

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/24150>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

Interleukin-6 and its soluble receptor during acute meningococcal infections: Effect of plasma or whole blood exchange

Johan T. M. Frieling, MD; Marcel van Deuren, MD; John Wijdenes, PhD; Roelof van Dalen, MD; Anton K. M. Bartelink, MD; Cees J. van der Linden, MD, PhD; Robert W. Sauerwein, MD, PhD

Objectives: To determine the pattern of the soluble interleukin (IL)-6 receptor during acute meningococcal infections and recovery phase, and to measure the effect of plasma or whole blood exchange on the plasma concentrations of these mediators.

Design: Prospective, descriptive patient study.

Setting: University Hospital intensive care unit.

Patients: Patients with bacteriologically proven meningococcal infections were entered in the study. Three groups were formed: a) patients with meningitis without shock (group A); b) patients with meningitis and shock (group B); and c) patients with shock only (group C).

Interventions: Part (n = 9) of the patients with shock underwent plasma or whole blood exchange.

Measurements and Main Results: Serum concentrations of interleukin-6 and soluble IL-6 receptors were determined sequentially during the acute and recovery phases. Peak concentrations of IL-6 were highest in group C, followed by group B and group A.

Soluble IL-6 receptor concentrations showed an opposite pattern and were all below normal. Soluble IL-6 receptor concentrations were negatively correlated with the IL-6 concentrations. During recovery, IL-6 rapidly decreased and soluble IL-6 receptors increased to supranormal concentrations, after which concentrations returned to normal. Plasma or whole blood exchange did not significantly influence IL-6 concentrations but did increase the soluble IL-6 receptor concentration directly after an exchange session followed by a rapid decrease.

Conclusions: Soluble IL-6 receptor concentrations are low in acute meningococcal infections. Plasma or whole blood exchange temporarily increases these concentrations. It needs to be determined whether the effect of this therapy is beneficial to the patient. (Crit Care Med 1996; 24:1801-1805)

KEY WORDS: interleukin-6; *Neisseria meningitidis*; plasma exchange; interleukin-6 receptor; bacterial infection; mediators; cytokines; infection; critical illness

Among the acute bacterial infections, meningococcal infections are one of the most life-threatening diseases. The Gram-negative bacterium, *Neisseria meningitidis*, can induce a clinical disease that varies from meningitis to a rapidly deteriorating sepsis syndrome with severe shock and a mortality rate of 30% to 70% (1). High concentrations of the proinflammatory cytokines, interleukin (IL)-6 and tumor necrosis factor (TNF), are found in these patients, and these cytokine concentrations correlate with disease severity and outcome (2-4). The role

of IL-6 in the pathogenesis of septic shock has not been elucidated. An important function of IL-6 is presumably to act as a mediator between damaged tissues and the liver, where it is a potent inducer of acute-phase proteins.

Soluble receptors for various cytokines have been shown to modulate the biological effects of their ligand (5). TNF activity, for example, is decreased in the presence of soluble TNF receptor by competitive inhibition (6); in contrast, low concentrations of soluble TNF receptor can increase the effects of TNF by prolonging its half-life (7).

Soluble IL-6 receptor, however, seems to play a different modulating effect on IL-6 activity. The ligand binding part of the cellular IL-6 receptor (gp80) is either shed from the surface or secreted by the cell (8, 9). A complex of the soluble IL-6 receptor and IL-6 can interact with the signal transducing part of the cellular IL-6 receptor (gp130) and generate a signal into the cell. Through this mechanism

the presence of soluble IL-6 receptor enhances the biological activity of IL-6 (10, 11). Studies on the patterns and effects of this soluble receptor are necessary to understand the biological significance of this phenomenon.

We studied the pattern of IL-6 and its soluble receptor in the acute and recovery phases of meningococcal infections. A number of the study patients underwent plasma or whole blood exchange, which possibly improves clinical signs of sepsis and survival (12-15). Because the mechanism behind the beneficial effect of this procedure has yet to be elucidated, the effects of plasma or whole blood exchange on the patterns of the plasma concentrations of IL-6 and soluble IL-6 receptor were also measured in this study.

MATERIALS AND METHODS

Patients with bacteriologically proven meningococcal infections admitted to the intensive care unit

From the Departments of Surgery (Drs. Frieling and van der Linden), Internal Medicine (Dr. van Deuren), Medical Microbiology (Dr. Sauerwein), and Intensive Care (Dr. van Dalen), University Hospital Nijmegen, Nijmegen, The Netherlands; Diaclone (Dr. Wijdenes), Besançon, France; and the Department of Internal Medicine (Dr. Bartelink), Eemland Hospital, Amersfoort, The Netherlands.

Supported, in part, by funds from the Departments of Surgery and Medical Microbiology of the University Hospital Nijmegen.

Copyright © 1996 by Williams & Wilkins

were included in the study. Cultures for *Neisseria meningitidis* had to be positive from at least one of the following sites: blood, cerebrospinal fluid (CSF), and/or skin lesion. According to Halstensen et al. (16), three groups were discriminated. Group A (n = 13) showed a meningococcal infection of the central nervous system without shock; group B (n = 5) showed a meningococcal infection of the central nervous system plus shock; and group C (n = 5) showed no sign of inflammation of the central nervous system but only shock. Infection of the central nervous system was defined as a leukocyte count of >100 cells $\times 10^6/L$ in

CSF. During the first hours after admission, shock was defined prospectively as a systolic blood pressure of <100 mm Hg in patients >14 yrs of age, <85 mm Hg in children <14 yrs of age, and <75 mm Hg in patients <4 yrs of age. Demographics of the patients are given in Table 1. Four patients in group B and all patients in group C underwent plasma or whole blood exchange (12). In patients with a body weight of <25 kg, 50 to 60 mL of whole blood/kg were exchanged each session. In patients with body weight of ≥ 25 kg 30 to 40 mL plasma/kg were exchanged with fresh frozen plasma each session. The exchange was started

as soon as possible after admission and was repeated after 12 hrs. When the patients' condition remained critical, the exchange was repeated 24 and 48 hrs later.

After admission, serum samples were collected serially during the first day and each following day. Blood was allowed to clot before centrifugation, and serum was stored at $-20^\circ C$ until tested. Samples were also taken directly before and after the exchange of plasma or blood.

Soluble IL-6 receptor and IL-6 concentrations were determined by enzyme-linked immunosorbent assays (ELISAs) (17). These ELISAs are not influenced by the presence of soluble IL-6 receptor in the IL-6 ELISA or IL-6 in the soluble IL-6 receptor ELISA (17). Detection limits for the IL-6 ELISA and the soluble IL-6 receptor ELISA were 20 pg/mL, and 0.4 ng/mL, respectively. Concentrations in normal volunteers for IL-6 and soluble IL-6 receptor are <20 pg/mL and 76.6 ± 19.3 (SD) ng/mL, respectively (17).

Statistical Analysis. Differences between groups were calculated with the Wilcoxon rank-sum test. Differences were considered significant with a two-tailed p value of $<.05$. Relationships between IL-6 and soluble IL-6 receptor were calculated using the Spearman correlation coefficient.

Table 1. Patient demographics

	Group A (n = 13)	Group B (n = 5)	Group C (n = 5)
Male/female	5/8	3/2	4/1
Age ^a (yr)	15 (2-64)	15 (0-17)	8 (2-18)
Prehospital disease period ^a (hr)	23.5 (12.5-84)	14 (5-30)	14 (7-16.5) ^b
Mortality (n)	1	1	2
PE/BE (n/n)	0/0	3/1	3/2
Leukocytes in CSF ^a ($10^6/L$)	21674 (3900-70000)	417 (107-6000) ^b	14 (1-45) ^{b,c}

Group A, meningococcal infection of the central nervous system without shock; Group B, meningococcal infection of the central nervous system with shock; Group C, meningococcal infection of the central nervous system with shock but no signs of inflammation of the central nervous system; PE, plasma exchange; BE, blood exchange; CSF, cerebrospinal fluid.

^aMedians, with ranges in parentheses; ^bsignificantly different from group A; ^csignificantly different from group B.

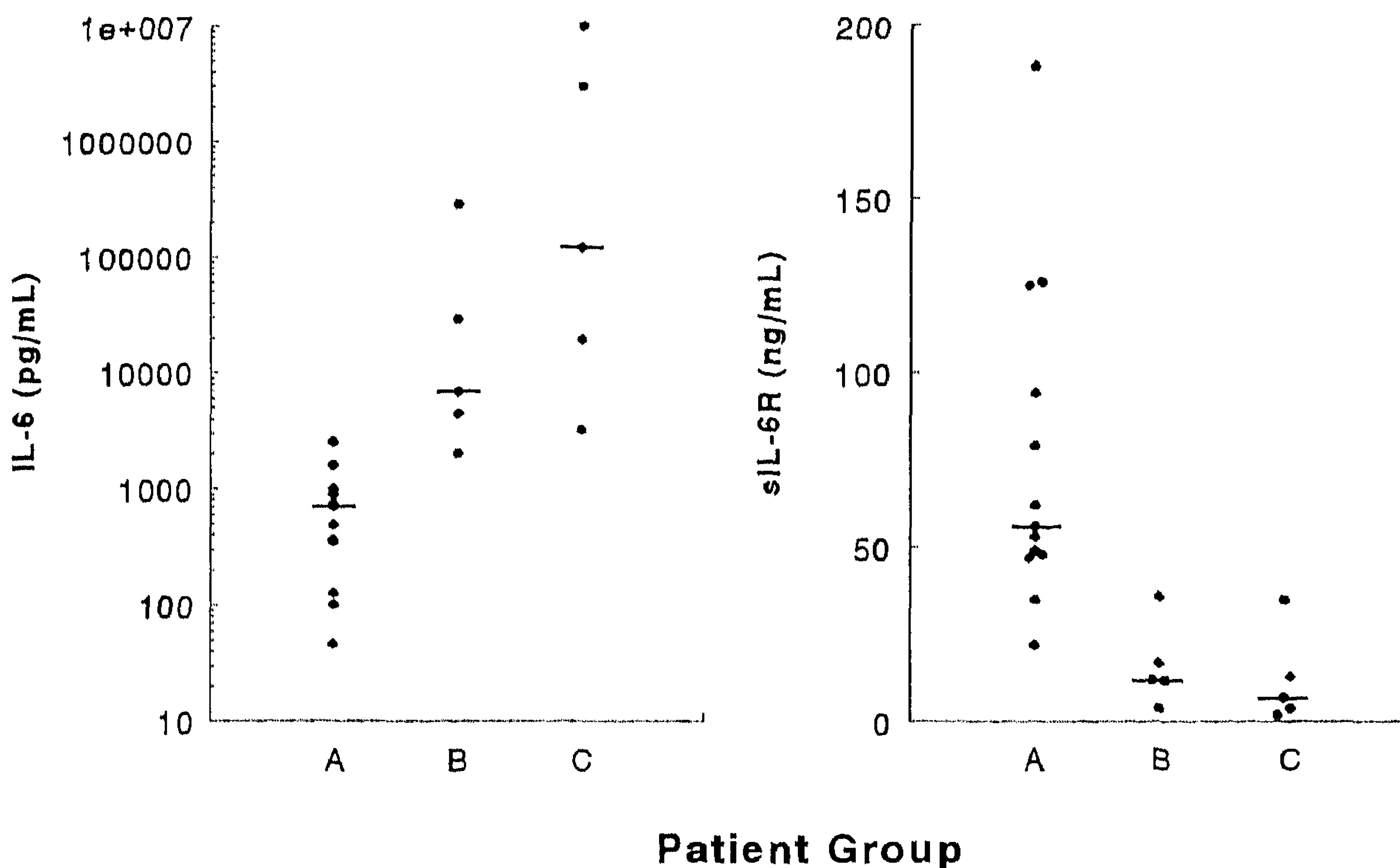


Figure 1. Peak concentrations for interleukin-6 (IL-6) and soluble interleukin-6 receptor (sIL-6R) of each individual patient; medians are indicated (A vs. B, and A vs. C: $p < .001$). Group A, meningococcal infection of the central nervous system without shock; group B, meningococcal infection of the central nervous system with shock; group C, meningococcal infection of the central nervous system with shock but no signs of inflammation of the central nervous system.

RESULTS

Figure 1 shows the peak concentrations of IL-6 and concomitant soluble IL-6 receptor concentration for each individual patient subdivided into the three groups. Median IL-6 peak concentrations were 703 pg/mL, 6942 pg/mL, and 120,800 pg/mL in group A (meningococcal infection of the central nervous system without shock), group B (meningococcal infection of the central nervous system with shock), and group C (meningococcal infection of the central nervous system with shock but no signs of inflammation of the central nervous system), respectively. For soluble IL-6 receptor, the concentrations were 56 ng/mL in group A, 12 ng/mL in group B, and 7 ng/mL in group C. The peak values for IL-6 differed significantly between groups A and B ($p = .0009$), and groups A and C ($p = .0002$), but not between groups B and C ($p = .31$). For soluble

IL-6 receptor concentrations, the differences between groups A and B, and groups A and C were significant ($p = .0009$ and $.0005$, respectively). There was no statistically significant difference between groups B and C ($p = .42$).

All patients in each group had detectable IL-6 concentrations on entry in the study which gradually decreased during recovery. In contrast, soluble IL-6 receptor concentrations were low on admission and increased to supra-normal concentrations before leveling off to normal concentrations. IL-6 concentrations returned to normal after ~48 hrs. Soluble IL-6 receptor concentrations, however, returned to normal ranges only after 120 to 160 hrs.

There was a strong negative correlation between IL-6 and soluble IL-6 receptor concentrations. For the peak concentration of IL-6 and its relationship with soluble IL-6 receptor concentration, the Spearman correlation coefficient was -0.82 .

Figure 2 shows the patterns of IL-6 and Figure 3 illustrates the patterns of soluble IL-6 receptor values over time in all patients of each group. In patients who underwent plasma or whole blood exchange, the sessions are indicated by thick lines. Soluble IL-6 receptor concentration is temporarily increased after a plasma or whole blood exchange session. At the onset of the disease, when IL-6 concentrations are high, this increase of soluble IL-6 receptor concentration is quickly nullified. At low IL-6 concentrations, the effect of plasma exchange is followed by an increase in the soluble IL-6 receptor concentration. This phenomenon can be visualized by the calculation of the change of soluble IL-6 receptor concentration per hour after an exchange session by the following formula: $(\text{soluble IL-6 receptor})_B - (\text{soluble IL-6 receptor})_A / \text{hrs}$ between A and B, where $(\text{soluble IL-6 receptor})_A$ is the concentration of soluble IL-6 receptor in ng/mL measured just after an exchange session, and $(\text{soluble IL-6 receptor})_B$ is the concentration of soluble IL-6 receptor in ng/mL measured in the next sample after A. Negative changes, therefore, mean that the soluble IL-6 receptor concentration decreases after an exchange session. Positive changes indicate that the soluble IL-6 receptor concentration increases after the exchange session.

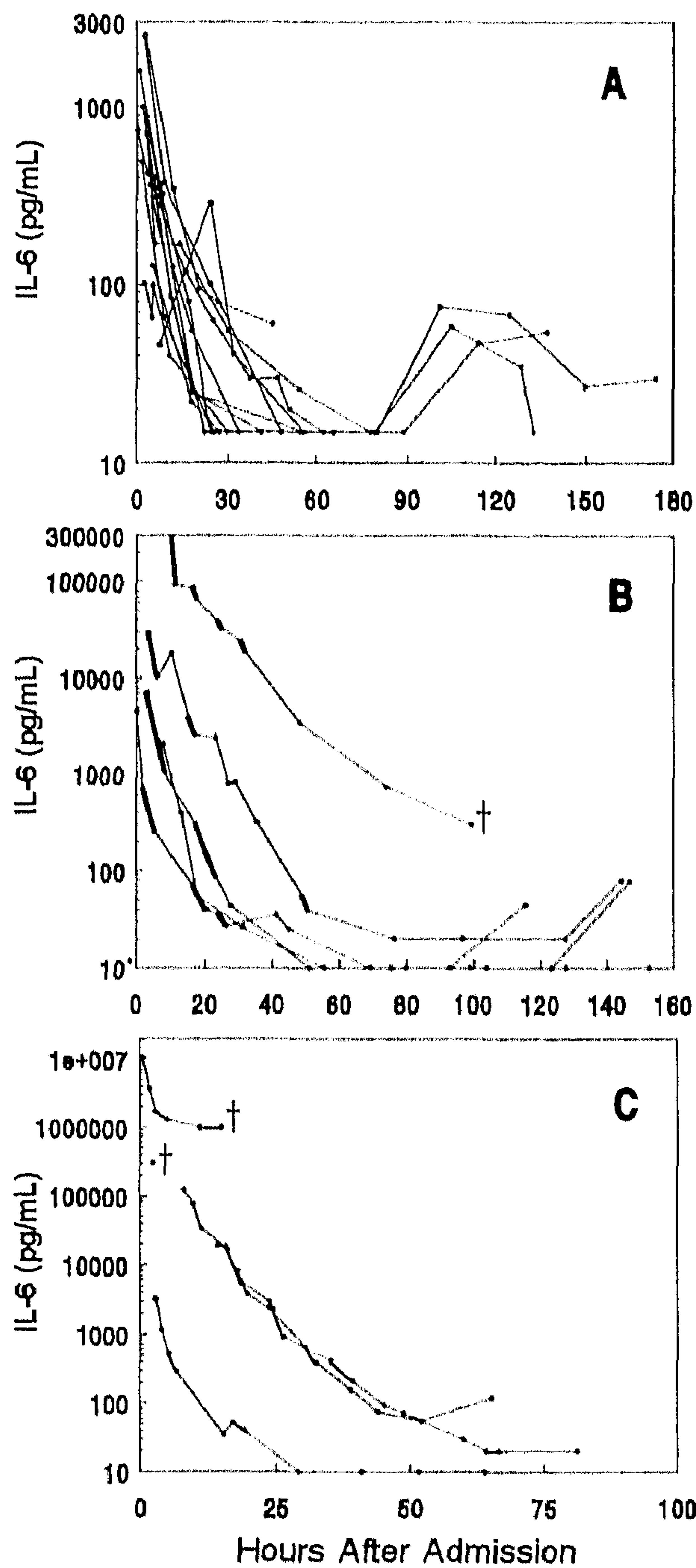


Figure 2. Patterns of interleukin-6 (IL-6) reactivity of all patients in groups A, B, and C. Solid lines indicate plasma or whole blood exchange sessions. Group A, meningococcal infection of the central nervous system without shock; group B, meningococcal infection of the central nervous system with shock; group C, meningococcal infection of the central nervous system with shock but no signs of inflammation of the central nervous system.

Figure 4 shows the calculated changes in relation to the IL-6 concentration at point A. The Spearman correlation coefficient is -0.81 ($p < .0001$).

DISCUSSION

Our data confirm previous studies showing increasing IL-6 concentrations with increasing severity of disease (group C > B > A) (3). In contrast, increasing severity of meningococcal disease is negatively correlated with soluble IL-6 receptor concentrations. A strong negative correlation is found between IL-6 and soluble IL-6 receptor

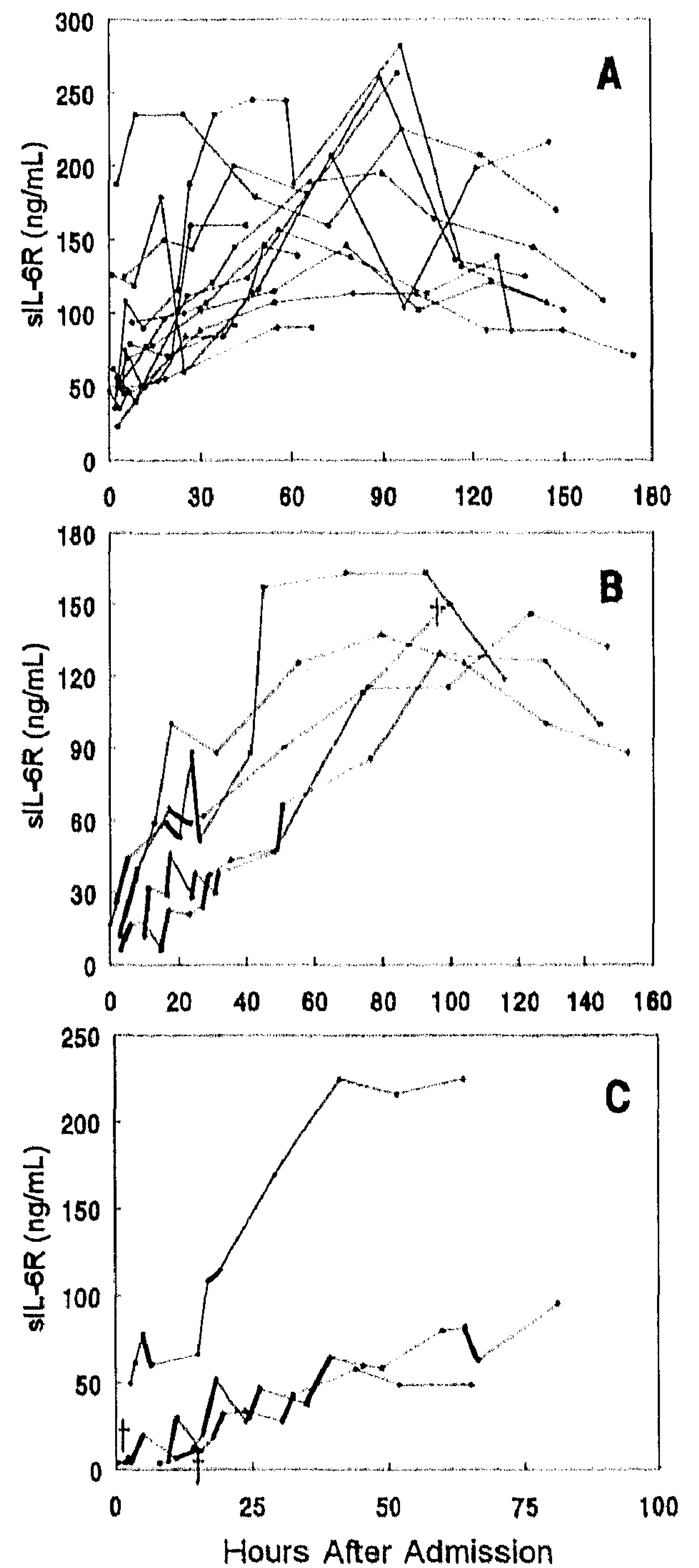


Figure 3. Patterns of soluble interleukin-6 receptor (sIL-6R) of all patients in groups A, B, and C. Solid lines indicate plasma or whole blood exchange sessions. Group A, meningococcal infection of the central nervous system without shock; Group B, meningococcal infection of the central nervous system with shock; Group C, meningococcal infection of the central nervous system with shock but no signs of inflammation of the central nervous system.

concentrations, indicating a close relation of these two parameters.

Recently, we (18) reported that the soluble IL-6 receptor concentration was decreased in patients with sepsis compared with healthy humans. Here, we confirm this finding for patients with meningococcal infection. Patients from group A without septic symptoms also showed low concentrations of soluble IL-6 receptor, indicating that sepsis is not obligatory for soluble IL-6 receptor values to be decreased. The concentration of IL-6 appears to be the main determinant for the soluble IL-6 receptor concentration, which is

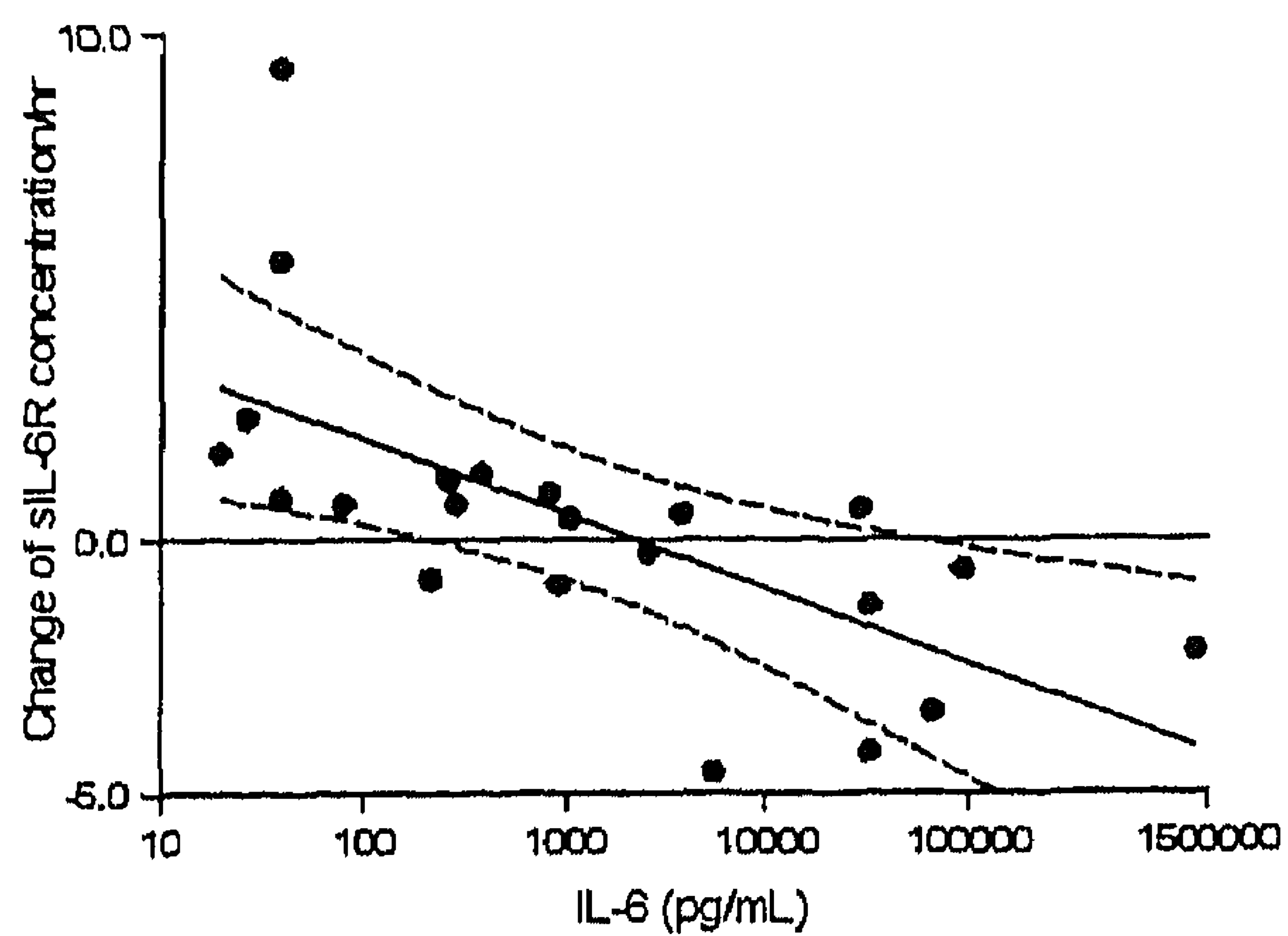


Figure 4. Change of soluble IL-6 receptor (*sIL-6R*) concentration per hour (for the formula, see the Results section) after a plasma or whole blood exchange session related to the interleukin-6 (*IL-6*) concentration. Dashed lines indicate the 95% confidence interval.

in agreement with the negative correlation between concentrations of IL-6 and soluble IL-6 receptor (Figs. 2 and 3).

The supranormal concentrations of soluble IL-6 receptor that we see in patients with undetectable concentrations of IL-6 could be explained by a delay in the regulation of soluble IL-6 receptor concentrations. Assuming that under conditions with high IL-6 concentrations, soluble IL-6 receptor or IL-6/soluble IL-6 receptor complexes are rapidly cleared from the circulation, a counter regulation starts leading to increased production or shedding of soluble IL-6 receptor. Temporarily increased soluble IL-6 receptor concentrations may be the result of continuing high IL-6 production and reduced clearance of soluble IL-6 receptor.

The concentrations of soluble IL-6 receptor in the patients undergoing plasma or whole blood exchange are markedly increased after an exchange session. This finding can be explained by the fact that plasma with a relatively low concentration of soluble IL-6 receptor is partially replaced with plasma containing normal concentrations of soluble IL-6 receptor. Plasma soluble IL-6 receptor concentration of one patient, for instance, was 5 ng/mL before and 30 ng/mL after the first plasma exchange session with 2400 mL of fresh frozen plasma. If the mixture of donor blood with the patient's blood after each portion is taken into account, and the plasma soluble IL-6 receptor concentration of the donor blood is estimated to be 80 ng/mL, the concentration in the

patients plasma would be ± 65 ng/mL at the end of the session. The difference with the actual concentration could be the result of ongoing clearance of soluble IL-6 receptors in either free or complexed form with IL-6. Plasma or whole blood exchange did not significantly influence the IL-6 concentration. It needs to be determined whether the increase in soluble IL-6 receptor concentrations is of benefit for the patient, because an increase of the biological activity of IL-6 by binding to soluble IL-6 receptors may be harmful to the patient. However, beneficial effects of plasma or whole blood exchange have been reported. High concentrations of cytokines may not be the one and only determinant for the outcome of sepsis patients, as suggested by lack of efficacy of cytokine antagonists in clinical trials (19).

After an exchange session, the soluble IL-6 receptor concentration rapidly decreases, which indicates that the turnover of soluble IL-6 receptor is high. The rate of decrease is dependent on the IL-6 concentration. In an early phase of the illness with high IL-6 concentrations, soluble IL-6 receptors are more quickly cleared from the exchanged plasma than in a later phase when plasma IL-6 concentrations are low. At low IL-6 concentrations, soluble IL-6 receptor concentrations do not further decrease but increase after an exchange session. This finding indicates that IL-6 is an important factor for the clearance of soluble IL-6 receptor. *In vitro* studies, however, are not conclusive about the effect of IL-6 on the IL-6 receptor expression or soluble IL-6 receptor production. Some reports (20, 21) indicated a decrease of the expression of IL-6 receptor, but another report (22) showed no effect. These studies (20–22) were performed on different cell types under different experimental conditions. Very little is known about the mode of clearance of the soluble IL-6 receptor. Minute amounts of soluble IL-6 receptor are found in the urine, and moderate renal impairment does not influence the soluble IL-6 receptor concentration (17). However, preliminary results in patients with almost absent renal function do indicate a role for the kidneys in maintaining soluble IL-6 receptor concentrations (Frieling et al., unpublished observation).

To our knowledge, this study is the first report to strongly point to an important role for IL-6 in maintaining soluble IL-6 receptor concentrations and in clearance of the soluble IL-6 receptor in patients. Studies on the underlying mechanisms, however, still have to be done.

REFERENCES

- Giraud T, Dhainaut J-F, Schremmer B, et al: Adult overwhelming meningococcal purpura. A study of 35 cases 1977–1989. *Arch Intern Med* 1991; 151: 310–316
- Van Deuren M, Van der Ven-Jongekrijg J, Bartelink AKM, et al: Correlation between proinflammatory cytokines and antiinflammatory mediators and the severity of disease in meningococcal infections. *J Infect Dis* 1995; 172: 433–439
- Waage A, Brandtzaeg P, Halstensen A, et al: The complex pattern of cytokines in serum from patients with meningococcal septic shock. *J Exp Med* 1989; 169:333–338
- Hack CE, De Groot ER, Felt-Bersma RJF, et al: Increased plasma levels of interleukin-6 in sepsis. *Blood* 1989; 74:1704–1710
- Girardin E, Roux-Lombard P, Grau GE, et al: Imbalance between tumour necrosis factor- α and soluble TNF receptor concentrations in severe meningococcaemia. *Immunology* 1992; 76:20–23
- Van Zee KJ, Kohno T, Fischer E, et al: Tumor necrosis factor soluble receptors circulate during experimental and clinical inflammation and can protect against excessive tumor necrosis factor- α *in vitro* and *in vivo*. *Proc Natl Acad Sci USA* 1992; 89:4845–4849
- Aderka D, Engelmann H, Maor Y, et al: Stabilization of the bioactivity of tumor necrosis factor by its soluble receptors. *J Exp Med* 1992; 175:323–329
- Müllberg J, Schooltink H, Stoyan T, et al: The soluble interleukin-6 receptor is generated by shedding. *Eur J Immunol* 1993; 23:473–480
- Lust JA, Donovan KA, Kline MP, et al: Isolation of an mRNA encoding a soluble form of the human interleukin-6 receptor. *Cytokine* 1992; 4:96–100
- Mackiewicz A, Schooltink H, Heinrich P, et al: Complex of soluble human IL-6-receptor/IL-6 upregulates expression of acute phase proteins. *J Immunol* 1992; 149:2021–2027
- Gaillard J-P, Bataille R, Brailly H, et al: Increased and highly stable levels of functional soluble interleukin-6 receptor in sera of patients with monoclonal gammopathy. *Eur J Immunol* 1993; 23: 820–824
- Van Deuren M, Santman FW, Van Dalen R, et al: Plasma and whole blood

- exchange in meningococcal sepsis. *Clin Inf Dis* 1992; 15:424-430
13. Janbon B, Vuillez J, Carpentier F, et al: Removal of circulating tumor necrosis factor. Its role in septic shock treatment. *Ann Med Interne* 1992; 143(Suppl 1): 13-16
 14. Brandtzæg P, Sirnes K, Folsland B, et al: Plasmapheresis of severe meningococcal septicaemia with DIC and fibrinolysis. *Scand J Clin Lab Invest* 1985; 45(Suppl 178):53-55
 15. BJORVATN B, BJERTNAES L, FADNES HO, et al: Meningococcal septicaemia treated with combined plasmapheresis and leukapheresis or with whole blood exchange. *BMJ* 1984; 288:439-441
 16. Halstensen A, Pedersen SHJ, Haneberg B, et al: Case fatality of meningococcal disease in western Norway. *Scand J Infect Dis* 1987; 19:35-42
 17. Frieling JTM, Sauerwein RW, Wijdenes J, et al: Soluble interleukin-6 receptor in biological fluids from human origin. *Cytokine* 1994; 6:376-381
 18. Frieling JTM, Van Deuren M, Wijdenes J, et al: Circulating interleukin-6 receptor in patients with sepsis syndrome. *J Infect Dis* 1995; 171:469-472
 19. Suffredini AF: Current prospects for the treatment of clinical sepsis. *Crit Care Med* 1994; 22:S12-S18
 20. Hoffmann R, Henninger H-P, Schulze-Specking A, et al: Regulation of interleukin-6 receptor expression in rat Kupffer cells: Modulation by cytokines, dexamethasone and prostaglandin E₂. *J Hepatol* 1994; 21:543-550
 21. Bauer J, Bauer TM, Kalb T, et al: Regulation of interleukin 6 receptor expression in human monocytes and monocyte derived macrophages. *J Exp Med* 1989; 170:1537-1549
 22. Schoester M, Heinrich PC, Graeve L: Regulation of interleukin-6 receptor expression by interleukin-6 in human monocytes—A re-examination. *FEBS Lett* 1994; 345:131-134

SCCM PRACTICE PARAMETERS

A publication containing the complete unabridged documents of **Practice Parameters for Intravenous Analgesia and Sedation for Adult Patients in the Intensive Care Unit** and **Practice Parameters for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient** is available for purchase from the Society of Critical Care Medicine for \$40 plus \$5 for shipping and handling charges (SCCM membership discount applies).

Order Form for SCCM Practice Parameters

Name _____

Mailing Address _____

City _____

State/Province _____

Zip/Postal Code _____

Country _____

(Area) Daytime Phone _____

(Area) Fax Number _____

Check # _____

Am. Express MasterCard Visa

Credit Card No. _____

Expir. Date _____

Signature _____

Mail to: SCCM, 8101 E. Kaiser Boulevard, Suite 300, Anaheim, CA 92808-2259. Phone: (714) 282-6056. Fax: (714) 282-6050.