Granulocyte colony-stimulating factor (G-CSF) and interleukin (IL)-8 in sera from patients with Staphylococcus aureus septicemia

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Objective: To determine the concentrations of granulocyte colony-stimulating factor (G-CSF) and interleukin (IL)-8 in sera from patients with Staphylococcus aureus septicemia and to correlate the results to peripheral neutrophil counts and the clinical outcome.

Methods: Serum samples from 64 consecutive patients with S. aureus septicemia were sequentially collected in a prospective study.

Results: The mean ± standard deviation (SD) serum G-CSF value on admission was 348 ± 830 with a range of 8 to 5400 pg/mL. G-CSF concentrations were elevated (> 76 pg/mL) in 38/64 patients (59%) as were serum IL-8 concentrations (> 67 pg/mL) in 23/64 patients (36%) on admission. The mean ± SD IL-8 value was 266 ± 422 pg/mL with a range of 2 to 1366 pg/mL. A correlation was found between serum IL-8 and white blood cell count on admission (p = 0.008).

Conclusions: Patients with uncomplicated septicemia frequently have elevated G-CSF values (84%) in comparison to patients with complicated septicemia (49%; p = 0.02), indicating a possible protective effect of G-CSF in septic complications.

Key words: Septicemia, Staphylococcus aureus, cytokine, granulocyte colony-stimulating factor, interleukin-8

Cytokines are important mediators of the inflammatory and immune responses in severe infections [1]. Much interest has been focused on gram-negative infections and the central role of endotoxin/lipopolysaccharide (LPS) in initiating the 'sepsis cascade', thereby stimulating the release of various cytokines [2]. Staphylococcus aureus is a common and significant pathogen of serious infections such as septicemia. The pathogenesis of gram-positive infections is not fully understood and no such key factor as LPS/endotoxin in gram-negative infections has yet been demonstrated. In gram-positive infections, the importance of various cell-wall components and toxins as inducers of cytokine production has been investigated [3-7].

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in sera from patients with clinical sepsis and septic shock [33-35] as well as in experimental endotoxinemia [36,37].

The aim of the present study was to determine the concentrations of G-CSF and IL-8 in sequential serum samples from patients with a well-defined gram-positive infection, such as septicemia caused by \textit{S. aureus}, and to correlate the results to peripheral neutrophil counts and the clinical outcome.

\section*{Patients and Methods}

Patients admitted to the Department of Infectious Diseases at the Örebro Medical Center Hospital during 1988 to 1992 with \textit{S. aureus} septicemia were included in this prospective study, which was approved by the Ethics Committee of the Örebro Medical Center Hospital. Sera from these patients were collected as soon as possible after \textit{S. aureus} septicemia was suspected or verified. Samples were again collected at least 3 and 7 days later, then once a week. Sera were stored at -70°C pending analysis. The diagnosis of \textit{S. aureus} septicemia was verified by positive blood cultures performed with Bactec® 660 HP (Becton Dickinson, Towson, MD, USA).

**Patients**

G-CSF and IL-8 concentrations were assayed in 331 serum samples from 64 consecutive patients with verified \textit{S. aureus} septicemia. The median age of the study population was 71 (range 10 to 91) years and 59% were men. Immunosuppression was found in seven patients and malignant diseases in four. Thirteen patients had diabetes mellitus and two had non-diabetic renal insufficiency. A total of 48 patients had community-acquired septicemia whereas 16 cases had been contracted during a hospital stay. None of the study patients had human immunodeficiency virus (HIV) infection.

Two or more persistently positive blood cultures were found in 58 patients whereas only one positive blood culture was obtained from six patients. On admission, these patients displayed clinical signs of septicemia, including fever > 38.5°C, shaking chills, tachypnea, tachycardia, hypotension, leukocytosis and/or elevated C-reactive protein.

Complicated septicemia, defined as a clinical course with septic metastasis such as acute osteomyelitis, septic arthritis or extensive abscesses (long-standing, insufficiently drained), was found in 45 patients; 15 patients fulfilled the criteria of endocarditis (one definite, six probable and eight possible) according to the strict case-definitions stated by von Reyn and colleagues [38]. Five patients (8%) died within a short time of the acute septicemic event (3 to 15 days after admission to hospital). Uncomplicated septicemia, defined as septicemia with no apparent metastatic foci, was seen in 19 patients.

The study patients served as their own controls; they were followed-up throughout the clinical course of the disease and serum samples were collected sequentially. Serum samples from blood donors were analyzed as negative controls.

**Enzyme immunoassay**

The Quantikine™ human G-CSF immunoassay (R&D Systems, Minneapolis, MN) is a quantitative immunometric, 'sandwich'-type, enzyme immunoassay. Microtiter plates are coated with a specific monoclonal antibody against G-CSF acting as a capture antibody. Standards and samples (recombinant human G-CSF) are added and, after incubation and washings, horseradish peroxidase-labelled polyclonal antibodies against G-CSF are added. Following further incubation and washings, substrate solution (tetramethylbenzidine) is added. Color development is stopped and optical density measured at 450 nm.

The IL-8 enzyme-amplified sensitivity immunoassay (EASIA; Medgenix Diagnostics, Fleurus, Belgium) is based on an oligoclonal system in which several monoclonal antibodies are directed against distinct epitopes of IL-8. The test gives a high sensitivity and a short incubation time. These assays were performed according to the manufacturer's instructions.

**Blood donors**

In the blood-donor population, the upper limits for normal serum G-CSF and IL-8 concentrations were defined as mean values ± 2 standard deviations (SD). In 28 patients of this population, the mean G-CSF concentration was 36.6 ± 19.7 (range 14 to 85) pg/mL with a cut-off point for normal G-CSF levels calculated as 76 pg/mL. In 20 patients in this population, the mean serum IL-8 concentration was 20.3 ± 23.3 (range 4 to 87) pg/mL and the normal cut-off point was 67 pg/mL.

**Peripheral white blood cell (WBC) count**

This was determined according to the routine method used in the Department of Clinical Chemistry. Normal WBC counts were defined as 4.0 to 9.0 × 10^9/L.

**Statistical analysis**

The Mann-Whitney \textit{U} test was used for comparing the cytokine levels in different groups. Correlations between parameters were made using Spearman's rank correlation test, and the chi-square test with continuity correction was used for comparing proportions. A \textit{p
value of $<0.05$ was considered significant. The statistical software program StatView II™ was used for the calculations.

**RESULTS**

**Kinetics of G-CSF in patients with *S. aureus* septicemia**

The serum G-CSF levels in 64 patients on admission with *S. aureus* septicemia are presented in Table 1 and Figure 1. On admission, 38/64 patients (59%) had elevated (>76 pg/mL) G-CSF concentrations. In the remaining 26, G-CSF levels <76 pg/mL were found, although four of these patients showed a rise in G-CSF (>76 pg/mL) during the first day after admission, resulting in a total of 66% (42/64 patients) with elevated concentrations of G-CSF on either admission or the following day. Six patients showed high serum G-CSF values (>1000 pg/mL) on admission (Figure 1) but, in most cases, the initially high G-CSF values decreased rapidly within 1 week (Figure 2).

There was a negative correlation ($r = -0.37$, $p = 0.003$) between delay (number of days from onset of the disease to admission) and G-CSF concentrations on admission. A significant difference ($p = 0.007$) in G-CSF values between patients with a short delay (<1 week) and those with a delay of $\geq 1$ week (Figure 3) was also found.

There was no correlation between G-CSF concentrations and WBC counts on admission. Patients with an elevated (>76 pg/mL) G-CSF concentration on admission did not have higher mean WBC counts than those with low or normal G-CSF concentrations ($\leq 76$ pg/mL). Six patients had high G-CSF values (>1000 pg/mL) on admission, but their WBC counts were not higher than those with G-CSF values <1000 pg/mL. Only in one of these six patients with high admission G-CSF values did the WBC count increase during the course of the disease.

On admission, there was a statistically significant difference in serum G-CSF concentration between patients with complicated septicemia and those with uncomplicated septicemia ($p = 0.022$; Table 1). The patients with complicated septicemia included both those with very high and low G-CSF values. Elevated serum G-CSF concentrations (>76 pg/mL) were found in 16/19 patients (84%) with uncomplicated septicemia compared with 22/45 patients (49%) with complicated septicemia ($p = 0.02$; Figure 4). Five of the six patients with G-CSF concentrations >1000 pg/mL had complicated septicemia. Patients with extensive abscesses ($n = 15$) had lower G-CSF levels than those without abscesses (Table 1), but this difference was not significant. Patients with endocarditis ($n = 15$) had higher G-CSF values than those without signs of endocarditis (Table 1), but the difference was not statistically significant ($p = 0.07$). There was no statistically significant difference in serum G-CSF levels between survivors and non-survivors (Tables 1 and 2).

### Table 1: Distribution of granulocyte colony-stimulating factor (G-CSF), interleukin-8 (IL-8) and white blood cell (WBC) count at the time of hospital admission in 64 patients with *Staphylococcus aureus* septicemia

<table>
<thead>
<tr>
<th>Blood donors (n = 38)</th>
<th>All patients (n = 64)</th>
<th>Complicated (n = 45)</th>
<th>Uncomplicated (n = 19)</th>
<th>EC (n = 15)</th>
<th>Non-EC (n = 49)</th>
<th>Abscess (n = 15)</th>
<th>Non-abscess (n = 49)</th>
<th>Fatalities (n = 5)</th>
<th>Survivors (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G-CSF (pg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>36.6</td>
<td>348</td>
<td>377</td>
<td>280</td>
<td>697</td>
<td>242</td>
<td>164</td>
<td>405</td>
<td>450</td>
</tr>
<tr>
<td>(± SD)</td>
<td>(19.3)</td>
<td>(830)</td>
<td>(959)</td>
<td>(396)</td>
<td>(1417)</td>
<td>(518)</td>
<td>(294)</td>
<td>(930)</td>
<td>(841)</td>
</tr>
<tr>
<td>Median</td>
<td>32</td>
<td>93.5</td>
<td>55</td>
<td>125</td>
<td>180</td>
<td>80</td>
<td>54</td>
<td>110</td>
<td>50</td>
</tr>
<tr>
<td><strong>IL-8 (pg/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20.3</td>
<td>266</td>
<td>318</td>
<td>144</td>
<td>307</td>
<td>254</td>
<td>584</td>
<td>170</td>
<td>436</td>
</tr>
<tr>
<td>(± SD)</td>
<td>(23.3)</td>
<td>(422)</td>
<td>(459)</td>
<td>(294)</td>
<td>(441)</td>
<td>(420)</td>
<td>(500)</td>
<td>(347)</td>
<td>(562)</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
<td>31</td>
<td>27</td>
<td>35</td>
<td>56</td>
<td>18</td>
<td>537</td>
<td>18</td>
<td>65</td>
</tr>
<tr>
<td>(range)</td>
<td>(4-87)</td>
<td>(2-1366)</td>
<td>(3-861)</td>
<td>(5-1271)</td>
<td>(2-1366)</td>
<td>(8-1366)</td>
<td>(2-1282)</td>
<td>(2-1055)</td>
<td>(2-1366)</td>
</tr>
<tr>
<td><strong>WBC (x10⁹/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>13.6</td>
<td>13.1</td>
<td>14.8</td>
<td>15.8</td>
<td>12.9</td>
<td>17.3</td>
<td>12.4</td>
<td>17.3</td>
<td>13.3</td>
</tr>
<tr>
<td>(± SD)</td>
<td>(6.8)</td>
<td>(7.1)</td>
<td>(6.2)</td>
<td>(7.7)</td>
<td>(6.5)</td>
<td>(8.6)</td>
<td>(5.8)</td>
<td>(12.6)</td>
<td>(6.2)</td>
</tr>
<tr>
<td>Median</td>
<td>12</td>
<td>11.5</td>
<td>13.8</td>
<td>15.4</td>
<td>11.3</td>
<td>16.3</td>
<td>11</td>
<td>15.4</td>
<td>12.0</td>
</tr>
<tr>
<td>(range)</td>
<td>(3.4-38.2)</td>
<td>(3.4-38.2)</td>
<td>(3-26.2)</td>
<td>(3.4-26.6)</td>
<td>(4.8-38.2)</td>
<td>(7.5-38.2)</td>
<td>(4.4-26.2)</td>
<td>(5.4-38.2)</td>
<td>(3.4-26.6)</td>
</tr>
</tbody>
</table>

Complications = complicated; Uncomplications = uncomplicated; EC = endocarditis.
Kinetics of IL-8 in patients with *S. aureus* septicemia

The serum IL-8 levels in 64 patients on admission with *S. aureus* septicemia are presented in Table 1 and Figure 2. Serum IL-8 concentrations were elevated (> 67 pg/mL) in 23/64 (36%) patients. In addition, the IL-8 concentrations in sera from three patients rose to > 67 pg/mL during the first day after admission; thus, a total of 26/64 patients (41%) showed elevated levels of IL-8 either on admission or during the following day. High concentrations on admission (> 750 pg/mL) were found in 12/64 patients (Figure 2), but a rapid decrease in serum IL-8 was noted in most patients during the course of the disease (Figure 3).

No overall correlation between delay and serum IL-8 concentrations was found. However, patients with a shorter delay (< 1 week) between the onset of disease and admission to hospital showed lower serum IL-8 levels than those with a longer delay (> 1 week; Figure 3; *p* = 0.056). There was a significant correlation between the serum IL-8 concentrations on admission and WBC counts (*r* = 0.34; *p* = 0.008), and patients with elevated (> 67 pg/mL) IL-8 concentrations had higher mean WBC counts than those with low (< 67 pg/mL) IL-8 concentrations (*p* = 0.048).

There was no statistically significant difference in serum IL-8 concentrations on admission between patients with complicated septicemia and those with uncomplicated septicemia (Table 1). However, the 15 patients with extensive abscesses showed significantly higher serum IL-8 levels compared with those without abscesses (*p* = 0.001), although there was no statistically significant difference in serum IL-8 concentration on admission between patients with and without endocarditis. Non-survivors (*n* = 5) had higher serum IL-8 values than survivors, but the difference was not statistically significant (Table 2). However, two of the non-survivors had high IL-8 levels (>1000 pg/mL) and

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**Table 2** Characteristics of five patients with *Staphylococcus aureus* septicemia and a fatal outcome

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Delay* (days)</th>
<th>Temperature on admission (°C)</th>
<th>WBC count on admission</th>
<th>IL-8 (pg/mL) on admission</th>
<th>G-CSF (pg/mL) on admission</th>
<th>Diagnosis</th>
<th>Cause of death</th>
<th>Died after admission (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>3</td>
<td>39.8</td>
<td>15.4</td>
<td>5</td>
<td>1950</td>
<td>EC, definite</td>
<td>Septic shock, DIC</td>
<td>3</td>
</tr>
<tr>
<td>83</td>
<td>1</td>
<td>39.8</td>
<td>38.2</td>
<td>&gt; 750</td>
<td>47 (80)</td>
<td>Renal abscess</td>
<td>Renal abscess</td>
<td>10</td>
</tr>
<tr>
<td>81</td>
<td>3</td>
<td>38.0</td>
<td>10.1</td>
<td>65</td>
<td>50 (108)</td>
<td>Uncomplicated septicemia</td>
<td>Myocardial infarction</td>
<td>14</td>
</tr>
<tr>
<td>79</td>
<td>3</td>
<td>38.5</td>
<td>5.4</td>
<td>9 (150)</td>
<td>195</td>
<td>SA, coxitis</td>
<td>Progressive renal insufficiency</td>
<td>15</td>
</tr>
<tr>
<td>76</td>
<td>7</td>
<td>38.1</td>
<td>17.3</td>
<td>&gt; 750</td>
<td>&lt; 10</td>
<td>SA, coxitis</td>
<td>Progressive renal insufficiency</td>
<td>14</td>
</tr>
</tbody>
</table>

IL-8 = interleukin-8; G-CSF = granulocyte colony-stimulating factor; EC = endocarditis; SA = septic arthritis; DIC = disseminated intravascular coagulation.

* = number of days between onset of illness and admission to hospital.

( ) = maximum white blood cell (WBC) count during the course of disease.
three had low IL-8 levels (< 67 pg/mL) on admission. One patient who died during the early phase of septicemia had a clinical picture of septic shock and low levels (5 pg/mL) of IL-8. A further four patients, all of whom died during a later phase of the disease, also showed low levels of IL-8 in their final phase.

**White blood cell counts in patients with *S. aureus* septicemia**

The leukocyte counts in 17 (27%) patients on admission with *S. aureus* septicemia (Table 1) were normal. There was no statistically significant difference in leukocyte count on admission between patients with complicated and uncomplicated septicemia nor between those with or without endocarditis. Patients with a fatal outcome (n = 5, Tables 1 and 2) had higher WBC counts on admission than did survivors, but the difference was not statistically significant.

**DISCUSSION**

In a previous study, we described the kinetics of IL-6, TNF-α and IL-1β in serum samples from patients with well-defined gram-positive infections such as *S. aureus* septicemia [39]. In the present study, we present the corresponding results regarding serum G-CSF and IL-8 concentrations.

On admission, the majority (59%) of patients showed elevated serum G-CSF concentrations and about one-third (36%) had elevated serum IL-8 levels. The WBC counts were increased in most patients (73%) on admission. Previously, elevated serum levels of G-CSF have only been reported from a small number of patients with various bacterial infections, including bacteremia/septicemia [27–32]. The kinetics of G-CSF during septicemia have not hitherto been reported.

The kinetics of serum G-CSF levels have been studied in an experimental model [40] wherein G-CSF levels increased approximately 24 h after initiation of infection, reaching a maximum after 3 days. In the present study, patients with elevated G-CSF concentrations showed a rapid decrease in parallel with initiation of treatment and clinical improvement. This rapid decline may be an effect of treatment or reflect the natural course of G-CSF kinetics during the acute phase of an infection. The latter explanation may be
supported by the fact that patients with a short delay (< 1 week) had significantly higher levels of G-CSF compared with those with a longer delay (≥ 1 week; Figure 4). A negative correlation was also found between the serum G-CSF concentration on admission and delay.

The present study results show no overall correlation between serum G-CSF concentration and WBC count on admission, which is in accordance with the findings of Kawakami and coworkers [27], who found no association between serum G-CSF level and WBC count in either healthy controls or patients with various infections. However, those patients had higher serum G-CSF levels as well as higher WBC counts during the acute phase of infection compared with the recovery phase. Nevertheless, administration of G-CSF (> 1 μg/kg/day) to healthy subjects resulted in a sustained dose-dependent increase in circulating neutrophil counts within 3 to 5 days; after stopping G-CSF treatment, the neutrophil counts returned to baseline levels within 4 to 7 days [41].

The patients in the present study who had complicated staphylococcal septicemia had higher mean G-CSF values on admission compared with patients with uncomplicated septicemia. However, patients with complicated septicemia had lower median values than those with uncomplicated septicemia, reflecting the fact that the group with complicated septicemia included both patients with very high and patients with low G-CSF values. The most remarkable finding was that a majority (16/19) of the patients with uncomplicated septicemia had elevated (> 76 pg/mL) G-CSF concentrations on admission, in contrast to only about half of the patients (22/45) with complicated septicemia (Figure 5). This may be an indication that a high G-CSF concentration may have a protective effect on the development of septic complications such that patients who are able to produce an increase in G-CSF levels in response to bacterial infection may be less prone to develop complicated septicemia with septic metastases such as septic arthritis, osteomyelitis and formation of abscesses.

This possibility is supported by the findings in animal experimental infections [42] wherein pretreatment with G-CSF appears to increase the magnitude of the neutrophil response and thereby facilitate the recruitment of neutrophils to the inflammatory focus/tissue and more effectively reduce the bacterial load, limit proliferation of the bacteria and prevent dissemination of the infection. Such findings also
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accord with our results as patients with abscesses had lower G-CSF concentrations on admission than those who did not develop abscesses. Other experimental studies have shown that G-CSF can protect animals from lethal infections caused by various pathogens and, in addition, improve survival when G-CSF and antibiotics were combined [43-48].

Similar studies have not been performed in humans, although patients with infections such as endocarditis [49] and acquired immunodeficiency syndrome (AIDS) with concomitant neutropenia [50] have been treated with G-CSF. However, in studies where G-CSF has been administered to patients with chemotherapy-induced [50] and other drug-induced neutropenia [51], a reduction in the duration of neutropenia and the number of infections has been reported.

However, patients with complicated septicemia, such as a septic metastasis, may seek medical attention later than those without septic complications, as a septic metastasis is usually preceded by a bacteremia and a patient is not admitted until symptoms from a localized infection, or bacteremia with origin from a focal infection, is recognized. This also underlines the difficulties in determining the precise time of initiation of infection and, thus, in establishing the actual delay.

In previous studies, IL-8 was detected in serum and cerebrospinal fluid from patients with sepsis, septic shock and meningitis [33-35]. No differences in serum IL-8 levels were found between patients with gram-negative and those with gram-positive infections [34]. Endotoxin [36,37] as well as IL-1 [52] and TNF-α [37] have been shown to induce IL-8 production in vivo. The kinetics of IL-6 and IL-8 were similar [37,52,53] with concentrations that peaked later than that of TNF-α. It was therefore suggested that the endotoxin-induced release of IL-8 is mediated by TNF-α [37].

The effects of bacterial components from gram-positive organisms as inducers of IL-8 production have been investigated in only one, recently published, study [54]. Lipoteichoic acid (LTA) purified from *S. aureus* induced expression of IL-8 messenger ribonucleic acid (mRNA) and production of IL-8 from human peripheral blood monocytes. Cell-associated IL-8 has also been demonstrated in endocardial specimens from patients with acute *S. aureus* endocarditis.

In the present study, a correlation was found between serum IL-8 concentration and WBC count, which is in accordance with the results of experimental studies of animals without septic shock that were challenged with *Escherichia coli*, LPS or IL-1α [52]. Patients with elevated (> 67 pg/mL) or high (> 750 pg/mL) serum IL-8 levels on admission had significantly higher WBC counts compared with corresponding patients who had low serum IL-8 levels (≤ 67 pg/mL) or serum IL-8 levels ≤ 750 pg/mL, respectively.

However, in a study of patients with meningococc disease [35], a negative correlation was found between serum IL-8 and peripheral blood leukocyte count. There were also higher levels of IL-8 in patients with septic shock compared with those without shock [35]. All five patients with a fatal outcome had septic shock and four of the five showed extremely high serum IL-8 concentrations; the remaining patient had no detectable IL-8 in the serum. Similar findings have also been reported in patients with sepsis and septic shock caused not only by gram-negative, but also by gram-positive, bacteria [34]. These earlier results are supported by the findings in the present study wherein two of five non-survivors had high IL-8 levels (> 1000 pg/mL) and three had low (≤ 67 pg/mL) levels.

A sustained release of degraded microbial cell-wall components and exotoxins is conceivable if a septic metastasis such as an abscess is present, which may result in long-lasting and continuous stimulation of synthesis of neutrophilic chemoattractants such as IL-8 and, consequently, accumulation of neutrophils within the abscess. This may explain why patients with extensive abscesses had significantly higher serum IL-8 levels than those without abscesses.

In conclusion, cytokines are among a number of important factors involved in the host response to acute infection. Both G-CSF and IL-8 mediate a number of functional effects of neutrophils, which play a particularly important role in the defense against bacterial infection. However, among patients with *S. aureus* septicemia in the present study, 59% had elevated serum G-CSF concentrations and 36% had elevated IL-8 values on admission, indicating that other mechanisms for neutrophil activation may also be present.

These findings raise the question of whether low concentrations of G-CSF may indicate an insufficient activation of neutrophils and, thus, an increased risk of developing more extensive infection and secondary septic complications. IL-8 is a chemoattractant factor for neutrophils and, although local IL-8 production is important, elevated serum levels may be detected and correlate with the extent, severity and duration of infection.

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