Comparison of C-Reactive Protein and Serum Amyloid A Protein in Septic Shock Patients

Domingos Dias Cicarelli, Joaquim Edson Vieira, and Fábio Ely Martins Benseñor

Divisão de Anestesia, Departamento de Cirurgia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, 01246-903 São Paulo, SP, Brazil

Correspondence should be addressed to Domingos Dias Cicarelli, dcicarelli@uol.com.br

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Septic shock is a severe inflammatory state caused by an infectious agent. Our purpose was to investigate serum amyloid A (SAA) protein and C-reactive protein (CRP) as inflammatory markers of septic shock patients. Here we evaluate 29 patients in postoperative period, with septic shock, in a prospective study developed in a surgical intensive care unit. All eligible patients were monitored over a 7-day period by sequential organ failure assessment (SOFA) score, daily CRP, SAA, and lactate measurements. CRP and SAA strongly correlated up to the fifth day of observation but were not good predictors of mortality in septic shock.

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1. INTRODUCTION

Severe sepsis and septic shocks are a common cause of mortality in intensive care unit (ICU) [1]. They are a state of systemic inflammation in response to infectious agents that can lead to multiple organ system failure and death.

The systemic inflammatory response to infection involves the release of several mediators, which has led to the suggestion that some of these mediators could be used as markers of sepsis severity [2]. Among the acute-phase proteins that participate in the inflammatory response, C-reactive protein (CRP) is a component of the innate immune system that binds phosphocholine and recognizes some foreign pathogens as well as phospholipid constituents of damage cells; serum amyloid A (SAA) protein is an apolipoprotein that rapidly binds to high-density lipoprotein after their synthesis, influencing cholesterol metabolism during inflammatory states, causing adhesion and chemotaxis of phagocytic cells and lymphocytes [3, 4]. In some patients with chronic inflammation, the net effect of increased SAA production may be deleterious due to tissue deposition of its fragments and the development of systemic amyloidosis [3, 5].

CRP and SAA display a similar pattern in most inflammatory diseases, reaching a maximum serum concentration about 24 hours after the inflammatory process sets in and slowly decreasing [6]. CRP is commonly used as a marker of an acute inflammatory state, produced by the liver in response to tissue injury or infection [7]. Its plasma concentration has been reported to parallel the clinical course of infection and the fall of the protein level indicates the resolution of infection [1]. SAA is the other major acute-phase protein in humans, with the earliest and highest increase rate of all acute-phase proteins, including CRP [4, 8]. SAA concentrations usually parallel those of CRP. Some authors have been reported that SAA appears to be a clinically useful marker of inflammation in bacterial or viral infection likewise CRP [9]. Although some studies suggest that SAA is a more sensitive marker of inflammatory disease, assays for SAA are not widely available at present [4].

Until now, no study has compared daily CRP to SAA plasma concentrations in postoperative patients with septic shock, or has correlated them to the severity of patients represented by SOFA score. This study aimed to evaluate CRP and SAA measurements as markers of severity of septic shock patients during postoperative period.

2. METHODS

This study was prospective at a surgical ICU. After approval by a local ethics committee, informed consent was obtained from patients or from their next of kin prior to enrollment.
Twenty-nine patients admitted into the surgical ICU of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo had taken part in the study. Additional three patients were excluded after their next of kin gave up the signed consent. Patients with septic shock diagnosed during ICU stay were eligible for the study. We used the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definition of sepsis [11]. Patients under 18 were excluded. Patients with septic shock diagnosed during ICU stay were eligible for the study. We used the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definition of sepsis [11]. Patients under 18 were excluded.

Severity of illness at the baseline was assessed based on the acute physiology and chronic health evaluation II (APACHE II) score [12]. Patients were assessed daily for 7 consecutive days using the sequential organ failure assessment score (SOFA) or until their discharge from the ICU when occurring in less than 7 days [13–15]. C-reactive protein and serum amyloid A protein were also measured daily.

The patients received conventional therapy regarding antibiotic regimens, serial blood cultures (whenever that body temperature >38°C), and discharge criteria. Relevant clinical and laboratory tests were conducted daily throughout the study.

Blood samples for CRP and SAA dosage were thawed and assayed in batches in an automated analyzer (Behring Nephelometer Analyzer II, Dade Behring, Marburg, Denmark) for particle-enhanced immunonephelometry using commercial kits. The analytical sensitivity and accuracy for CRP was 0.0175 mg/L (coefficient of variation (CV) 7.6%). The analytical sensitivity and accuracy for SAA was determined by the lower limit of the reference curve and thus depended on the concentration of the protein in SAA standard test (CV between 5.4% and 6.4%).

Statistical analysis was performed using commercial available package. Multiple logistic regressions were performed to test mortality of 7 or 28 days follow-up. A distribution analysis was made by the Kolmogorov-Smirnov test, Pearson correlation coefficients were determined, and repeated measures were tested by ANOVA. A \( P \) value < .05 was considered significant.

### 3. RESULTS

The mean (±SD) age of the 29 patients was 65 ± 13.9 years (range, 34 to 88 years). The study involved 13 males and 16 females (45%/55%). The APACHE II score of these patients was 19.8 ± 4.5 (Table 1). Table 2 represents the microbiological characteristics of the studied patients.

SOFA did not show increase from Day 0 to Day 7 of observation (\( P = .589, \) ANOVA) while CRP reduced significantly from Day 0 till the end of observation period (\( P < .001, \) ANOVA followed by Holm-Sidak test) as well as SAA (\( P < .001, \) ANOVA followed by Holm-Sidak test) (Table 3).

CRP and SAA concentrations did not present any correlation with SOFA.

On the other hand, CRP and SAA have shown a good correlation from Day 0 till Day 5 (Table 4).

Mortality of these patients in 7 days was 44.8% (13 in 29) and in 28 days was 65.5% (19 in 29). CRP and SAA concentrations were not associated with Day 7 mortality (Table 5).

CRP and SAA concentrations evolution during the first week comparing survivors and nonsurvivors were not statistically significant (Figures 1 and 2).

### 4. DISCUSSION

The present study revealed significant positive correlation between SAA and CRP in postoperative septic shock patients. SOFA or APACHE II did not correlate with those serum measurements. Neither marker nor index was associated with mortality rate.
SAA has been considered by some authors to be equivalent to CRP in patients with bacterial infectious diseases in clinical practice [16]. Other authors suggest that SAA is a more sensitive marker than CRP in infections with low inflammatory activity (including many viral infections) and in other clinical conditions, especially those involving the lung tissue [16, 17]. Yet other studies have confirmed the role of SAA and CRP in diagnosis and management of neonatal infections [2, 18].

The patterns of cytokine production and the acute-phase response differ for different inflammatory conditions. Acute-phase changes reflect the presence and intensity of inflammation and they have long been used as a clinical guide for diagnosis and management. Among patients with plasma CRP concentrations higher than 10 mg/dL, 80-to-85 percent have sepsis [4, 19]. In our study, all the patients were presented plasma CRP concentrations greater than 10 mg/dL, according to results that Gabay et al. in a review article cited [4]. This fact could indicate that sepsis is secondary to bacterial infections. In relation to plasma SAA concentrations, a

Table 2: Microbiological characteristics of patients.

| Patient | Surgery/phatology | Antibiotics | Type of organism | Type of culture |
|---------|--------------------|-------------|-----------------|----------------|
| 1       | Cholecistectomy/biliary abscess | Vanco + cefepime | S. aureus | Abscess culture |
| 2       | Empyema pleural drainage | Ceftriaxone + clindamycin | S. pyogenes | Pleural abscess culture |
| 3       | Cholecistectomy/biliary abscess | Ceftriaxone + metronidazole | — | Negative cultures |
| 4       | Cystectomy/pyuria | Ceftriaxone + metronidazole | — | Negative cultures |
| 5       | Aortic bypass/leg amputation | Cefazidime + clindamycin | P. aeruginosa | Surgical site culture |
| 6       | Colectomy/cavity contamination | Ceftriaxone + metronidazole | — | Negative cultures |
| 7       | Calcaneal exposure fracture | Ciprofloxacin | E. faecalis | Surgical site culture |
| 8       | Pyonephrosis drainage | Ceftriaxone | K. pneumoniae | Urinary culture |
| 9       | Sigmoidectomy | Ceftriaxone + metronidazole | A. baumanii | Blood culture |
| 10      | Hemicolecotomy | Ceftriaxone + metronidazole | Candida albicans | Blood culture |
| 11      | Enterectomy/mesenteric ischemia | Ceftriaxone + metronidazole | — | Negative cultures |
| 12      | Pancreatic-duodenal resection | Ceftriaxone | Serratia marcescens | BAL |
| 13      | Pancreatic-duodenal resection | Ceftriaxone + metronidazole | S. coag negative | Blood culture |
| 14      | Retropertitoneal abscess drainage | Cefepime + vanco + imipenem | P. aeruginosa | Blood culture |
| 15      | Abdominal aeurysm repair | Vanco + imipenem | S. aureus | Blood culture |
| 16      | Sigmoidectomy/perforative lesion | Ceftriaxone + metronidazole | Serratia marcescens | Ascite culture |
| 17      | Colectomy | Cefepime + vanco | S. aureus | Blood culture |
| 18      | Gastric ulcer | Ceftriaxone + metronidazole | — | Negative cultures |
| 19      | Cholecistectomy | Cipro + metronidazole | Escherichia coli | Urinary culture |
| 20      | Hemicolecotomy | Cefepime + vanco + metro | E. cloacae | Blood culture |
| 21      | Enterectomy/cavity contamination | Vanco + imipenem | — | Negative cultures |
| 22      | Colectomy | Ceftriaxone + metronidazole | A. baumanii | Blood culture |
| 23      | Colectomy | Ceftriaxone + metronidazole | P. aeruginosa | Blood culture |
| 24      | Enterectomy/cavity contamination | Ceftriaxone + metronidazole | — | Negative cultures |
| 25      | Cervical abscess drainage | Imipenem + vanco + metro | K. pneumoniae | Blood culture |
| 26      | Sigmoidectomy/perforative lesion | Ceftriaxone + metronidazole | P. aeruginosa | Blood culture |
| 27      | Sigmoidectomy | Cefepime + metronidazole | S. aureus | Blood culture |
| 28      | Pyonephrosis drainage | Cefepime + metronidazole | — | Negative cultures |
| 29      | Colectomy | Ceftriaxone + metronidazole | P. aeruginosa | BAL |

Vanco: vancomycin, Cipro: ciprofloxacin, Metro: metronidazole, S. aureus: Staphylococcus aureus, S. pyogenes: Streptococcus pyogenes, P. aeruginosa: Pseudomonas aeruginosa, E. faecalis: Enterobacter faecalis, K. pneumoniae: Klebsiella pneumoniae, A. baumanii: Acinetobacter baumanii, S. coag negative: Staphylococcus coagulase negative, E. cloacae: Enterobacter cloacae, BAL: bronchoalveolar lavage.

Table 3: SOFA, CRP, and SAA during the study period (mean ± SD).

|            | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|------------|-------|-------|-------|-------|-------|-------|-------|-------|
| SOFA       | 9.6 ± 2.3 | 10 ± 2.6 | 9.4 ± 4.1 | 9.8 ± 4.4 | 9.4 ± 4.2 | 9.9 ± 3.7 | 8.7 ± 4.1 | 8.6 ± 5.5 |
| CRP        | 19.8 ± 8.4 | 20.9 ± 9.1 | 16.3 ± 6.2 | 13.2 ± 5.9 | 11.8 ± 7.7 | 12.7 ± 11.2 | 11.9 ± 8.3 | 10.0 ± 4.4 |
| SAA        | 47 ± 39.8 | 37.2 ± 28.1 | 29 ± 21.48 | 22.7 ± 18.4 | 18.6 ± 20.8 | 24.7 ± 25.8 | 22.2 ± 20.5 | 21.7 ± 16.8 |

SOFA: sequential organ failure assessment, CRP: C-reactive protein, SAA: serum amyloid A. ANOVA. Equal variance test: SOFA P = .956, CRP P = .062, SAA P = .055.
cutoff value has not been determined from previous studies. We observed a level higher or closer to 20 mg/dL, but more studies were needed to find a cutoff value for SAA as an early diagnostic tool for patients with infection.

We did not observe difference between CRP and SAA early (Day 1) concentrations in patients who survived compared with those who died. Other authors have found that these proteins were not prognostic markers in patients with septic shock [7, 19]. This fact is in concordance with our results.

Previous reports have observed that CRP level was associated with organ failure in critically ill patients, although not specifically under septic shock [14]. This study could not find any good correlation between CRP or SAA with SOFA, probably not in agreement with other authors [20]. They believe that both CRP and SAA are good markers of organ dysfunction, considering the established diagnostic of septic shock.

Study limitations are attributed primarily to the small sample size and the age of the patients that could influence CRP levels. Some authors believe that the older the patient is, the higher CRP levels that can be observed [21].

In conclusion, SAA protein and CRP are strongly correlated, but were not good predictors of organ dysfunction and mortality in septic shock.

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