

Utility of procalcitonin and C-reactive protein in the septic patient in the emergency department

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Objective: To analyze the utility of procalcitonin (PCT) and C-reactive protein (CRP) as criteria for admission or discharge, or to indicate the need for immediate antimicrobial treatment in the emergency department in patients with systemic inflammatory response syndrome (SIRS), sepsis, or septic shock.

Materials and method: This was a prospective study with a duration of 14 months, performed in adults with SIRS, sepsis, or septic shock. CRP (normal value, 0-8 mg/mL) and PCT (normal value, 0.5 ng/mL) were requested in the emergency department. Records were kept of the PCT and CRP values, microbiological samples collected and their results, antibiotic administration, need for admission, and mortality.

Results: There were 300 patients with SIRS of noninfectious etiology, 100 with sepsis, and 20 with septic shock. Significantly higher CRP and PCT values were found in sepsis than in SIRS ($P < .01$ for both comparisons), and CRP values were higher in septic shock than in sepsis ($P < .01$). There was a nonsignificant trend towards a higher 30-day mortality rate in patients with sepsis and septic shock in whom intravenous fluids and antibiotic therapy were not started in the emergency room (27% mortality) compared with those in whom this treatment was started (22%). PCT levels over 2 ng/mL and CRP levels over 60 mg/L were associated with higher rates of admission, including to the observation ward and short-stay unit, (elevated PCT in 88% of admissions vs 36% of discharges, $P < .001$; elevated CRP, 72% vs 40%, $P < .01$), with positive blood cultures (PCT, 20% vs 2%, $P < .001$; CRP, 16% vs 2%, $P < .01$), length of hospital stay (PCT, 8.5 d vs 5.5 d, $P < .01$; CRP, 7 d vs 5 d, $P < .01$), and 30-day mortality (PCT, 21% vs 8%, $P < .01$; CRP, 16% vs 7%, $P < .01$).

Conclusions: Elevated CRP levels and, in particular, elevated PCT levels can be used to differentiate between SIRS of bacterial or other aetiology. These values also indicate the need for admission and for the immediate administration of antimicrobial agents in the emergency room. [Emergencias 2009;21:23-27]

Palabras clave: Systemic inflammatory response syndrome. SIRS. Sepsis. Septic shock. Procalcitonin, C-reactive protein. Emergency room.

Introduction

Systemic inflammatory response syndrome (SIRS) is a severe clinical condition of general inflammatory response to an insult, whether due to infection, surgery, trauma, burn or other medical situation. Early detection and treatment is required to reduce the rates of morbidity and mortality in these patients. SIRS due to infection is called sepsis (S), and when S induces persistent hypotension after liquid replacement and causes hypo-perfusion with organ dysfunction the condition is called septic shock (SS).

One tenth (10.4%) of patients attended in a hospital emergency department (ED) are diagnosed with infection^{1,2}, of whom 5-10% meet the criteria for S^{3,4}, and of these 5-15% evolve to SS. SS-associated mortality is 55-70%, and the determinant factors are delayed administration of antimicrobials and fluid-therapy^{2,5}. In SS, delayed antibiotic therapy as from the onset of hypotension increases mortality: if the delay is 0-59 minutes, mortality increases by 17-22% and with 9-12 hours of delay, it increases by 75%. However, before administration of antimicrobials and fluid-

therapy, it is necessary to identify the patients with S.

C reactive protein (CRP) has a sensitivity of 78% and a specificity of 60% for differentiating bacterial infection from other causes of SIRS, while the respective values for procalcitonin (PCT) are 85% and 83%. CRP > 20 mg/L and PCT > 2 ng/ml suggest severe infection and and/or a bacterial cause rather than viral or an inflammatory disease. If CRP is lower than 8 mg/L and PCT lower than 0.5 ng/ml, the probability of bacterial sepsis is less than 2%. Of these two, PCT is considered a more specific and earlier marker of inflammation^{2,7}. The objective of this study was to analyse the utility of CRP and PCT in patients with SIRS, S and SS, to distinguish one from another and aid in the decision to admit or discharge the patient and whether or not to administer antimicrobials immediately in the ED.

Method

Our ED serves a population of 410.000 inhabitants and is visited by 430 patients a day, of whom 11.8% are diagnosed with infection⁸. During 14 months (1 January 2006 – 28 February 2007), we included in the study consecutive patients aged >14 years that met the criteria for SIRS, S and SS according to internationally accepted definitions^{3,4}. Inclusion in the study was performed for all the days when the authors were on duty until completing the sample size required (SIRS = 300, S = 100 and SS = 30). Paediatric and gynaecologic-obstetric patients were excluded. The following variables were recorded: blood pressure, cardiac and respiratory frequency, leucocytes and plasma values of CRP and PCT. Normal values established by our laboratory are CRP: 0-8 mg/L and PCT: < 0.5 ng/ml. CRP was determined by enzyme immunoassay absolute quantitative method, with a sensitivity of 1 mg/L (VITROS CRP slides®), while PCT was measured using the immunochromatographic (strip test) semi-quantitative method (B.R.A.H.M.S-PCT-Q®) with different cut offs in ng/ml (< 0.5; 0.5-2; 2-5; 5-10; > 10).

We then revised all the clinical records during 3 months and confirmed the diagnoses and microbiological results. A descriptive analysis was performed using absolute values, proportions, means and standard deviation (SD). The statistical study was performed using SPSS (v.11). Student t test was used to compare q variables and Chi square test with Yates correction was used to

compare proportions. Differences with a p value of < 0.01 were considered significant. For the performance of statistical graphs relating to PCT, this discrete variable was converted to a continuous variable taking the class mean values in the lower categories and the values immediately below (0.4 ng/ml) and > (10.1 ng/ml) for the extreme categories.

Results

Of the 430 patients included in the study, 252 (58%) were men and 178 (42%) women. Regarding age groups, 25.5% were between 15 and 40 years; 31.4% between 41 and 65 years and 43.1% were older than 65 years.

Of the 130 patients with S or SS, 76% had one or more underlying diseases: 25 arterial hypertension, 22 diabetes, 18 cardiopathy, 17 pneumopathy, 13 pharmacological and/or steroid immunodepression, 11 neoplasia, 9 renal failure, 7 hepatopathy and 5 neurological disease. Table 1 shows the diagnoses and aetiology of SIRS, S and SS in the patients included in this study.

Figure 1 shows patient CRP and PCT means \pm SD; we observed significant increases in patients with S versus SIRS ($p < 0.01$ for both), and with SS versus S in the case of CRP ($p < 0.01$). Figure 2 shows the dispersion of PCT values in the different clinical situations analysed.

Microbiological samples (consisting of blood and urine cultures, and antigens in urine and/or ascetic, pleural or cephalorachidian liquid) were obtained. For 64 of the 100 patients with S, 22 (34%) were positive; for 25 (83%) of the 30 patients with SS, 13 (52%) were positive. A significant correlation was observed between PCT > 2 ng/ml and positivity in these microbiological samples ($p < 0.01$). Table 2 shows the relation between some microbiological diagnoses and PCT values, where, with the same diagnoses, higher PCT was found in those with bacteraemia (positive blood culture) and/or SS.

In ED, fluid therapy and antibiotic therapy were initiated in 25% and 46% of S, and in 43.3% and 50% of SS, respectively. We observed a tendency to greater mortality (27%) in cases of S and SS without initiation of ED fluid and antibiotic therapy than in those receiving such treatment (mortality 22%) ($p = \text{NS}$).

Levels of PCT > 2 ng/ml and CRP > 60 mg/L were associated with higher rates of: admission, including the ED observation unit and short stay

Table 1. Diagnoses of patients included in the study

Aetiology and main diagnoses		N° patients	%
SIRS n = 300	Cardiorespiratory (PTE, chest pain, CF-APE)	76	25.3
	Genito-urinary (renal colic, acute scrotum)	34	11.3
	Trauma and wounds (polytrauma, CET, chest trauma)	31	10.3
	Digestive (abdominal pain, pancreatitis, mesenteric ischemia)	28	9.3
	Allergic-anaphylactic reaction	27	9
	Acute intoxication (alcohol, cocaine, other substances)	21	7
	Neurological (ACCVA, anxiety attack)	17	5.6
	Dermatological (burns, herpes zoster, others)	15	5
	Other	51	17
Sepsis n=100	Lower respiratory pathways (pneumonia, CCOPD)	36	36
	Urinary tract (APN)	32	32
	Intra-abdominal (cholecystitis, peritonitis, infectious diarrhoea)	12	12
	Upper respiratory pathways (sinusitis, pharyngoamigdalitis)	5	5
	Febrile syndrome without initial focus	5	5
	Skin and soft tissue (cellulites)	4	4
	Central nervous system (meningitis)	2	2
	Viriasis	2	2
	Other	2	2
Septic shock n = 30	Lower respiratory pathways (pneumonia)	10	33.3
	Urinary tract (PNA)	6	20
	Intra-abdominal (cholecystitis, peritonitis)	5	16.6
	Febrile syndrome without initial focus	4	13.3
	Central nervous system (meningo-encephalitis)	3	10
Skin and soft tissue (cellulites)	2	6.6	

SIRS: Systemic inflammatory response syndrome; PTE: pulmonary thromboembolism; CF: cardiac failure; APE: acute pulmonary edema; CET: craneoencephalic trauma; ACCVA: acute cerebro-cardiovascular accident; CCOPD: complications of chronic obstructive pulmonary disease; APN: acute pyelonephritis.

unit (88% versus 36% for PCT, $p < 0.001$; and 72% versus 40% for CRP, $p < 0.01$), positive blood culture (20% versus 2% for PCT, $p < 0.001$; and 16% versus 2% for CRP, $p < 0.01$), hospital stay (mean 8.5 days versus 5.5 days for PCT, $p < 0.01$; and a mean 7 days versus 5 days for CRP, $p < 0.01$) and 30-day mortality (21% versus 8% for PCT, $p < 0.01$; and 16% versus 7% for CRP, $p < 0.01$). In addition, of the 21 patients with PCT > 10 ng/ml, 100% were admitted; mi-

crobiological diagnosis was obtained for 14 of them (66.6%); mean hospital stay was 7 days higher than in those admitted for S and 11 days higher than those admitted for SIRS, while 30-day mortality was 52.3%.

Discussion

Despite the limitation that we did not record the number of days of symptom evolution or antibiotic duration before CRP and PCT values were determined, we believe our study reflects the real situation in emergency departments of patients with SIRS, where suspicion of aetiology and immediate treatment reduce morbidity and mortality in these patients. Both CRP and PCT proved useful to distinguish infectious from other non-infectious causes of SIRS^{6,7,11}.

The greater these values, especially CRP > 60 mg/L and PCT > 2 ng/ml, the greater their sensitivity and specificity in identifying S and SS of bacterial origin^{6,7}. The results of our study are similar to those reported by other authors^{6,7}, although there are meta-analyses and reviews which cast doubt on their utility^{12,13}.

A striking finding was that fluid and antibiotic therapies were initiated in ED in less than half the patients with S and SS, which was associated

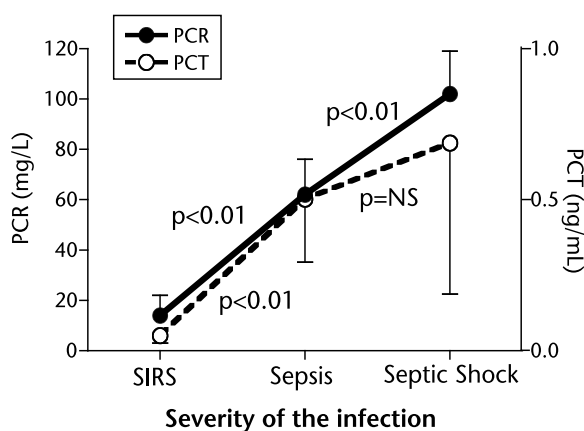


Figure 1. Values of c-reactive protein (CRP) and procalcitonin (PCT) in systemic inflammatory response syndrome (SIRS) to sepsis and septic shock.

Table 2. Correlation between certain microbiological diagnoses and procalcitonin (PCT) levels

	Clinical diagnosis	Total N° patients	Patients according to levels of PCT (ng/ml)				
			< 0.5	0.5-2	2-5	5-10	> 10
Patients with sepsis	CAP due to <i>Streptococcus pneumoniae</i> with H+	3	–	–	–	2	1
	CAP due to <i>Streptococcus pneumoniae</i> with H–	5	–	–	3	2	–
	CAP due to <i>M. pneumoniae</i> or <i>C. pneumoniae</i>	3	–	3	–	–	–
	UTI due to <i>E. coli</i> with H+	2	–	–	1	1	–
	UTI due to <i>E. coli</i> with H–	4	–	1	3	–	–
	Bacterial meningitis due to <i>N. meningitides</i> with H+	1	–	–	–	–	1
Patients with septic shock	CAP due to <i>Streptococcus pneumoniae</i> with H+	3	–	–	–	–	3
	CAP due to <i>Streptococcus pneumoniae</i> with H–	3	–	–	–	1	2
	UTI due to <i>E. coli</i> with H+	3	–	–	–	1	2
	UTI due to <i>E. coli</i> with H–	1	–	–	–	–	1
	Bacterial meningitis due to <i>N. meningitides</i> with H+	1	–	–	–	–	1

CAP : community acquired pneumonia; UTI: urinary tract infection; H+: hemoculture positive; H–: hemoculture negative. Diagnosis of CAP: urine antigen test, sputum culture, serology; Diagnosis of UTI: urine culture; Diagnosis of meningitis: cephalorachidian liquid culture.

with greater mortality of these patients. This fact is a cause for concern and should lead to measures aimed at changing this reality. We also believe it important to highlight that in S and SS, more microbiological tests are requested and prove positive, as reported previously in similar studies^{7,14,15}. When S or SS in ED are suspected, and moreover PCT is > 2 ng/ml, cultures show a greater proportion of positivity and allow identification of the causal agent, a fact that becomes even more evident when PCT > 10 ng/ml is found.

We therefore believe that the utility of determining PCT is evident in ED; given that it is a simple and rapid test, it may be generally incorporated

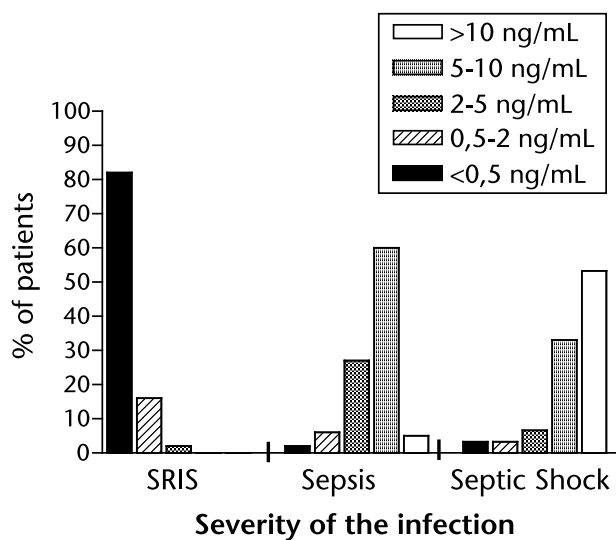


Figure 2. Semi-quantitative values of procalcitonin according to clinical situations. SIRS: Systemic Inflammatory Response Syndrome.

in emergency departments. However, to confirm the results obtained in this study, it is necessary to perform studies using quantitative PCT methods and to consider previous antibiotic administration and symptom evolution time before the determination of CRP and PCT. In addition, a greater sample size could possibly reveal significant correlation between clinical diagnoses, the presence or absence of bacteraemia, the micro-organism responsible and the situation of S or SS, as suggested by this study.

Meanwhile, based on our findings and those reported in the literature, we may consider that in SIRS patients, CRP is a marker of systemic inflammation when > 20-40 mg/L, when > 60 mg/L it allows ruling out S. On the other hand, when PCT is > 2 ng/ml, S may be ruled out but when it is > 5 ng/ml it indicates that the probability of S and/or SS is > 94%; and especially when PCT is > 10 ng/ml, it is associated with higher rates of bacteraemia and mortality, which changes the prognosis, management and selection of treatment (as in the case of community-acquired pneumonia) and predicts more prolonged hospital stay and greater mortality. If CRP is > 90 mg/L and PCT > 2 ng/ml, S must be considered with a probability of >90% and indicate the need for admission, at least to an observation unit.

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Utilidad de la procalcitonina y la proteína C reactiva en el paciente con sepsis en urgencias

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Objetivos: Analizar la utilidad de la procalcitonina (PCT) y proteína C reactiva (PCR) en situaciones de respuesta inflamatoria sistémica (SIRS), sepsis (S) y *shock séptico* (SS) para decidir ingreso o alta y la necesidad de administración de tratamiento antimicrobiano inmediato en urgencias (SUH).

Método: Estudio prospectivo descriptivo durante 14 meses de adultos diagnosticados de SIRS, S y SS donde se solicitó PCR (valor de referencia 0-8 mg/L) y PCT (valor referencia inferior a 0,5 ng/ml) en el SUH. Se cosignaron los valores de PCT y PCR así como la recogida de muestras microbiológicas, su resultado, la administración de antibiótico, la necesidad de ingreso y la mortalidad.

Resultados: Se incluyeron 300 pacientes con SIRS (etiología distinta de infección), 100 con sepsis y 30 con SS. Se observaron valores significativamente superiores de PCR y PCT en la S con respecto al SIRS ($p < 0,01$ para ambas), así como lo fueron los de la PCR en el SS con respecto a la S ($p < 0,01$). Se observó una tendencia a una mayor mortalidad a los 30 días en los casos de S y SS donde no se inició fluidoterapia y antibioterapia en el SUH (mortalidad 27%) que en los que sí se inició (mortalidad 22%) ($p = NS$). Los niveles de PCT superiores a 2 ng/ml y de PCR superiores a 60 mg/L se asociaron a mayores tasas de ingreso incluyendo observación y unidad de corta estancia (88% *versus* 36% para PCT, $p < 0,001$; y 72% *versus* 40% para PCR, $p < 0,01$), de hemocultivos positivos (20% *versus* 2% para PCT, $p < 0,001$; y 16% *versus* 2% para PCR, $p < 0,01$), de estancia hospitalaria (8,5 días de media *versus* 5,5 días de media para PCT, $p < 0,01$; y 7 días de media *versus* 5 días de media para PCR, $p < 0,01$) y de mortalidad en 30 días (21% *versus* 8% para PCT, $p < 0,01$; y 16% *versus* 7% para PCR, $p < 0,01$).

Conclusiones: Niveles elevados de PCR y más aún los de PCT, nos diferencian la etiología infecciosa bacteriana del resto de SIRS, así como nos indicarán la necesidad de ingreso y administración inmediata de antimicrobianos en el SUH. [Emergencias 2009;21:23-27]

Palabras clave: Síndrome de respuesta inflamatoria sistémica (SIRS). Sepsis. *Shock séptico*. Procalcitonina. Proteína C reactiva. Urgencias.