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Soluble Interleukin-6 Receptor in Patients with Severe Sepsis

To the Editor—We read with interest the recent study of Frieling et al. [1], which showed that patients with sepsis syndrome have lower circulatory concentrations of soluble interleukin-6 (IL-6) receptor (sIL-6R) and higher concentrations of IL-6 than do healthy volunteers. In addition, the study showed that serum levels of sIL-6R were not significantly different in surviving and nonsurviving patients.

We recently investigated serum IL-6 and sIL-6R levels at the time of admission to an intensive care unit and on day 4 in patients with severe sepsis, as defined by recent consensus definitions [2]. The initial severity of illness was assessed using the simplified acute physiology score (SAPS) [3]. As controls, blood samples were drawn from 7 healthy hospital employees. Serum levels of IL-6 and sIL-6R were measured by ELISA: Detection limits were 25 pg/mL (IL-6) and 5 ng/mL (sIL-6R).

Statistical analyses were done using Student's *t* test to calculate intergroup differences, paired Student's *t* test to calculate intragroup differences, and Pearson's correlation to test the relationship between IL-6 and sIL-6R levels and SAPS scores. Results were expressed as mean \pm SE. $P < .05$ was considered significant.

Serum cytokine levels were measured in 18 consecutive patients (13 men, 5 women) with severe sepsis. Their mean age was 55 ± 4 years (range, 22–86), and the mean SAPS was 19.6 ± 1.2 (range, 15–31). All but 1 patient had documented infection: gram-negative infections (7) and both gram-negative and -positive infections (10). Four patients had gram-negative bacteremia. Sources of infection were urinary (1), intraabdominal (7), and respiratory (10) tracts. Fourteen patients had septic shock and 13 had adult respiratory distress syndrome (8 with pneumonia); all patients were ventilated. By day 28, 33% of the patients had died.

IL-6 was detected in all patients at study entry (range, 64–88,300 pg/mL): The mean serum level was higher for the 6 nonsurvivors ($20,931 \pm 12,789$ pg/mL; range, 160–75,850) than for the 12 survivors (7880 ± 7320 pg/mL; range, 181–37,650; $P = .4$), but the difference was not statistically significant. Mean sIL-6R was significantly decreased in patients with severe sepsis (73 ± 7 ng/mL; range, 17–135) compared with controls (103 ± 11 ng/mL; range, 75–166; $P = .04$); however, the level in survivors (76 ± 10 ng/mL; range, 17–135) was not significantly different than that in nonsurvivors (65 ± 9 ng/mL; range, 40–98; $P = .49$). For individual patients, there was a significant negative correlation between serum levels of IL-6 and sIL-6R at study entry ($r = -.59$; $P = .009$). There was also a strong correlation between concentrations of IL-6 and SAPS ($r = .73$; $P = .0005$), but there was no correlation between levels of sIL-6R and SAPS.

To determine the evolution of serum levels of IL-6 and sIL-6R during the course of severe sepsis, IL-6 and sIL-6R were measured at day 4 after study entry. The mean concentration of sIL-6R in

the 12 survivors increased from 76 ± 10 ng/mL at study entry to 110 ± 17 ng/mL on day 4 (range, 57–213; $P = .02$). By contrast, the mean concentration of sIL-6R remained low in the 6 nonsurvivors: 65 ± 9 ng/mL at study entry and 70 ± 9 ng/mL on day 4 (range, 48–103; $P = .62$). As a result, mean sIL-6R on day 4 was significantly lower in nonsurvivors than in survivors ($P = .04$). However, compared with levels at entry, concentrations of IL-6 on day 4 were decreased significantly in survivors (227 ± 24 ng/mL; range, 25–716; $P = .03$) but not in nonsurvivors (8205 ± 5400 ng/mL; range, 181–37,650; $P = .13$). No correlation was found between levels of IL-6 and sIL-6R at day 4.

In our study and as previously found by Frieling et al. [1], decreased levels of sIL-6R with simultaneously increased levels of IL-6 in patients with severe sepsis at study entry did not correlate with severity or outcome of illness; however, concentrations of sIL-6R remained low during the course of severe sepsis in patients who died. In patients surviving severe sepsis, concentrations of sIL-6R increased to levels seen in healthy subjects. By contrast, the high concentrations of IL-6 decreased in both survivors and nonsurvivors. However, the decrease of IL-6 levels did not reach statistical significance in the nonsurvivor group probably due to the small number of patients involved in that study.

IL-6 levels seem to be a good marker of the severity of sepsis [4] and are well correlated with patient outcome [5, 6]. On the other hand, the clinical relevance of sIL-6R concentrations during sepsis is not yet clear. sIL-6R seems not to play an antagonist role like the soluble receptor for tumor necrosis factor [7] but, on the contrary, seems to enhance the biologic activity of IL-6 [8]. In the IL-6 signaling pathway, the stimulation of target cells with a complex of sIL-6R and IL-6 induces the homodimerization of a non-binding signal transducer (gp130) and the tyrosine-specific phosphorylation of gp130 [8]. The persistence of low levels of sIL-6R in nonsurvivors could be a host defense mechanism due to the severity of the sepsis injury. Further studies are warranted to best understand the role of sIL-6R during sepsis.

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Reply

To the Editor—The study by Zeni et al. [1] confirms our findings regarding soluble interleukin-6 (IL-6) receptor (sIL-6R) concentrations in patients with sepsis syndrome [2]. Their data obtained on day 4 after study entry provide additional information on the course of sIL-6R concentrations in such patients. The differences in concentrations of IL-6 and sIL-6R among survivors and nonsurvivors are of interest, since they are not significantly different at study entry but become so at day 4. This raises an interesting point and can be explained by the fact that IL-6 concentrations did not decrease at the same rate in nonsurvivors and survivors.

In a new study of patients with meningococcal infections, we found that sIL-6R added to the circulation by plasma or whole blood exchange is cleared at a much faster rate in the presence of high rather than low concentrations of IL-6 (unpublished data). Because the IL-6 concentration in nonsurvivors of sepsis syndrome remains relatively high, the concentration of sIL-6R will remain lower than normal levels. Whether the persistence of a low concentration of sIL-6R is a host defense mechanism or merely a result of clearance rate remains to be investigated.

Another issue of interest is that the correlation between IL-6 and sIL-6R concentrations, which was significant at study entry, is not significant on day 4. This is probably due to the number of

patients with near-normal IL-6 concentrations. In patients with low concentrations of IL-6 in the previously mentioned unpublished study, sIL-6R concentrations exceeded the normal range before returning to normal. These patients offset the correlation found at study entry.

The statement by Zeni et al. [1] that in our study [2], we found no relation between IL-6 and sIL-6R concentrations and severity of illness is only partly correct: We did find a significant correlation between APACHE scores and IL-6 but not between sIL-6R and APACHE scores, which is in agreement with their study.

The renal function of patients should be considered in studies of soluble cytokine receptors. As indicated in our study [2], moderate renal impairment did not influence the concentration of sIL-6R. Subsequent to that study, however, it was shown in patients with severe renal insufficiency requiring renal replacement therapy that sIL-6R concentrations are increased, dependent on the mode of therapy (unpublished data).

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Polymerase Chain Reaction for Assessing Treatment Response in Patients with Pulmonary Tuberculosis

To the Editor—Kennedy et al. [1] recently compared the value of stain, culture, and polymerase chain reaction (PCR) for the diagnosis of pulmonary tuberculosis using data from 10 patients; they suggested that PCR could be used to assess treatment response in these patients. Although the authors did not describe how they selected these 10 patients from their 200 with smear-positive tuberculosis, the high reliability of PCR for sputum samples obtained as late as 4 months after onset of successful treatment is surprising. In our experience, it is extremely difficult to obtain sputum samples of good quality because patients no longer expectorate after a few

weeks of treatment, and the number of residual microorganisms in sputum must be extremely low. The detection of *Mycobacterium tuberculosis* by PCR in these samples suggests that this technique may be useful even for low-quality sputum samples that contain few microorganisms.

To test this hypothesis, we used a semiquantitative PCR technique with serial early morning sputum samples of different quality (collected every 10 days for up to 3 months) from 5 patients with smear-positive pulmonary tuberculosis. Sputum specimens from 2 healthy volunteers were used as negative controls. The quality of all samples was assessed by Gram's stain and scored as 0 to 3+, depending on the number of leukocytes or squamous epithelial cells per low-power field [2]. All sputum samples were stained by auramine-rhodamine dye and cultured in solid medium by standard procedures [3]. The numbers of acid-fast bacilli in stained smears were scored as 1+ to 3+, following a standard semiquantitative technique [4]. For cultures, a score of 1+, 2+, or 3+ indicated the amount of colonies in Löwenstein-Jensen medium (20, 20–100, >100, respectively). An aliquot of each decontaminated and suspended product was stored at –20°C until processing for PCR.

PCR was done as previously described [5] with minor modifications. Briefly, the mycobacterial DNA was amplified using the Taq Start antibody technique (Clontech, Palo Alto, CA) to avoid cross-

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