Lipopolysaccharide-Binding Protein: A New Biomarker for Infectious Endocarditis?
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BACKGROUND: Infectious endocarditis (IE) is a bacterial infection of the endocardium. Diagnosis is based on results obtained from echocardiography, blood cultures, and molecular genetic screening for bacteria and on data for inflammatory markers such as the leukocyte (WBC) count and the C-reactive protein (CRP) concentration. The aim of the present study was to evaluate lipopolysaccharide-binding protein (LBP) as a supportive biomarker for the diagnosis and therapeutic monitoring of IE.

METHODS: We measured LBP and CRP concentrations and WBC counts in 57 IE patients at hospital admission, 40 patients with noninfectious heart valve diseases (HVDs), and 55 healthy blood donors. The progression of these 3 markers and the influence of cardiac surgery on them were evaluated in 29 IE patients and 21 control patients.

RESULTS: Serum LBP concentrations were significantly higher in IE patients [mean (SD), 33.41 (32.10) mg/L] compared with HVD patients [6.67 (1.82) mg/L, \( P < 0.0001 \)] and healthy control individuals [5.61 (1.20) mg/L]. The progression in the LBP concentration during therapy of IE patients correlated with the changes in the CRP concentration. The 2 markers were equally influenced by antibiotic treatment and surgical intervention.

CONCLUSIONS: Serial LBP measurement may provide an effective and useful tool for evaluating the response to therapy in IE patients. We found a strong correlation between LBP and CRP concentrations; LBP has a tendency to increase earlier in cases of reinfection.

Infectious endocarditis (IE), a relatively rare disease with an incidence of 30 per million population (1), is associated with high rates of mortality and morbidity. Rapid diagnosis of IE is critical for effective treatment. Diagnosis is based primarily on the results of echocardiographic examinations and blood culture tests [Duke criteria (2)], as well as on the results of serology tests and molecular genetic screening methods for bacteria in cases of heart valve replacement (3, 4). The initial diagnosis of IE can be difficult, however, because of nonspecific clinical symptoms, negative results in blood cultures, and ambiguous echocardiographic findings. In this context, the availability of biomarkers is of major interest. Several studies have investigated the application and usefulness of important laboratory markers for IE diagnosis (5–12). Other studies (13–16) have focused on the clinical usefulness of serum C-reactive protein (CRP), a marker most frequently used in Europe (13), in IE. CRP has been assumed to be primarily an indicator of local bacterial infections, but increased CRP concentrations have also been strongly associated with various nonbacterial infectious diseases, e.g., rheumatic disorders (17). CRP has been shown to have a limited ability to distinguish between bacterial and viral infections (18).

Lipopolysaccharide-binding protein (LBP), a glycosylated 58-kDa protein produced predominantly in hepatocytes, has recently been described as a promising novel diagnostic marker for the diagnosis of local bacterial infection (19–23). LBP is released constitutively into the bloodstream upon acute-phase stimulation (24). It has a high affinity for lipopolysaccharide (LPS) and other bacterial-surface components (25). Binding of LPS to LBP facilitates the transportation of endotoxin molecules to immune effector cells possessing surface CD14 receptors and further activates the proinflammatory cascade (24, 26). Association of the LPS/
LBP complex with HDL inactivates LPS, thereby protecting against LPS toxicity (24).

The aims of this study were to evaluate (a) the clinical usefulness of LBP as a supportive biomarker for IE diagnosis, (b) the applicability of LBP for monitoring the response to antibiotic therapy, and (c) the influence of cardiac surgery on the progression of LBP values in both IE patients and patients with noninfectious heart valve disease (HVD). The use of LBP as a marker was compared with the frequently used endocarditis markers CRP and the leukocyte (WBC) count.

Materials and Methods

PATIENTS AND CONTROLS

Between May 2005 and November 2007, serum samples were obtained from 57 patients with definite IE diagnosed according to the Duke criteria. The causative pathogens were identified with standard blood-culture methods or broad-range PCR of the gene for bacterial 16S ribosomal DNA, as described previously (27). Patients with immunosuppression, cardiogenic shock, or septic shock were excluded. Three of the patients had experienced 2 independent episodes of IE. Patients were subdivided into 4 groups according to the duration of antibiotic treatment [0–10 days (n = 38), 11–20 days (n = 7), 21–30 days (n = 6), and >30 days (n = 9)]. Serum samples were also collected from 40 control HVD patients before surgical intervention. HVDs consisted of noninfectious and nonrheumatic valve insufficiencies or stenosis. We measured serum LBP values in 55 healthy blood donors to confirm the previously determined reference interval of the commercially available LBP assay.

To examine the progression in LBP and CRP concentrations and the WBC count, we collected serum samples and EDTA-anticoagulated blood samples from 29 IE patients and 21 control patients with HVD during their admission at our hospital. Samples were collected daily. The study protocol was approved by the institutional review board, and all patients gave their informed consent.

MEASUREMENT OF CRP, LBP, AND THE WBC COUNT

Serum samples were collected in serum Monovettes (Sarstedt). The samples were clotted, centrifuged at 4000g for 10 min, and stored at −70 °C within 2 days of collection. Samples were stored at this temperature until assayed.

Serum CRP was measured with the ultrasensitive latex immunoassay CRP Vario (Abbott Diagnostics), and the total LBP concentration in serum samples was measured with a commercially available chemiluminescence assay (IMMULITE LBP, Diagnostics Products Corporation/Siemens Healthcare Diagnostics) according to the manufacturer’s instructions. All samples were tested in random order with controls and calibration curves incorporated into each run. Blood samples were collected in EDTA Monovettes (Sarstedt), and WBCs were counted directly with the Cell-Dyn 3500 (Abbott Diagnostics).

STATISTICAL ANALYSIS

All data are presented as the mean (SD). The Mann–Whitney U-test and the Student t-test were used for statistical analyses as appropriate, and the assumption of a gaussian distribution was tested in all data sets with the Kolmogorov–Smirnov test. We used Pearson and Spearman correlation coefficients to assess correlations between variables. P values <0.05 were considered statistically significant. GraphPad Prism 4.0 software (GraphPad Software) was used for statistical analyses.

Results

Table 1 summarizes the clinical characteristics of the patients and the control cohorts. LBP was measured in serum samples obtained from 57 patients with 60 episodes of IE, a control group of 40 HVD patients, and a second control group of 55 healthy blood donors. We confirmed the manufacturer’s LBP reference interval in our healthy control population. Fig. 1A presents scatter plots of LBP concentration for the 3 cohorts. Serum LBP concentrations were increased in 58 episodes of IE, and the increases were independent of the duration of antibiotic treatment. In 2 episodes, the LBP concentration was within the reference interval. LBP concentrations were significantly higher in IE patients than in the 2 control groups [IE patients, 33.41 (32.10) mg/L; HVD patients, 6.67 (1.82) mg/L; healthy blood donor control group, 5.61 (1.20) mg/L] (see Fig. 1A). The diagnostic sensitivity was 96.7% [95% confidence interval (CI), 92.2%–100.0%], and the diagnostic specificity was 87.5% (95% CI, 77.3%–97.7%) with respect to the HVD patients and 94.5% (95% CI, 88.5%–100.0%) with respect to the healthy controls. The mean LBP concentration of the IE patient samples was 83.2% higher than the mean concentrations of the control groups.

With respect to the duration of antibiotic treatment, LBP concentrations were considerably lower after 11–20 days and >30 days of treatment [14.56 (5.29) mg/L and 15.71 (8.05) mg/L, respectively], compared with treatment for 0–10 days [41.97 (37.20) mg/L] (Fig. 1A, inset). Comparatively high LBP concentrations were observed after 21–30 days of antibiotic treatment [25.45 (7.30) mg/L]. The serum concentration of CRP in patients upon hospital admission showed a trend similar to that of LBP, with IE patients having significantly higher concentrations than the individu-
als in the 2 control groups [IE patients, 101.90 (81.67) mg/L; HVD patients, 2.31 (2.19) mg/L; healthy blood donor control group, 1.11 (1.18) mg/L] (see Fig. 1B). Likewise, WBC counts were higher in IE patients [10.54 \times 10^9/L (5.51 \times 10^9/L)] than in the HVD group [6.94 \times 10^9/L (1.55 \times 10^9/L)] and the healthy control group [7.37 \times 10^9/L (1.65 \times 10^9/L)] (Fig. 1C). The diagnostic sensitivities were 95.0% (95% CI, 89.5%–100.0%) for CRP and 26.7% (95% CI, 15.5%–37.9%) for the WBC count. The diagnostic specificity for CRP was 87.5% (95% CI, 77.3%–97.7%) with respect to the HVD patients and 100% (95% CI, 93.5%–100%) with respect to the healthy controls. Although the WBC count had the lowest diagnostic sensitivity (26.7%), it had a high diagnostic specificity [100% (95% CI, 91.2%–100%) with respect to HVD patients and 96.3% (95% CI 91.3%–100.0%) with respect to the healthy controls]. Combining the LBP and CRP markers produced a diagnostic sensitivity of 95.8% (95% CI, 92.2%–99.4%) and a specificity of 87.5% (95% CI, 80.3%–94.7%) with respect to HVD patients and 97.3% (95% CI, 94.3%–100.0%) with respect to the healthy controls.

LBP and CRP values were significantly higher ($P < 0.0014$, and $P < 0.0009$, respectively) in the HVD control group than in the healthy blood donor control group, although all observed LBP concentrations were within the reference interval. In contrast, the WBC counts in the 2 control groups were not significantly different. Comparisons of LBP and CRP concentrations and the WBC count according to the infecting microorganisms showed no differences in mean values for any of the variables tested (data not shown). The examined markers had equivalent positive predictive values (LBP, 87.9%; CRP, 91.9%; WBC count, 88.9%) compared with the average of the 2 control groups. The negative predictive values were 97.8% (LBP), 96.8% (CRP), and 67.9% (WBC count). A correlation analysis of LBP, CRP, and WBC values for IE patients showed a strong correlation between LBP and CRP concentrations (Spearman rank correlation coefficient $r = 0.70$; $P < 0.0001$) and a moderate correlation between the LBP concentration and the WBC count ($r = 0.33; P < 0.001$). We found weak correlations between the CRP concentration and the WBC count ($r = 0.26; P < 0.05$). No correlations between the 3 variables were found in the HVD patients or the healthy blood donors.

Fig. 2A presents an example of the progression in LBP and CRP concentrations and the WBC count during an uncomplicated episode of IE. The temporal progression in the concentration of LBP strictly followed that of CRP. Both LBP and CRP showed increased concentrations upon hospital admission and a prompt decrease after the administration of adequate antibiotic treatment. CRP and LBP concentrations increased within the first 48 h after surgical intervention and then decreased continuously toward reference values. WBC counts persisted within the upper portion of the reference interval during the entire IE episode, except for surgical intervention, which caused a moderate increase. This profile is typical and has been observed in most analyzed episodes of uncomplicated IE. Fig. 2B summarizes the progression in LBP and CRP concentrations and the WBC count in a patient with a noticeably low LBP response and typical progression in the CRP concentration and the WBC count during an uncomplicated IE episode. Even surgical intervention caused only a 2-fold increase in the LBP concentration. Fig. 2C summarizes the progression in a case of a com-

### Table 1. Demographic characteristics of the patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>IE patients</th>
<th>HVD patients</th>
<th>Healthy blood donors</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male (n = 42)</td>
<td>64.67 (14.05), 21–102</td>
<td>61.63 (16.36), 29–82</td>
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<tr>
<td>Female (n = 15)</td>
<td>66.00 (15.35), 41–89</td>
<td>73.19 (7.32), 59–86</td>
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<tr>
<td>Affered valves, %</td>
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<td></td>
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<tr>
<td>Native</td>
<td>70</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Prosthetic</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Causative microorganism, no. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Coagulate-negative staphylococci</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus spp.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus spp.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
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<td>Culture-negative endocarditis</td>
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<td></td>
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<td>Surgical intervention, no. of episodes</td>
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*Age data are presented as the median (SD), range.
Fig. 1. Serum LBP and CRP concentrations and the WBC count in IE patients, patients with HVDs, and healthy blood donor controls.

Serum LBP concentrations (A), serum CRP concentrations (B), and the WBC count (C) in IE patients (n = 60), HVD patients (n = 40), and healthy control individuals (n = 55). Scatter plots show the distributions of values for the 3 markers in the 3 groups (**P < 0.001, IE patients vs HVD patients and vs healthy controls, HVD patients vs healthy controls; ***P < 0.001, HVD patients vs healthy controls). Insets display the distributions of values for the 3 markers according to the length of empirical antibiotic treatment of IE patients. Solid horizontal lines represent mean values; dotted horizontal lines represent reference values.
Fig. 2. Different progressions of LBP and CRP concentrations and the WBC count during 3 IE episodes. Examples of the progression of LBP and CRP concentrations and the WBC count during an uncomplicated IE episode (A), a noticeably low LBP response during an IE episode (B), and a complicated IE course with recurrent infectious episodes (C). Arrows indicate the onset of the LBP concentration increase compared with the CRP concentration. X, initiation of antibiotic treatment; S, surgical intervention.
Fig. 3. Comparison of LBP and CRP concentrations and the WBC count in IE patients and HVD patients before and during the 5-day follow-up after surgical intervention.

Progression of LBP and CRP concentrations and the WBC count in IE patients (□, n = 23) and HVD patients (■, n = 21). Data are presented as the mean and SD values for LBP (A) and CRP (B) concentrations and the WBC count (C) immediately before surgical intervention and their progression during the 5 days after surgical intervention. Dotted horizontal lines indicate reference values for each variable. ***P < 0.0001; **P < 0.001; *P < 0.05.
plicated IE course. The patient experienced 28 days of recurrent infectious episodes while receiving antibiotic treatment. LBP and CRP concentrations showed related progression patterns; however, postoperative increases in LBP values occurred 3 days earlier than the increases in CRP concentrations. A similar progression pattern was observed in 2 other cases with recurrent infectious episodes (data not shown). WBC counts were increased considerably compared with an uncomplicated IE course.

The progression in LBP and CRP concentrations and the WBC count was measured before and within 5 days after surgical intervention in 29 IE patients and 21 HVD patients. At the time of surgery, LBP and CRP concentrations were within the reference interval in 5 IE patients and 2 IE patients, respectively, and the WBC count was within the reference interval in 14 IE patients. LBP and CRP concentrations and the WBC count were within their respective reference intervals for all HVD patients. Preoperative LBP and CRP concentrations remained significantly higher in IE patients than in HVD patients ($P < 0.0001$; Fig. 3, A and B). Similarly, the preoperative WBC count was higher in IE patients than in HVD patients ($P < 0.001$, Fig. 3C); however, more than half of the evaluated IE patients had WBC counts within the upper portion of the reference interval. Peak LBP concentrations were observed 24–48 h after surgical intervention [34.64 (12.85) mg/L in IE patients vs 33.90 (10.12) mg/L in HVD patients, Fig. 3A]. Peak CRP concentrations were also observed during this period [179.40 (59.84) mg/L in IE patients vs 177.40 (50.82) mg/L in HVD patients, Fig. 3B]. In contrast, peak WBC counts were observed 0–12 h after surgical intervention. We no longer observed a statistically significant difference between IE patients and HVD patients in LBP values, whereas these 2 patient groups showed statistically significant differences in the CRP concentration and the WBC count up to 12 h after surgical intervention (see Fig. 3, B and C).

Discussion

Several studies have reported increased LBP serum concentrations in patients with severe sepsis due to gram-positive, gram-negative, and fungal infections (19, 20). IE is a bacterial infection comparable to sepsis, but infection of the endocardium usually is associated with a low-level and noncontinuous bacteremia, a situation that contrasts with that of sepsis. To date, the CRP concentration and the WBC count have commonly been used for IE diagnosis and monitoring a patient’s response to therapy. No systematic data have previously been published on the progression of serum LBP concentrations in IE or the potential of LBP as a diagnostic marker for this disease.

In this study, we evaluated the clinical applicability of LBP as a supportive biomarker for IE diagnosis and monitoring disease progression and compared the results with those obtained for CRP and the WBC count. LBP and CRP values were significantly higher in IE patients upon their admission to the hospital than in the HVD patients and the healthy controls (Fig. 1, A and B). Mean LBP concentrations decreased with previous antibiotic treatment, with a notable decrease apparent after 10 days of antibiotic treatment, although comparatively high concentrations were still observed in some patients after 21–30 days of antibiotic treatment. The patients with the higher LBP concentrations during this later time interval experienced IE episodes with major complications and severe bacteremia. This observation leads to the assumption that the occurrence of high LBP concentrations after prolonged antibiotic treatment may be correlated with a complicated disease progression; however, because our study cohort included only 15 patients with long-term antibiotic treatment (>20 days), this hypothesis will have to be validated with a larger group of patients to exclude the possibility that these observations are merely random outliers. We did not observe a statistically significant difference in LBP values linked to the causative pathogen (data not shown); however, the pathogen species and the access of antibiotics to the infected area of the heart valve still influence the effectiveness of antibiotic treatment and thus the reduction in the inflammatory trigger. We are aware of only one other published study regarding the value of serum LBP measurements at hospital admission for the diagnosis of IE, and the results of that study contradict those of our study (12). Watkin et al. (12) observed that serum LBP concentrations were slightly but not significantly higher in IE patients than in controls. The mean LBP concentration was noticeably higher in the Watkin et al. control group, with a broader range (mean, 15.76 mg/L; range, 8.97–30.73 mg/L), than in our control group (mean, 5.62 mg/L; range, 3.50–8.90 mg/L). One possible explanation for these divergent results is that the study of Watkin et al. and our study used different LBP assays.

We found the diagnostic sensitivities and specificities of both LBP and CRP to be high (>90%). The WBC count had a low diagnostic sensitivity (26.7%) but a high diagnostic specificity (100%). All of the examined markers had nearly equivalent high positive predictive values. The WBC count had the lowest negative predictive value (67.9%), whereas LBP and CRP had equivalent high negative predictive values (97.8% and 96.8%, respectively). In short, serum LBP and CRP concentrations were the most sensitive laboratory vari-
ables for the detection of bacterial infection in IE patients and had comparable diagnostic sensitivities and specificities. The use of LBP and CRP markers separately or in combination does not alter their diagnostic effectiveness. Remarkably, the concentrations of both LBP and CRP were within their reference intervals in 2 IE episodes. This finding reflects a serious limitation and suggests that neither the LBP concentration nor the CRP concentration should be used to rule out IE. Therefore, it is of major importance to consider the complete clinical presentation, including echocardiographic findings and blood-culture results.

The applicability of LBP for monitoring the response to antibiotic therapy was determined by means of serial LBP measurements. Antibiotic treatment influenced LBP and CRP values substantially, whereas antibiotic treatment influenced the WBC count only in complicated IE courses. The progression in the concentration of LBP in our patients corresponded very closely with that of CRP, and the high correlation observed between LBP and CRP strongly suggests a common origin of stimulation. This supposition leads to the inevitable question: Why implement a new marker for clinical use if its characteristics are very similar to those of an established marker? Certainly, we recognized a distinction between LBP and CRP in complicated IE courses, in which the LBP concentration was more likely to increase earlier in cases of reinfection. The profile shown for a complicated course (Fig. 2C) was observed in 2 other cases with multiple periods of infection. In this context, serial measurements of both LBP and standard laboratory variables may allow earlier recognition of a new local septic crisis. Additionally, an increased CRP concentration is also strongly associated with rheumatic disorders (17), and in such cases the potential of CRP to distinguish between bacterial and viral infection is low (18). There have been 2 studies regarding the clinical value of LBP in this context. Kaden et al. observed that cytomegalovirus infection is not associated with increased LBP concentrations (21), and Heumann and coworkers noted increased LBP concentrations in patients with rheumatic disorders (28). By comparison, the percent increases in LBP concentrations calculated for patients with rheumatic disorders (degenerative arthritis, 6.3%; rheumatoid arthritis, 25.8%; reactive arthritis, 46.0%) were lower than the 83.2% increase seen in our IE cohort. These preliminary results support the hypothesis of an increased specificity of LBP for the detection of bacterial infection in the evaluation of inflammatory processes and a potential for distinguishing between bacterial and nonbacterial infections.

We examined the influence of cardiac surgery on LBP concentrations in IE and HVD patients to evaluate the effect of surgery on the diagnostic specificity and sensitivity of LBP and its utility in monitoring disease progression. The inflammatory response caused by cardiac surgery is due to several stimuli, including exposure of the blood to nonphysiological surfaces, surgical trauma, and endotoxin release (29). CRP is strongly affected by surgical intervention within the first 24 h, independently of any existing bacteremia. A similar influence on the progression of the LBP concentration has been noted for abdominal surgery, although only a few studies have reported LBP concentrations in patients who have undergone cardiovascular interventions (30, 31). Consequently, we investigated the influence of cardiac surgery on LBP values and whether they were less influenced by cardiac surgery than CRP or WBC values. We expected postoperative LBP concentrations to be significantly increased within the first 24 h in IE patients compared with HVD patients because of an increased distribution of LPS or other bacterial components as a consequence of the infected valve. In our study, the serum concentrations of LBP and CRP were considerably increased in both groups within the first 24–72 h after surgical intervention, and no reduced influence of surgery on LBP was seen. In addition, we observed no difference between IE patients and HVD patients in the courses of LBP concentrations following surgical intervention. Nevertheless, the heterogeneity in biomarker concentrations is remarkably high, especially for LBP and CRP. Given individual differences in inflammatory responses in general, the different severities of infections, and the different stages of antibiotic treatment in IE patients, the averaging of biomarker time courses may not be sufficient to recognize trends in marker progression. The averaging of measurements of clinical markers in larger patient cohorts often obscures particular case effects that could provide additional important information. Thus, it is of major importance to base decisions in particular cases on the progression of the individual biomarkers. The specificities and sensitivities for LBP and CRP were determined before surgical intervention, and their concentrations are likely to be higher if patients have undergone surgery, because of the additional stimulation of the inflammatory response. In contrast, the use of LBP and CRP values for monitoring disease progression is not limited by the time of surgery.

Our study has some limitations. IE is a relatively infrequent disease, and the availability of a large number of patients in an appropriate time frame is limited. Although the sizes of the IE and HVD cohorts of patients available for measuring progression were relatively small, the power of the present study was sufficient to show the value of serial LBP measurement for monitoring antibiotic therapy. We consciously chose the HVD and healthy control groups to exclude any
influences on LBP caused by HVDs or LBP fluctuations in healthy individuals; however, the typical clinical situation in the diagnosis of IE is a patient with prolonged fever and other nonspecific complaints. In a follow-up clinical study, a cohort of other patients with fever would be an ideal control group and would provide additional data regarding the sensitivity and specificity of LBP for evaluating fever. Also, beneficial would be adequate patient cohorts for evaluating LBP for distinguishing between bacterial infection, viral infection, and general inflammatory responses. Another general problem is the heterogeneity of the IE patient cohort. Patients exhibit different infection severities, show individual inflammatory responses, and may be at different stages of antibiotic treatment. Hence, results primarily depend on the patient population and pretest probabilities. The advantages of LBP in cases of infection or a complicated disease progression require validation with a larger group of IE patients.

The data of our study demonstrated that LBP is strongly correlated with CRP and appears to be a useful tool for the diagnosis of IE and following the response of the disease to therapy; however, we have found no significant benefit that would legitimize the standard use of LBP as a marker instead of CRP. The value of LBP as a marker for early recognition of a new local septic crisis that we have highlighted has to be thoroughly established in further investigations. Nevertheless, we propose the use of LBP as a marker in addition to CRP for the diagnosis of IE and for monitoring the response to therapy, particularly in cases with recurrent infection.

References

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Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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