C-Reactive Protein Kinetics after Major Surgery

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BACKGROUND: Diagnosis of sepsis in the postoperative period is a challenge. Measurements of inflammatory markers, such as C-reactive protein (CRP), have been proposed in medical patients, but the interpretation of these values in surgical patients is more difficult. We evaluated the changes in blood CRP levels and white blood cell count in postoperative patients with and without infection.

METHODS: All patients admitted to our 34-bed Department of Intensive Care after major (elective or emergency) cardiac, neuro-, vascular, thoracic, or abdominal surgery during a 4-month period were prospectively included. Patients were screened daily and characterized as infected or noninfected. CRP levels and white blood cell counts were recorded daily in all patients for up to 7 days after the surgical intervention.

RESULTS: Of the 151 patients enrolled, 115 underwent elective surgery and 36 emergency surgery; cardiac surgery was performed in 49 patients, neurosurgery in 65, abdominal surgery in 25, vascular surgery in 7, and thoracic surgery in 5. In noninfected patients (n = 117), mean CRP values increased from baseline to postoperative day (POD) 3 ($P < 0.0001$, estimated mean difference [EMD] = 99.7 mg/L [95% confidence interval, 85.6–113.8]) and then decreased until POD 7 but remained higher than the level at baseline ($P < 0.0001$, EMD = 49.2 mg/L [95% confidence interval, 27.1–71.2]). Postoperative infection occurred in 20 patients (13.2%). In these patients, CRP values were already higher on POD 1 than in noninfected patients ($P = 0.0054$).

CONCLUSIONS: CRP levels increase in the first week after major surgery but to a much larger extent in infected than in noninfected patients. Persistently high CRP levels after POD 4, especially when >100 mg/L, suggest the presence of a postoperative infection. (Anesth Analg 2014;XXX:00–00)

Sepsis is a major complication in critically ill surgical patients despite the use of modern antibiotics and resuscitation therapies.[1] The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, humoral and cellular reactions, and circulatory abnormalities. Biomarkers are important in evaluating this process and can help identify the presence of sepsis and assess its severity.[2]

Many biomarkers have been proposed to help establish an early diagnosis in sepsis, including C-reactive protein (CRP), procalcitonin (PCT),[3] interleukin-6,[4] interleukin-8,[4] neopterin,[5] and expression of cellular receptors, such as CD64,[6] among many others.[7] Of these, CRP, an acute-phase protein synthesized by the liver, is one of the most routinely measured and widely used biomarkers.

CRP has been used for many years as an inflammatory marker of sepsis[8,9] and is considered sensitive but not specific for sepsis. Indeed, CRP levels also increase in response to trauma, ischemia, burns, and other inflammatory conditions.[10] Hence, it may be difficult to use CRP to differentiate sepsis from other noninfectious causes of inflammation after surgical trauma. Nevertheless, measurement of CRP levels is widely available and inexpensive, and elevated serum CRP concentrations are correlated with an increased risk of organ failure and death.[9] Although CRP levels are often used as a diagnostic marker of sepsis and a severity marker in medical patients, their interpretation in surgical patients is more controversial.[11–14] There are remarkably few data about changes in CRP during the postoperative period. The aim of this study was, therefore, to prospectively study the changes in CRP levels in patients admitted to the intensive care unit (ICU) after major surgery according to the presence of infection and the type of surgery. We hypothesized that levels of this biomarker would remain elevated longer in patients with than in those without infection.

METHODS

The study was approved by the Institution Ethics Committee, which waived the need for informed consent in view of the noninterventional nature of the study.

Study Population

Over a 4-month period (May–August 2011), we prospectively enrolled all consecutive postoperative patients admitted to our 34-bed Department of Intensive Care after elective or emergency major neurosurgery, cardiac surgery, abdominal surgery, thoracic surgery, or vascular surgery. Exclusion criteria were: age younger than 18 years, medical admission, laparoscopic interventions, polytrauma, and organ transplantation (Fig. 1).

An Acute Physiology and Chronic Health Evaluation II score was calculated for the first 24 hours, and a Sequential

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Accepted for publication March 13, 2014.

Funding: No external funding.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000000263

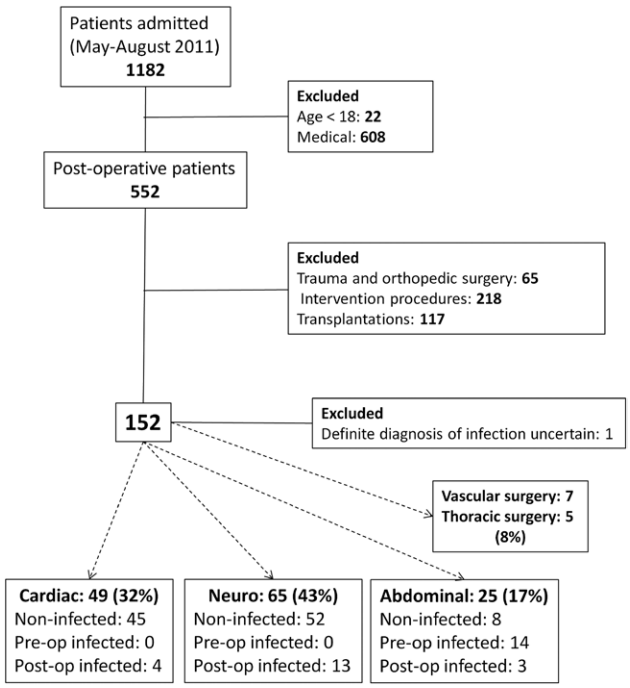

Figure 1. Patient population (flow chart).

Organ Failure Assessment score was determined daily for up to 1 week. As is routine in our department, blood CRP values and white blood cell (WBC) counts were measured daily for up to 1 week after the surgical intervention during the ICU stay or on the regular ward for patients who were discharged from the ICU. For the same time period, that is, up to 1 week after surgical intervention, patients were characterized into those with and those without infection, according to the International Sepsis Forum (ISF) Consensus Conference on Definitions of Infection in the ICU[15]; this characterization was verified by an infectious disease consultant. Infected patients were further classified into those who developed infection preoperatively and those in whom infection developed postoperatively.

Statistical Analysis

Statistical analyses were performed using SPSS® Statistics 22 for Windows (IBM, Armonk, NY). Continuous variables are presented as mean ± standard deviation (SD) or median [25%–75% interquartile range (IQR)] and categorical variables as number and percentage (%). Mixed-effects polynomial regression models with restricted maximum likelihood (REML) estimation and first-order autoregressive (AR1) covariance structure were used to examine the differences in CRP levels and WBC counts between noninfected and infected patient groups at 8 time points: daily from baseline (operation day) to postoperative day (POD) 7. Because the trajectories of CRP level and WBC count were unlikely to follow a straight line, we considered up to the third-degree polynomial models of day so that the effects of day, day^2, and day^3 on CRP level and WBC count were tested as fixed effects. Interaction effects between groups and day, day^2, and day^3 were also tested. No correction was performed for the multiple comparisons test made across the groups for each day or between days within groups. Model checking was performed by inspection of residual and normal plots. After the general analysis for all patients, we performed a separate analysis for the subgroups of patients who had undergone cardiac surgery, neurosurgery, or abdominal surgery. Sensitivity, specificity, and their approximate 95% confidence intervals (CIs) were computed for CRP. The optimal cut off for CRP levels for diagnosis of infection was chosen using a receiver operating characteristic curve (ROC) analysis and identifying the maximal Youden's index. All tests were 2 sided, and $P < 0.05$ was considered statistically significant.

Table 1. Clinical Data on Admission to the Intensive Care Unit (ICU)

No. patients	151
Age (y)	60 ± 16
APACHE II score, median [IQR]	9 [6–11]
SOFA score, median [IQR]	4 [2–6]
ICU mortality	9 (7%)
Postoperative infection	20 (13%)
No infection	117 (78%)
Preoperative infection	14 (9%)
Type of surgery: elective/emergency	115 (76%)/36 (24%)

SOFA = sequential organ failure assessment; APACHE II = acute physiology and chronic health evaluation II.

RESULTS

One hundred fifty-two patients were initially enrolled in the study. In 1 patient, it was not possible to determine whether he was infected because he met some clinical criteria for infection, but all microbiology results were negative, raising doubts about the diagnosis, so the patient's data were deleted from the analysis. The baseline characteristics of the remaining 151 patients are presented in Table 1: 49 patients (32%) underwent cardiac surgery, 65 (43%) neurosurgery, 25 (17%) abdominal surgery, 7 (5%) vascular surgery, and 5 (3%) thoracic surgery (Fig. 1). The subgroups of vascular and thoracic postoperative patients were not considered for the subgroup analysis but only for the general population analysis because of the small number of patients enrolled in these 2 groups.

Patients Without Infection

In the 117 patients who had no infection during the study period, mean CRP values increased from baseline to POD 3 ($P < 0.0001$, estimated mean difference [EMD] = 99.7 mg/L [95% CI, 85.6–113.8]) and then decreased until POD 7 but remained higher than the level at baseline ($P < 0.0001$, EMD = 49.2 mg/L [95% CI, 27.1–71.2]) (Fig. 2A). The WBC count increased until POD 1 ($P < 0.0001$, EMD = 2.15×10^3/mm^3 [95% CI, 1.60–2.70]) and then decreased to baseline values by POD 7, (P day 7 vs day 0 = 0.0789, EMD = -1.39×10^3/mm^3 [95% CI, −2.94 to −1.61]) (Fig. 2B).

Patients with Postoperative Infections

Twenty patients developed a postoperative infection, a median of 2 [2–4] days after surgery. In these patients, CRP levels increased from baseline to POD 7 ($P < 0.0001$, EMD = 117.9 mg/L [95% CI, 77.9–157.8]). CRP values in

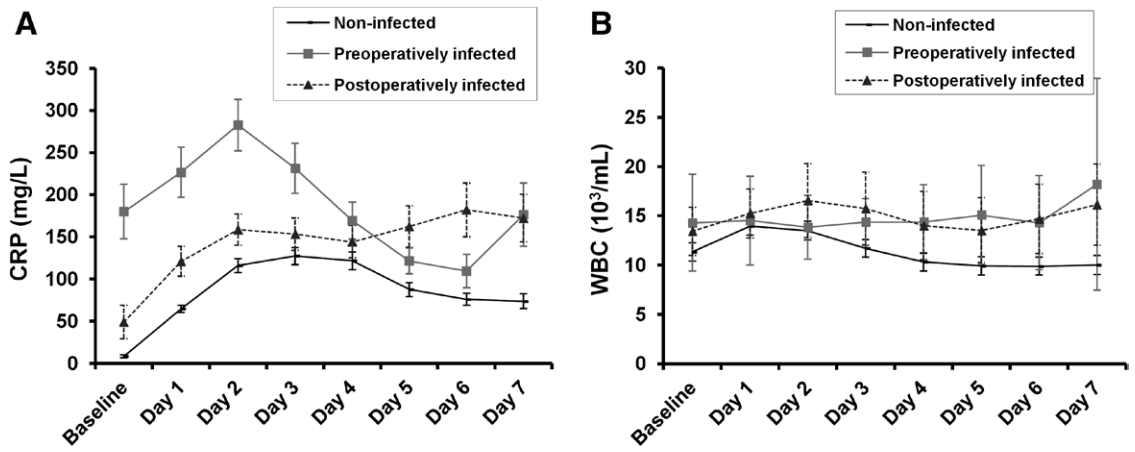

Figure 2. C-reactive protein (CRP), levels (A) and white blood cell (WBC) count (B) in noninfected patients, and patients with pre- and postoperative infections (mean [95% CI]). Values of CRP at baseline were different for the 3 groups ($P < 0.0001$). There was no statistically significant difference at the 5% level in the WBC count at baseline among the 3 groups ($P = 0.078$). Changes in CRP levels and WBC count over time were nonlinear (all P values for day, day^2, and day^3 <0.0001). The rate of change for CRP levels and for WBC count differed for the 3 groups as indicated by the P values for the 3 covariate day by group interactions (for CRP 0.304, 0.001, and 0.0002, respectively, and for WBC 0.0051, 0.0042, and 0.0271, respectively).

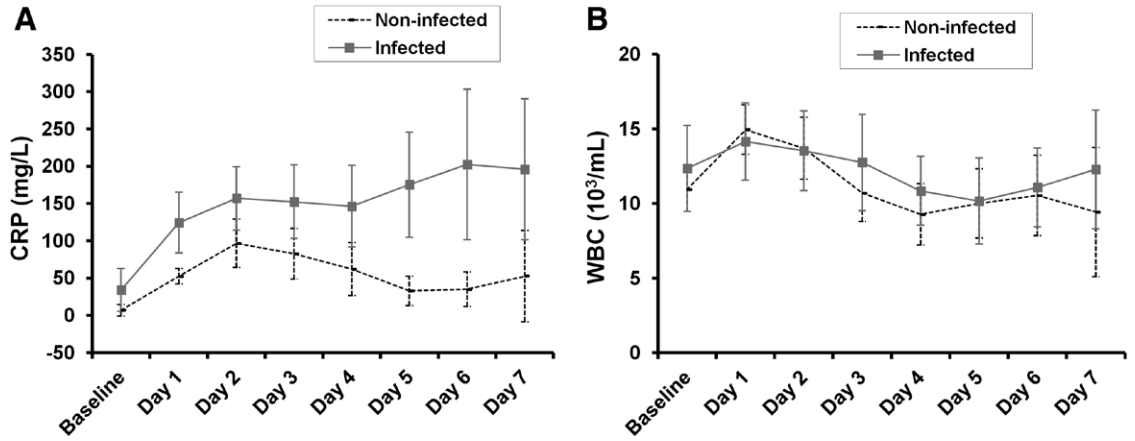

Figure 3. C-reactive protein (CRP), levels (A) and white blood cell (WBC) count (B) in infected and noninfected neurosurgical patients (mean [95% CI]). Values of CRP ($P = 0.095$) and WBC ($P = 0.396$) at baseline were not statistically different for the 2 groups. Changes in CRP levels and WBC count over time were nonlinear (all P values for day, day^2, and day^3 <0.0001). In addition, the rate of change for CRP differed between the groups (days by group interaction $P < 0.0001$). However, the rate of change for WBC was not different between the 2 groups (all P values for days by group interaction were >0.05).

these patients were significantly higher than in noninfected patients on PODs 1 ($P = 0.0054$) and 2 ($P = 0.0014$) and from POD 5 (all $P < 0.0001$) (Fig. 2A). From POD 5, a cutoff CRP value of 100 mg/L had a specificity of 64% (approximate 95% CI, 50%–76%) and a sensitivity of 69% (approximate 95% CI, 51%–81%) for diagnosis of postoperative infection.

In 13 patients who developed a postoperative infection after neurosurgery (median at 2 [2–4] days after surgery), CRP levels increased until POD 7 ($P < 0.0001$, EMD = 153.4 mg/L [95% CI, 103.4–203.4]) (Fig. 3A). CRP levels were higher in infected than in noninfected patients from POD1 ($P = 0.0023$, EMD = 52.8 mg/L [95% CI, 19.3–86.3]) through POD 7 ($P < 0.0001$, EMD = 172.1 mg/L [95% CI, 126.7–217.5]). A cutoff CRP value of 104 mg/L on POD 1 had a sensitivity of 62% (approximate 95% CI, 32%–86%) and a specificity of 94% (approximate 95% CI, 84%–99%) for diagnosis of infection. The differences in WBC count between infected and noninfected patients were not significant (Fig. 3B).

Among the 25 patients who underwent abdominal surgery, 3 developed a postoperative infection; their CRP levels were higher than in the 8 noninfected patients at baseline ($P = 0.0378$, EMD = 140.3 mg/L [95% CI, 009.2–270.8]).

Four patients developed an infection a median of 4 [3–6] days after cardiac surgery. There were no significant differences in CRP levels between these patients and the 45 noninfected cardiac surgery patients (Fig 4A). The WBC count was higher in infected than in noninfected patients from POD 2 ($P = 0.0188$, EMD = 5.0×10^3/mm^3 [95% CI, 0.9–9.1]) through POD 7 ($P < 0.0001$, EMD = 9.5×10^3/mm^3 [95% CI, 4.5–14.4]) (Fig 4B).

Patients with Preoperative Infections

Preoperative infection was present only in the patients who underwent abdominal surgery. In this subgroup, 14 patients were already infected at the time of surgery and had higher CRP levels than the noninfected patients of the

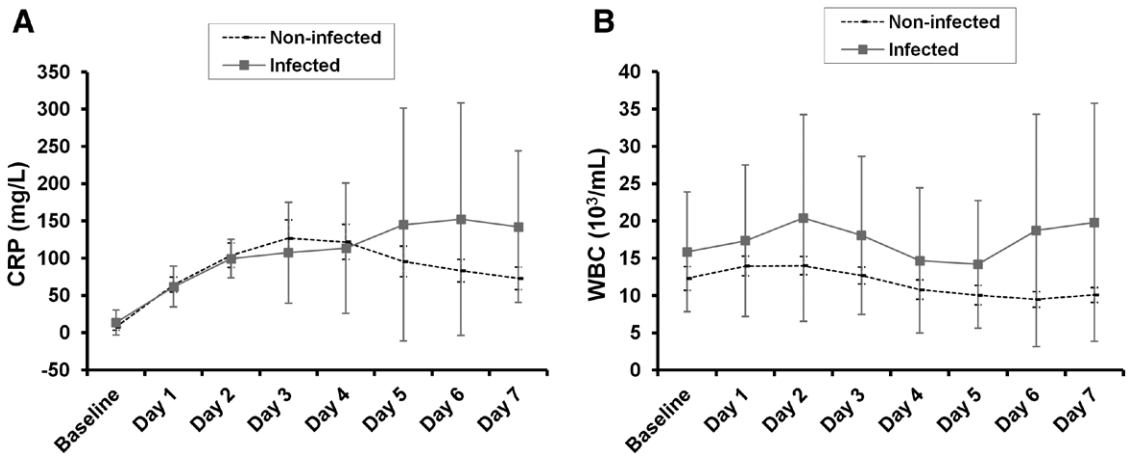

Figure 4. C-reactive protein (CRP) (A) and white blood cell (WBC) (B) levels in infected and noninfected cardiac surgery patients (mean [95% CI]). Values of CRP (P = 0.104) and WBC (P = 0.200) at baseline were not statistically different for the 2 groups. Changes in CRP levels and WBC count over time were nonlinear (all P values for day, day^2, and day^3 <0.0001). In addition, the rate of change for CRP did not differ between the groups (all P values for days by group interactions were <0.05). However, the rate of change for WBC between the groups was statistically significant at the 5% level (days by group interaction P = 0.045).

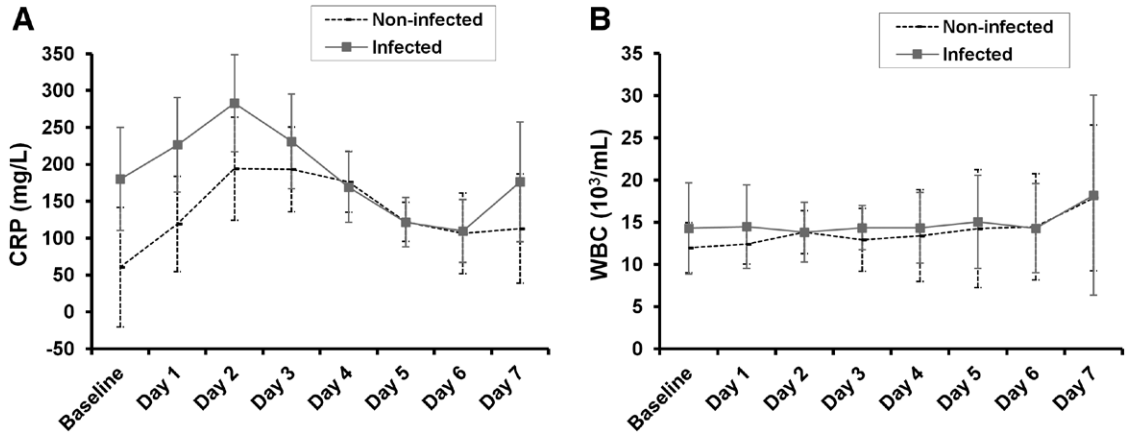

Figure 5. C-reactive protein (CRP) (A) and white blood cell (WBC) (B) levels in noninfected and preoperatively infected abdominal surgery patients (mean [95% CI]). Values of CRP at baseline were statistically different for the 2 groups (P = 0.0005). Changes in CRP levels over time were nonlinear (all P values for day, day^2, and day^3 <0.0001). In addition, the rate of change for CRP differed between the groups as indicated by the P values for the days by group interactions (0.0082 for day by group and 0.0280 for day^2 by group). However, the WBC count did not change over time.

same subgroup at baseline (P = 0.0005, EMD = 143.1 mg/L [95% CI, 064.9–221.3]) and at POD 1 (P = 0.01, EMD = 91.0 mg/L [95% CI, 23.2–158.9]) (Fig 5A). At baseline, a cutoff CRP value of 72 mg/L had a sensitivity of 75% (approximate 95% CI, 48%–93%) and a specificity of 89% (approximate 95% CI, 52%–98%) for diagnosis of infection. There were no significant differences in WBC count between infected and noninfected patients (Fig 5B).

DISCUSSION

Diagnosis of postoperative infection after major surgery is a challenge. Fever and other clinical signs and symptoms reflecting an inflammatory response are not specific, and microbiological results are often not immediately available. The use of a biomarker may help detect and guide treatment of these complications. CRP levels are often used in medical patients[16] with reasonable sensitivity and specificity. These levels also have prognostic value, being correlated with severity scores, including the Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores.[17]

A major surgical intervention always triggers a significant inflammatory response; hence, the value of CRP for identifying sepsis in postoperative patients has been challenged, with some data demonstrating good accuracy of CRP for identifying sepsis,[11,12,18–20] and others not.[13,14,21,22] In the abdominal surgery setting, Kørner et al.[11] reported that CRP had good sensitivity (82%) and specificity (73%) for identifying infection after colorectal resection. Similarly, in patients after esophagogastric cancer resection, Dutta et al.[12] demonstrated that on POD 3, a CRP value higher than 180 mg/L was associated with development of an anastomotic leak associated with a surgical site infection, with 82% sensitivity and 63% specificity. However, Cicarelli et al.[13] reported no correlation between CRP and diagnosis of infection among 54 postoperative patients; plasma CRP concentrations were larger than 100 mg/L during the 7-day observation period in infected and noninfected patients. In

contrast, our results showed a significant difference in CRP values between noninfected patients and those with infection. CRP levels increased in all patients during the first few days after surgery but were higher in infected than in noninfected patients throughout the first 7 days. Moreover, in noninfected patients, levels decreased to < 110 mg/L after the fourth POD but remained substantially higher in infected patients.

The infection rate after cardiac surgery was relatively low, but infection may be particularly difficult to recognize in these patients because of the presence of a marked inflammatory response after cardiac surgery.[23] Sponholz et al.[24] demonstrated that PCT may be of more value for diagnosing infection in these patients than other inflammatory markers, including CRP. However, Nahum et al.[25] identified the CRP velocity trend as an important marker of infection in children after cardiac surgery; the authors reported that a cutoff CRP velocity of 40 mg/L per day had a positive predictive value of 86% for bacterial infection, with 95% specificity. In our study, CRP values were no better than the WBC count at predicting infection in cardiac surgery patients. In contrast, after neurosurgery, CRP levels were higher in infected than in noninfected patients from POD1 through POD7, with a sensitivity of 62% and a specificity of 95%.

Our study can help interpret trends in CRP values in the postoperative period. In particular, postoperative infection should be suspected in patients who still have CRP values >100 mg/L from POD5, with a sensitivity of 69% and a specificity of 64%. Duration of antibiotic therapy may be guided by repeated CRP levels, or surgical reexploration may be considered if CRP levels do not decrease as expected. These hypotheses need further study.

Other sepsis markers, such as PCT, have been used, but are more costly and less widely available. Some authors consider that PCT is more reliable than CRP for identification of infection,[26] but its superiority over CRP is not definitely established.[3] Moreover, PCT levels also increase after surgery,[27] in trauma or in burns,[28] even when no infection is recognized. A similar analysis should be performed for PCT as was done for CRP.

The limitations of this study include the limited number of patients and the single center setting; moreover, we did not screen the patients for the presence of immunocompromise, so we cannot comment on the CRP response specifically in such patients.

CONCLUSIONS

CRP levels increase in the first few days after major surgery but to a larger extent in infected than in noninfected patients. CRP values decreased in noninfected patients after POD5. Lack of a decrease in CRP after POD4, in association with suggestive clinical assessment and microbiological cultures, suggest a diagnosis of postoperative infection.

DISCLOSURES

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Attestation: Cristina Santonocito attests to having approved the final manuscript.
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Contribution: Jean-Louis Vincent helped design the study and critically review the manuscript.
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ACKNOWLEDGMENTS

We thank Hassane Njimi, MSc, PhD, Department of Intensive Care, Erasme University Hospital, Brussels, Belgium, for his help with the statistical analyses.

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