompt institution of adequate supportive treatment in febrile patients with increased plasma levels of HBP would reduce the risk of developing circulatory failure.

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Potential conflicts of interest. A.L., B.C., H.H., L.B., and P .A˚. are listed as inventors on a pending patent application on the use of HBP as a diagnostic tool in sepsis filed by Hansa Medical AB.

References


