To assess the diagnostic value of procalcitonin (PCT), interleukin (IL)-6, IL-8, and standard measurements in identifying critically ill patients with sepsis, we performed prospective measurements in 78 consecutive patients admitted with acute systemic inflammatory response syndrome (SIRS) and suspected infection. We estimated the relevance of the different parameters by using multivariable regression modeling, likelihood-ratio tests, and area under the receiver operating characteristic curves (AUC). The final diagnosis was SIRS in 18 patients, sepsis in 14, severe sepsis in 21, and septic shock in 25. PCT yielded the highest discriminative value, with an AUC of 0.92 (CI, 0.85 to 1.0), followed by IL-6 (0.75; CI, 0.63 to 0.87), and IL-8 (0.71; CI, 0.59 to 0.83; p < 0.001). At a cut-off of 1.1 ng/ml, PCT yielded a sensitivity of 97% and a specificity of 78% to differentiate patients with SIRS from those with sepsis-related conditions. Median PCT concentrations on admission (ng/ml, range) were 0.6 (0 to 5.3) for SIRS; 3.5 (0.4 to 6.7) for sepsis; 6.2 (2.2 to 85) for severe sepsis; and 21.3 (1.2 to 654) for septic shock (p < 0.001). The addition of PCT to a model based solely on standard indicators improved the predictive power of detecting sepsis (likelihood ratio test; p = 0.001) and increased the AUC value for the routine value-based model from 0.77 (CI, 0.64 to 0.89) to 0.94 (CI, 0.89 to 0.99; p = 0.002). In contrast, no additive effect was seen for IL-6 (p = 0.56) or IL-8 (p = 0.14). Elevated PCT concentrations appear to be a promising indicator of sepsis in newly admitted, critically ill patients capable of complementing clinical signs and routine laboratory parameters suggestive of severe infection.

Keywords: Critical care; biological markers, blood; calcitonin, blood; protein precursors, blood; interleukin-6, blood; interleukin-8, blood; sepsis, blood, diagnosis; sepsis syndrome, blood, diagnosis

Sepsis can be difficult to distinguish from other noninfectious conditions in critically ill patients admitted with clinical signs of acute inflammation (1, 2). This issue is of paramount importance given that therapies and outcomes greatly differ between patients with and those without sepsis. Thus, there is an unmet need for clinical or laboratory tools distinguishing between the systemic inflammatory response syndrome (SIRS) and the various forms of sepsis. To date, no single clinical or biological indicator of sepsis has gained unanimous acceptance (3), although several attempts have been made to correlate cytokine levels with sepsis and patient prognosis (1, 4). Among the potentially useful sepsis markers, interleukin (IL)-6, IL-8, and procalcitonin (PCT) have been proposed to be the most promising candidates (1). The latter in particular has been postulated to be superior to clinical variables or commonly used laboratory tests, such as C-reactive protein or leukocyte count, and to even correlate with the severity of microbial invasion (5–9). However, several investigators have questioned the diagnostic and prognostic accuracy of routine PCT measurements, retrieving inconsistent and variable results depending on the severity of illness and infection in the studied patient population (10–14).

In view of these conflicting findings and the paramount importance of the timely diagnosis of sepsis at time of admission to the intensive care unit (ICU), the present cohort study prospectively investigated the diagnostic value of PCT, IL-6, and IL-8 in a group of severely ill patients admitted with signs of acute, severe inflammation. Specifically, we assessed whether PCT, IL-6, IL-8, or standard parameters at time of admission are helpful in distinguishing sepsis from severe systemic noninfectious inflammation in newly admitted, critically ill patients with suspected infection.

METHODS

Study Setting and Population

Over a 7-mo period, all consecutive patients admitted with a suspected diagnosis of infection and hospitalized in the medical and surgical ICUs of the University of Geneva Hospitals were eligible, including neutropenic and immunosuppressed patients. On average, 1,700 adult patients are admitted each year to the 18-bed medical ICU for a mean length of stay of 4 d. The surgical ICU is a 20-bed unit with 1,600 admissions and a mean length of stay of 4 d.

At time of enrollment, all included patients had to be newly admitted to one of the ICUs, had to have a clinically suspected infection, and had to fulfill at least two criteria of SIRS (15). Clinically suspected infection was defined as an explicit statement by the attending physician indicating the suspicion of an ongoing infection, combined with the initiation of a diagnostic work-up to rule out infection and the prescription of antimicrobial therapy (16). Patients were not enrolled in case of early discharge or death, withholding of life-support, or complete absence of antimicrobial treatment.

Every effort was made to identify patients with suspected sepsis as early as possible after ICU admission. This was accomplished by dedicated research fellows, who visited the ICUs twice daily, and by the cooperation of the attending physicians, who indicated to the research team each patient admitted with suspected sepsis. Patients originated either from the emergency room, the general wards, or from the operating room.
Data Collection
Variables recorded at baseline and several times daily during follow-up included patient demographics, principal diagnosis, vital signs, respiratory parameters, routine blood tests and microbiologic culture results. Survival or death in the ICU was assessed during a follow-up of as long as 28 d. Death was defined as sepsis-related or sepsis-unrelated (e.g., cerebral death or cardiogenic shock). The severity of the patients’ condition was measured according to the simplified acute physiology scoring (SAPS) II system (17). Microbiologic tests and antimicrobial therapy were prescribed by physicians on service according to the usual practice in the participating ICUs, without interference by the research team. The hospital ethics committee on human research approved the study protocol.

Included patients were classified as having SIRS, sepsis, severe sepsis, or septic shock at the time of admission, according to established consensus definitions (15, 16). Importantly, this case ascertainment was done retrospectively by two independent investigators without the knowledge of plasma PCT, IL-6, and IL-8 values, on the basis of the review of the complete patient charts, results of microbiologic cultures, chest radiographs, and, when available, postmortem examination reports. Concordance among the two independent investigators was excellent and the interrater reliability was high (κ = 0.9). Disagreement was settled by consensus involving a third party.

Measurements of Procalcitonin, IL-6, and IL-8 Plasma Levels
Within 12 h after admission and study entry, whole heparinized blood was drawn via an arterial line for cytokine measurements and daily thereafter at 6:00 a.m. during the entire ICU stay until ICU discharge or death. Blood was put on ice and plasma was collected by centrifugation at 4°C, aliquoted, and stored at −70°C until the day of assay. PCT, IL-6, and IL-8 plasma levels were determined batchwise using commercial assays. Plasma PCT concentrations were measured in duplicates using an immunassay with a sandwich technique and a chemiluminescent detection system, according to the manufacturer’s protocol (LumiTest; Brahms Diagnostica, Berlin, Germany). As recently pointed out by Müller and colleagues (9), the LumiTest does not measure exclusively the procalcitonin molecule, but also several other calcitonin precursors that are “captured” by the sandwich ELISA. The term “procalcitonin” as used here may therefore lack scientific precision, but it was favored over “calcitonin precursors” because it is widely used by critical care physicians and investigators.

PCT levels were found to be <0.2 ng/ml in plasma from 15 healthy donors. The coefficient of variation (CV) of the test was 9% at a PCT plasma concentration of 1.2 ng/ml, and 4.4% at 56 ng/ml.

IL-6 and IL-8 were measured using semiautomated chemiluminescent immunoassays (ImmuliteOne; DPC-Biermann, Bad Nauheim, Germany). The median value (range) of plasma IL-6 and IL-8 levels in 15 healthy blood donors was 2.6 (<1 to 11.3) pg/ml and 5 (4 to 27) pg/ml, respectively. The CVs were 4.3 and 8.8%, respectively. PCT, IL-6, and IL-8 plasma measurements were performed by trained laboratory technicians, blinded to the patients’ clinical course. In a randomly selected subgroup of 35 patients, we also quantified plasma levels of TNF-α (Medgenix, Belgium), soluble TNF receptors (sTNFR) I and II, IL-10, and IL-1ra, using ELISA tests (R&D Systems, Abingdon, UK).

Statistical Analysis
Values were expressed as the mean ± SD or as the median and interquartile range in case of a skewed distribution. Comparison of group differences for continuous variables was done by one-way ANOVA or nonparametric Kruskal-Wallis test, when appropriate. The significance of difference in proportions was tested with use of the χ²-test. We also used univariate-correlation analyses to establish the relation between parameters.

Sensitivity, specificity, and positive and negative predictive values of each cytokine parameter were calculated according to standard methods (18). The diagnostic accuracy of the cytokine plasma levels determined at study entry was expressed as the area under the receiver operating characteristic curve (AUC), which was derived from logistic regression analysis (19). These values were calculated for the cutoff that represented the best discrimination as derived from the AUCs. For the purpose of the logistic regression analysis, which requires binary outcome events, case subjects classified as confirmed sepsis, severe sepsis, or septic shock (= sepsis syndrome) were compared with control patients with SIRS and initial suspicion of infection.

We analyzed associations between different levels of each individual clinical and biological parameter and the risk of sepsis syndrome at admission, after dividing the values for each marker into quartiles. This was done because few continuous variables satisfied the linearity assumption. To estimate the potential clinical relevance of the cytokine measurements, we used likelihood-ratio tests to determine whether logistic regression models that included measurements of cytokines and routine clinical and laboratory variables provided a significantly better fit than did logistic regression models limited to standard laboratory and clinical measurements alone (20). In order to determine the prognostic power of the candidate parameters regarding patients’ survival, we used time-dependent Cox proportional hazards modeling (21).

Statistical software programs (STATA, version 6.0, Stata Inc.; Statview, version 4.1, Abacus Concepts, Berkeley, CA) were used for data processing and analyses. All p values were two-sided, and statistical significance was set at an α-value of 0.05.

Figure 1. Plasma levels of PCT, IL-6, and IL-8 in patients with SIRS (n = 18), sepsis (n = 14), severe sepsis (n = 21), and septic shock (n = 25). Data are presented as box plots with median lines, 25- and 75-percentile boxes, and 10- and 90-percentile error bars, using a log scale for the Y-axis. The circles represent the outliers.
RESULTS
Characteristics of the Study Population
We prospectively enrolled 78 adult ICU patients meeting the criteria for SIRS (n = 18), sepsis (n = 14), severe sepsis (n = 21), or septic shock (n = 25). The main patient characteristics are shown in Table E1 (see Online Data Supplement). As expected, patients admitted with septic shock were more severely ill at baseline than those without. The former were more likely to have a higher SAPS II score, heart rate, and lactate and to have a lower core temperature, mean arterial pressure, platelet count, arterial pH, and oxygenation status. Infections were microbiologically proven in 44 of 60 infected patients (73%) with 53% Gram-negative, 38% Gram-positive bacteria, and 9% mixed infections. Leading sources of infection were the respiratory tract (n = 38) and the intra-abdominal space (n = 10). Twenty-three infected patients had a documented bloodstream infection.

Baseline Plasma Levels of PCT, IL-6, and IL-8
Baseline plasma levels of the inflammation markers IL-6, IL-8, and PCT were higher among case subjects with severe sepsis or septic shock than among control subjects with SIRS only (Figure 1). PCT appeared to be most helpful in differentiating patients with sepsis from those with SIRS. Median PCT levels on admission (ng/ml, range) were 0.6 (0 to 5.3) for SIRS; 3.5 (0.4 to 6.7) for sepsis; 6.2 (2.2 to 85) for severe sepsis; and 21.3 (1.2 to 654) for septic shock (p < 0.001). The accuracy of the candidate parameters to distinguish patients with SIRS from those with septic conditions varied (Table 1). As shown in Figure 2 (upper panel), PCT yielded the highest discriminative value with an AUC of 0.92 (95% confidence interval [CI], 0.85 to 1.0) followed by IL-6 (AUC, 0.75; CI, 0.63 to 0.87) and IL-8 (AUC, 0.71; CI, 0.59 to 0.83; p < 0.001). At a cutoff point set at 1.1 ng/ml, PCT yielded a sensitivity of 97% and a specificity of 78% to differentiate patients with SIRS from those with sepsis, severe sepsis, or septic shock.

Serum C-reactive protein concentrations increased from 119 ± 89 mg/l for SIRS to 159 ± 51 mg/l for sepsis, 254 ± 181 mg/l for severe sepsis, and 228 ± 119 mg/l for septic shock (p = 0.04 in Table E1) (See Online Data Supplement). C-reactive protein yielded an AUC of 0.76 (CI, 0.58 to 0.93), a value similar to IL-6. At a cutoff value of 150 mg/l, the sensitivity and specificity were 68 and 73%, respectively.

Correlation of the Study Parameters with Other Sepsis Mediators
In a randomly selected subgroup of 35 patients, additional proinflammatory and antiinflammatory cytokines (TNF-α, sTNFR I, and II, IL-10, and IL-1ra) were determined and correlated with the main study parameters PCT, IL-6, and IL-8. Several of those cytokines levels were highly correlated (Table E2. See Online Data Supplement). For example, the correlation coefficient for the relation between PCT and TNF-α was 0.86; between PCT and sTNFR I, 0.78; and between IL-6 and TNF-α, 0.92 (all p < 0.001). In contrast, correlation coefficients between routinely available clinical and laboratory indicators of inflammation (e.g., leukocyte count, C-reactive protein, temperature) and the additionally measured cytokines were small; less than 40% of the variance in any of the cytokine markers was explained by any of the standard measures.

Discriminative Power of Clinical and Biological Sepsis Indicators
In an additional attempt to assess the diagnostic value of the sepsis indicators, we stratified the continuous values for each indicator into quartiles, and then analyzed associations between different levels of each individual clinical and biological marker and the risk of sepsis syndrome at admission (Table E3. See Online Data Supplement). No differences in clinical variables such as temperature or heart rate were observed between septic patients and noninfected patients with SIRS, except for the mean arterial pressure (p = 0.03). Conversely, six biological parameters predicted sepsis syndrome by bivariate analysis (Table E3). In order of significance, these were PCT, IL-6, IL-8, monocyte count, arterial pH, and C-reactive protein. PCT was the most powerful predictor of sepsis syndrome in this bivariate analysis (p < 0.001).

![Figure 2](image-url)

**Figure 2.** Receiver operating characteristics curves (ROC) of plasma parameters (PCT; IL-6; and IL-8; upper panel), and of a clinical model with and without PCT (lower panel). Areas under the ROC were: upper panel, PCT, 0.92; IL-6, 0.75; IL-8, 0.71; and lower panel, clinical model with PCT, 0.94, and clinical model without PCT, 0.77.

**TABLE 1. DIAGNOSTIC PERFORMANCE OF DIFFERENT SEPSIS INDICATORS**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cutoff value, ng/ml*</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive predictive value, %</th>
<th>Negative predictive value, %</th>
<th>Area under the receiver operating curve (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>1.1</td>
<td>97</td>
<td>78</td>
<td>99</td>
<td>88</td>
<td>(0.85–1.00)</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>200</td>
<td>67</td>
<td>72</td>
<td>89</td>
<td>39</td>
<td>(0.63–0.87)</td>
</tr>
<tr>
<td>Interleukin-8</td>
<td>30</td>
<td>63</td>
<td>78</td>
<td>90</td>
<td>39</td>
<td>(0.59–0.83)</td>
</tr>
</tbody>
</table>

* Sensitivity, specificity, and predictive values were calculated for the cutoff, which represented the best discrimination as derived from the receiver operating characteristic curves.
Clinical Significance of the Diagnostic Indicators

To explore the diagnostic performance of the parameters from a clinical perspective, we evaluated the accuracy of the cytokine levels and clinical indicators of inflammation as predictors of sepsis in a series of analyses. First, we determined the independent predictive value of the different clinical and biological sepsis indicators by performing multivariable logistic regression modeling. In the global stepwise analysis including all variables described in Table E3, only PCT (adjusted odds ratio [AOR] per 1-point increase, 2.3; CI, 1.4 to 3.7; \( p = 0.001 \)) was found to be an independent predictor of sepsis syndrome. In a similar model that was limited to the routinely available parameters without PCT, IL-6, and IL-8, increasing levels of C-reactive protein (AOR, 1.01; CI, 1.0 to 1.03; \( p = 0.023 \)) and an elevated proportion of leukocyte band forms (AOR, 1.06; CI, 1.0 to 1.14; \( p = 0.067 \)) tended to predict sepsis syndrome.

Second, likelihood-ratio tests were used to compare the fit of predictive models that were based on measurement of routinely available sepsis markers in combination with the study parameters to the fit of models based only on standard indicators (core temperature, heart rate, blood pressure, white blood cell count). In these models, the addition of PCT significantly improved the power of detecting sepsis syndrome (\( p = 0.001 \)). In contrast, no additive effect was seen for IL-6 (\( p = 0.56 \)) or IL-8 (\( p = 0.14 \)).

Third, as a measure of clinical usefulness, we evaluated the combined role of the cytokine levels and clinical markers as predictors of sepsis using AUC analysis. As shown in Figure 2 (lower panel), the inclusion of PCT increased the AUC value for the routine value-based model from 0.77 (CI 0.64 to 0.89) to 0.94 (CI 0.89 to 0.99; \( p = 0.002 \)). Again, no such effect was observed with IL-6 or IL-8.

Severity of Sepsis and Final Outcome

We further evaluated the time course of PCT, IL-6, and IL-8 in relation to the prognosis and severity of sepsis. The evolution of serum PCT concentrations during follow-up of patients with severe sepsis and septic shock are shown in Figure 3. A slow decrease or no decrease in PCT levels 48 h after admission was consistently associated with a poor outcome (Figure 3, panel B). All patients who died of sepsis or related complications never had PCT levels below 1.1 ng/mL, except for one single time point in one patient. Conversely, PCT levels decreased under the cutoff of 1.1 ng/mL within 8 d in all survivors except for one (Figure 3, panel A). In contrast, IL-6 and IL-8 did not demonstrate this uniform pattern in septic patients (Figure E1. See Online Data Supplement). Within the 8-d period after onset of severe sepsis or septic shock, six survivors still had elevated IL-6 or IL-8 levels. Interestingly, we observed that in four patients with prolonged ICU stay and com-

Figure 3. Daily variations of procalcitonin (PCT) levels during ICU hospitalization. (Panel A) Patients admitted with severe sepsis and septic shock who survived. (Panel B) Patients admitted with severe sepsis and septic shock who died. (Panel C) Control patients admitted with SIRS and initial suspicion of infection.

Figure 4. PCT, IL-6, and IL-8 baseline levels in patients with sepsis, severe sepsis, and septic shock who survived (n = 38) or who died (n = 18) of sepsis-related death. Four patients who died from causes unrelated to sepsis were omitted from the analysis. Data are presented as box plots with median lines, 25- and 75-percentile boxes, and 10- and 90-percentile error bars, using a log scale for the Y-axis. The circles represent the outliers.
plicated courses of sepsis, peaks in plasma PCT levels coincided with clinical episodes of septic shock (Figure 3, panel D) (Figure E2. See Online Data Supplement).

Values of plasma PCT, IL-6, and IL-8 in infected patients at the time of admission relative to sepsis-related death are shown in Figure 4. The most discriminative parameter to predict sepsis-related death in infected patients at the time of admission was an IL-6 value above 1,000 ng/ml.

Finally, we assessed all follow-up values of the candidate parameters as determinants of survival in the entire cohort of infected and noninfected patients. During 832 d at risk, the mean plasma levels of IL-6 (mean difference, 4,689.1 ng/ml; p = 0.0003), IL-8 (mean difference, 1021.9 ng/ml; p < 0.0001) and PCT (mean difference, 25.7 ng/ml; p = 0.004) differed between those patients who survived and those who died. We then included each cytokine measurement in a time-dependent Cox proportional hazards model. In this longitudinal analysis that also included noninfected patients, only increasing levels of IL-8 predicted death (AOR per 1,000 ng increment, 1.05; CI, 1.00 to 1.10; p = 0.046), whereas IL-6 (p = 0.82) and PCT (p = 0.36) did not indicate an increased risk of death.

**DISCUSSION**

The principal findings of this study performed in newly admitted, critically ill patients with suspected sepsis are: (1) the confirmation of the previously described good diagnostic accuracy of PCT; (2) the modest discriminative value of IL-6, IL-8, and other indicators of inflammation; (3) the additive effect of PCT to improve the predictive power of routinely available sepsis parameters; (4) the excellent correlation of PCT with other biologic markers of sepsis such as TNF-α; and (5) the good concordance of PCT plasma levels with the clinical evolution of septic patients.

Critical care physicians have at their disposal a variety of data to serve as a guide in discriminating infections from noninfectious conditions in newly admitted patients. In a number of cases, the diagnosis of sepsis becomes clear after completing the medical history and physical examination of a newly admitted patient (22). In other circumstances of noninfectious insults causing SIRS (e.g., trauma, burns, hemorrhages, hypothermia, pancreatitis, and surgery), or in comatose patients, the diagnosis of sepsis remains difficult. In these cases, several indicators have been proposed as new diagnostic tests to assess the competing probabilities of various candidate illnesses in the differential diagnosis of sepsis (23, 24). The present results confirm and extend earlier findings demonstrating that PCT is among the most promising sepsis markers in critically ill patients, capable of complementing clinical signs and routine laboratory parameters suggestive of severe infection at time of ICU admission. Recently, Müller and colleagues (9) investigated 101 patients admitted to a medical ICU and suggested that PCT is a more reliable marker of sepsis than is C-reactive protein, IL-6, and lactate levels. Another group from Germany (25) recently reported average PCT concentrations of 0.4 ± 3.4 ng/ml for SIRS, 0.5 ± 2.9 ng/ml for sepse, 6.9 ± 3.9 ng/ml for severe sepsis and 12.9 ± 4.4 ng/ml for septic shock. On the basis of their findings, the investigators concluded that PCT measurement appears to be useful to discriminate between sepsis and severe sepsis, in contrast to C-reactive protein, blood cell counts, or body temperature. Lastly, Viallon and colleagues (26) investigated 61 patients with cirrhotic ascites or spontaneous bacterial peritonitis and found PCT values similar to those in the present study: median PCT serum levels and interquartile ranges were 3.2 (2.3 to 10.1), 13.8 (8.7 to 18.4), and 26.5 (24.0 to 52.0) ng/ml in patients with sepsis, severe sepsis, and septic shock, respectively.

Our study has several important implications for clinicians. First, as a putative new test to diagnose sepsis on ICU admission, PCT offers a high level of certainty than other currently available candidates do. In the current study, a cutoff point of 1.1 ng/ml detected virtually all septic patients. This accuracy, although not perfect, may guide physicians in their clinical decision-making and their stepwise approach to the complex management of critically ill patients requiring several interventions in a short period of time. Second, in the recovery phase of severe sepsis or septic shock, a greatly decreased PCT level indicates a favorable clinical evolution and may prompt physicians to withdraw antimicrobial treatment. Third, measurement of PCT is of practical value since it increases 2 to 4 h after bacterial or endotoxin challenge (24). The test can be performed within 3 to 4 h and may give valuable information long before blood culture results are back. Thus, in contrast to many other cytokine markers with purely theoretical utility (27), measuring PCT with a commercially available assay is realistic, inexpensive and may even be cost-effective by better directing diagnostic and therapeutic interventions in critically ill patients with SIRS of undetermined origin. This, of course, requires further prospective testing. Finally, PCT is not only helpful in the diagnosis of sepsis, but also indicative of its severity. As previously suggested (9, 28), we demonstrated that constantly elevated PCT levels in infected patients were associated with poor prognosis. In contrast, the rapid decrease of PCT levels during the first week after ICU admission had a good prognostic value. The relation between these findings and the pathophysiology of sepsis remains to be elucidated. It is, however, tempting to hypothesize that persistently elevated PCT values during the course of sepsis may identify subgroups of patients who have difficulties in clearing their systemic infection.

One interesting finding was that PCT levels in infected patients correlated well with circulating cytokines such as TNF-α, thus representing a suitable surrogate marker for key cytokines during septic shock. Taking into account that poor immunologic characterization was one of the main reasons for failure in trials with immunomodulating agents, the rapid measurement of PCT may improve the results of future intervention trials to detect and treat patients with severe sepsis and septic shock (8, 29). Thus, bedside documentation of elevated PCT levels may become an additional entry criterion for sepsis trials (8).

Our study has several strengths. First, our study population was a large, diverse group of critically ill adult patients admitted to both medical and surgical ICUs in different phases of infectious and noninfectious conditions. This allowed us to make group comparisons not previously reported by other studies, in order to increase the generalizability of the study findings. In contrast, most of the previous studies that attempted to draw conclusions about PCT were based on small patient samples (30) or selected patient groups such as febrile children, postsurgical patients, or patients with specific diseases only (31–34). Second, following high methodologic standards (35), we used prospective surveillance and consecutive patient enrollment, intensive clinical and laboratory data collection and follow-up, and powerful statistical methods to accurately describe and analyze the diagnostic performance of the studied parameters. Third, outcomes were determined by blinded investigators without knowledge of the plasma cytokine levels, and vice versa. Fourth, we classified patients with SIRS and suspected infection according to predetermined, well-established outcome categories, after incorporation of all available clinical, laboratory, and histologic evidence. Fifth, in contrast to other studies (9, 30, 31), we did not include clinically unrealistic control patients without suspected infection, but only patients with a high pretest probability of sepsis, cov-
erating the spectrum of patients that is likely to be encountered in the future use of the tests (35). Finally, our study was designed as a real-life study, to closely resemble clinical practice. Therefore, we evaluated the combined role of the cytokines and clinical indicators of inflammation as predictors of sepsis in a series of analyses, in which we explored the diagnostic accuracy of these different parameters from a clinical perspective. In summary, in contrast to many previous studies, our study fulfills all important criteria for the optimal design of studies assessing the accuracy of diagnostic tests (35).

IL-6 and IL-8 are potent inflammatory mediators and their plasma concentrations have been tested as prognostic factors in several studies (27, 36, 37). The results of the present study suggest that measurement of these cytokines is not optimal for discriminating patients with infections from those with noninfectious conditions. In particular, we confirm the observation by other investigators that IL-8 is not a good indicator of systemic infection, although elevated IL-8 levels are indicative of multiple organ failure and an increased likelihood of death (38). Our findings are also consistent with the results reported by De Werra and colleagues (39), who observed increased IL-6 concentrations in patients with cardiogenic shock. Thus, persistently high IL-6 and IL-8 levels are very sensitive markers of inflammation and are likely to be of prognostic value in critically ill patients with multorgan failure (27, 40). However, their diagnostic accuracy is limited in critically ill patients by the unspecified elevation caused by the accompanying inflammation independent of the infection. In contrast to IL-6 and IL-8, PCT does respond rather to an infection than to the inflammation.

Several limitations of this study merit consideration. Using clinical criteria and microbiologic evidence, it may have been difficult to ascertain the exact etiology of SIRS in all patients. This may have introduced some misclassification bias, but since investigators blinded to the cytokine results performed the case ascertainment, we do not believe that this lack of a gold standard compromised our study conclusions. Our data are also limited because we did not include enough patients with underlying autoimmune disease or other diseases that may increase PCT levels without infection. Major surgery such as kidney transplantation or cardiopulmonary bypass surgery, in particular, may distort PCT measurement (32, 41). Moreover, antibiotic therapy may have an important impact on PCT values. Because antimicrobial treatment was a criterion for study inclusion, all patients in our study already received at least one dose of an antimicrobial agent at the time of first blood collection. Thus, similar studies should be conducted in order to elucidate the exact relation between adequate antibiotic treatment and the time course of daily PCT serum levels. Finally, our results may not apply to patients with localized or mild infections not requiring ICU treatment. In those patients, PCT levels may fall below the proposed cutoff and other parameters may be more useful to diagnose or exclude infection.

In conclusion, in this prospective, blinded evaluation of three different sepsis indicators in a consecutive series of patients, PCT proved to be the best indicator of infection in newly admitted critically ill patients. Our results indicate that clinical variables are of moderate diagnostic value for the diagnosis of sepsis on ICU admission. Thus, our data raise the possibility that the addition of PCT to the standard work-up of critically ill patients with suspected sepsis could increase diagnostic certainty and generate an improved patient management.

References


Appendix