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An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence in Acutely ill Patients (SOAP) study

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On behalf of the Sepsis Occurrence in Acutely Ill Patients investigators

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Abstract *Objective:* To define the frequency and prognostic implications of SIRS criteria in critically ill patients hospitalized in European ICUs *Design and setting:* Cohort, multicentre, observational study of 198 ICUs in 24 European countries. *Patients and interventions:* All 3,147 new adult admissions to participating ICUs between 1 and 15 May 2002 were included. Data were collected prospectively, with common SIRS criteria. *Results:* During the ICU stay 93% of patients had at least two SIRS criteria [respiratory rate (82%), heart rate (80%)]. The frequency of having three or four SIRS criteria vs. two was higher in infected than non-infected patients ($p < 0.01$). In non-infected patients having more than two SIRS criteria was associated with a higher risk of subsequent development of severe sepsis (odds ratio 2.6, $p < 0.01$) and septic shock (odds ratio 3.7, $p < 0.01$). Organ system failure and mortality increased as the number of SIRS criteria increased. *Conclusions:* Although common in the ICU, SIRS has prognostic importance in predicting infections, severity of disease, organ failure and outcome.

Keywords Infections · Systemic inflammatory response syndrome · Sepsis · Severe sepsis · Septic shock · Prognosis

Introduction

A little more than a decade ago an ACCP/SCCM consensus conference coined the term systemic inflammatory response syndrome (SIRS) [1]. Since that time there have been those who believe the term is a helpful one [2] and those who believe it is useless or potentially harmful [3]. Some think that SIRS and the consensus definitions provide a useful framework in the approach to patients with infectious diseases, and that the terms are clear, unambiguous and clinically meaningful [2]. Others consider SIRS to be too sensitive, it does not help physicians understand the pathophysiology of sepsis, does not help in clinical trials, and may even reduce the search for a source of infection [3, 4, 5, 6].

Despite the controversy SIRS has been used in the medical literature hundreds of times. Also, there is no doubt that SIRS has prognostic value. Having two or more SIRS criteria has been shown to be an independent predictor of infection, length of stay, and outcome in trauma patients [7, 8, 9]. SIRS has also been shown to predict mortality in patients with subarachnoid haemorrhage [10] or gastrointestinal bleeding [11] and in patients brought by ambulance to the emergency room [12, 13]. Recent consensus conferences have de-emphasized SIRS criteria as being descriptive of clinical syndromes rather than pathophysiological processes [4] or stated that SIRS criteria need to be revisited or modified [14].

As part of the Sepsis Occurrence in the Acutely ill Patients (SOAP) study data on SIRS signs were collected to ascertain the frequency of the SIRS criteria and to determine whether they are too sensitive, or whether they are helpful prognostically. The study involved investigators previously outspoken for and against the SIRS criteria so that agreement could be determined [1, 3].

Methods

This observational, multicentre, European cohort study evaluated all 3,147 adult patients admitted to 198 European intensive care units (ICUs) participating on a voluntary basis between 1 and 15 May 2002. Patient characteristics are summarized in Table 1. Data collection on admission included demographic data and comorbid diseases. Vital signs and laboratory data were collected over the entire ICU stay. Clinical and laboratory data for Simplified Acute Physiology Score (SAPS) II score [15] were collected as the worst value within 24 h after admission. Patients were followed for ICU length of stay, hospital discharge, ICU and in-hospital mortality, or for 60 days from ICU admission. SIRS, sepsis, severe sepsis and septic shock were defined according to the ACCP/SCCM consensus conference criteria [1]. Microbiological and clinical infections were reported daily as well as the antibiotics administered.

On admission patients were classified into infected and non-infected groups. Infection was defined as a clinical infection with antibiotic therapy or clinical bacteriology with antibiotic therapy. A daily evaluation of organ function based on a set of laboratory and clinical parameters according to the SOFA score [16] was derived centrally, with the most abnormal value for each of the six organ systems being collected on admission and every 24 h thereafter. Organ failure was defined using SOFA criteria with scores of 3 or 4 [16] of any of the following six organ systems: (a) respiratory, PaO_2/FIO_2 ratio 200 mmHg or less with respiratory support; (b) cardiovascular, acute circulatory failure requiring the use of vasopressor agents (circulatory shock); (c) haematological, platelet count 50,000/mm^3 or lower; (d) hepatic, bilirubin 6.0 mg/dl or higher, or 102 μmol/l or higher; (e) renal, creatinine 3.5 mg/dl or higher, or 300 μmol/l or higher, or urine output below 500 ml/day; (f) neurological, Glasgow Coma Score (GCS) 9 or lower. Organ failure present 48 h before the onset of sepsis was excluded.

For single missing values a replacement was calculated using the mean value of the results on either side of the absent result. When the first or last values were missing, the nearest values were carried backward or forward, respectively. When more than one consecutive result was missing, it was considered to be a missing value in the analysis.

Table 1 Characteristics of the study group; percentages are presented after exclusion of missing values ($n = 3,147$)

Age, median (years; IQR)[a]	64 (50–74)
Sex: M / F[b]	62% / 38%
Type of admission	
Medical	1759 (55.9%)
Surgical	1388 (44.1%)
Elective	778 (24.7%)
Emergency	610 (19.4%)
ICU admission source[c]	
ER, ambulance	913 (32.2%)
Hospital floor	793 (28.0%)
OR, recovery room	784 (27.7%)
Other hospital	345 (12.2%)
SAPS II score	36.5 ± 17.1
SOFA score	
Initial	5.1 ± 3.8
Mean	4.5 ± 3.5
Maximum	6.6 ± 4.4
Sepsis	1177 (37.4%)
Severe sepsis	930 (29.6%)
Septic shock	462 (14.7%)
Duration of ICU stay, median (days; IQR)	3.0 (1.7–6.9)
Duration of hospital stay, median (days; IQR)	15.0 (7.0–32.0)
ICU mortality[d]	583 (18.5%)
Hospital mortality[e]	747 (24.1%)

[a] 9 missing, [b] 35 missing, [c] 312 missing, [d] 1 missing, [e] 44 missing

Data management

Data were collected prospectively. Detailed instructions explaining the aim of the study, instructions for data collection, and definitions for various important items were available for all participants at www.intensive.org before starting data collection and throughout the study period. Data were entered centrally by medical personnel. Investigators were queried when data values were either questionable or were missing for required fields. A sample of 5% of the overall data was re-entered by a different encoder and revised by a third; consistency values of more than 99.5% per variable and 98.5% per file were observed during the whole process of data entry. In cases of inconsistency data were verified and corrected. Since this observational study required no deviation from routine medical practice, institutional review board approval was either waived or expedited in participating institutions, and informed consent was not required.

Statistical methods

Data were analysed using SPSS version 11.0 for Windows (SPSS, Chicago, Ill., USA). Descriptive statistics were computed for all study variables. The Klomogorov-Smirnov test was used, and stratified distribution plots were examined to verify the normality of distribution of continuous variables. Nonparametric measures of comparison were used for variables evaluated as not normally distributed. Difference testing between groups was performed using the χ^2 test and Fisher's exact test as appropriate. Bonferroni's correction was used for multiple comparisons. Analysis of Variance (ANOVA) was used to examine possible trends in SAPS II score and ICU length of stay (LOS) between categories of SIRS criteria. Univariate logistic regression analysis was performed with the target syndrome or ICU outcome as the dependent factor. Multivariate, forward stepwise, logistic regression analysis was performed with in-hospital mortality as the dependent variable. Variables included in the analysis were age, gender, admission type, comorbidities and SAPS II score on admission, onset of ICU and non-ICU acquired infection, site of infection, type of organism (Gram-positive, Gram-negative, anaerobic, atypical and fungal). The maximal number of SIRS criteria was entered into the model in the last step as a continuous variable. Prior to modelling variables associated with higher risk of hospital mortality were defined in a univariate analysis with a cut off p value of < 0.2 to select variables for the multivariate analysis. Colinearity and interactions between variables were excluded. Four subgroups were modelled separately: severe sepsis (including septic shock), all sepsis categories (including sepsis, severe sepsis and septic shock), only sepsis (excluding severe sepsis and septic shock), and no sepsis. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed. Data are presented as mean $\pm$ SD for parametric data and median with 25–75 percentiles (interquartile range, IQR) for non-parametric data. Sensitivity, specificity, positive and negative predictive values were calculated. Differences with a p value less than 0.05 were considered significant.

Results

At ICU admission 87% of patients had at least two SIRS criteria, most commonly respiratory rate (84%) or heart rate (71%; Table 2). There were no significant differences in mortality based on the presence of any single SIRS criterion on admission (Table 2). The maximum number of SIRS criteria or occurrence of severe sepsis or septic shock did not differ according to the site of infection except that the incidence of severe sepsis was lower and that of septic shock higher in patients with pure abdominal infection (compared with pure respiratory infection, $p < 0.01$; Table 3). At ICU admission as the number of SIRS criteria increased the SAPS II score ($p < 0.001$), ICU length of stay ($p < 0.001$) and mortality increased with increased number of SIRS criteria ($p < 0.001$, Table 4). At any time during the ICU hospitalization 93% of patients had at least two SIRS criteria, most commonly respiratory rate (82%) or heart rate (80%). All infected patients had two or more SIRS criteria (Table 5). ICU and hospital mortality increased as the number of SIRS criteria increased for patients without infections and patients with infections and the different grades of sepsis (Table 5).

The frequency of three or four SIRS criteria vs. two SIRS criteria was higher in infected than non-infected patients ($p < 0.01$) (Table 5). Table TabS.T1 in the Electronic Supplementary Material demonstrates the development of the different stages of sepsis according to the number of SIRS criteria on admission in infected or non-infected patients. In non-infected patients progression to sepsis occurred in 400 patients (16.9%), severe sepsis in 305 (12.9%) and septic shock in 127 (5.3%). In infected patients progression to severe sepsis occurred in 73 patients (9.4%) and septic shock in 29 (3.7%). In non-infected patients the presence of more than two SIRS criteria was associated with a significantly higher risk of subsequent development of severe sepsis (OR 2.6,

Table 2 ICU outcome according to individual SIRS criteria at admission

	Frequency		ICU mortality	
	n	%	*n*	%
Temperature	1,990	63.2	423	21.3
WBC count	1,563	49.7	352	22.5
Heart rate	2,231	70.9	478	21.4
Respiratory rate	2,642	84.0	552	20.9

Table 3 Maximum number of SIRS criteria according to the site of infection and stage of sepsis. Percentages are calculated for rows

	n[a]	2 SIRS ($n=67$)		3 SIRS ($n=365$)		4 SIRS ($n=745$)		Severe sepsis ($n=930$)		Septic shock ($n=462$)	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Respiratory	446	26	5.8	156	35	264	59.2	342	76.7	133	29.8
Abdominal	109	5	4.6	39	35.8	65	59.6	80	73.4	43	39.4
Skin	39	2	5.1	18	46.2	19	48.7	20	51.3	7	17.9
Blood	33	3	9.1	14	42.4	16	48.5	27	81.8	14	42.4
Urinary	39	6	15.4	12	30.8	21	53.8	22	56.4	6	15.4
Unknown	27	1	3.7	11	40.7	15	55.6	17	63	6	22.2
Catheter[b]	4	1	25	1	25	2	50	4	100	1	25
CSF[b]	4	0	–	1	25	1	25	2	50	0	–
Other[b]	25	7	28.0	9	36.0	9	36	12	48	3	12

[a] 453 (38.5%) of infected patients had infections in more than one site. Compared with respiratory infection, no comparisons were statistically significant (after Benferroni's correction for multiple comparisons) except for that the incidence of severe sepsis was lower and that of septic shock was higher in patients with pure abdominal infection (vs. pure respiratory infection, $p<0.01$), [b] Not included in the comparisons due to small sample size. All comparisons are referenced to respiratory infection after elimination of combined cases

Table 4 ICU outcome according to the maximum number of SIRS criteria at admission

	Frequency	SAPS II score[a]	Length of stay[a]	ICU mortality[b]
No SIRS	119 (3.8%)	24.4 ± 11.0	1.6 (0.8–3.3)	5 (4.2%)
One SIRS	303 (9.6%)	28.5 ± 14.6	2.1 (1.0–4.4)	26 (8.6%)
Two SIRS	812 (25.8%)	31.7 ± 15.1	2.7 (1.6–5.5)	89 (11.0%)
Three SIRS	1153 (36.6%)	38.7 ± 16.5	3.7 (1.9–8.9)	251 (21.8%)
Four SIRS	760 (24.1%)	43.3 ± 18.1	3.9 (1.9–8.9)	212 (27.9)

[a] $p<0.001$,
[b] $p<0.001$

Table 5 ICU outcome according to maximum number of SIRS criteria stratified by presence or absence of infection and by presence of severe sepsis and septic shock on admission[a]

	No infection ($n=2{,}370$)						Infection ($n=777$)					
	Frequency		ICU mortality		Hospital mortality		Frequency		ICU mortality		Hospital mortality	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
No SIRS	119	5.0	5	4.2	9	7.6	0	–	0	–	0	–
One SIRS	303	12.8	26	8.6	38	12.9	0	–	0	–	0	–
Two SIRS	677	28.6	68	10.0	88	13.2	135	17.4	21	15.6	34	25.6
Three SIRS	776	32.7	147	19.0	180	23.6	377	48.5	104	27.6	139	37.1
Four SIRS	495	20.9	126	25.5	149	30.5	265	34.1	86	32.5	110	42.0

	Severe sepsis ($n=552$)						Septic shock ($n=243$)					
	Frequency		ICU mortality		Hospital mortality		Frequency		ICU mortality		Hospital mortality	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
No SIRS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
One SIRS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Two SIRS	77	13.9	17	22.1	25	33.3	11	4.5	4	36.4	5	45.5
Three SIRS	271	49.1	92	33.9	120	44.6	111	45.7	50	45.0	59	53.2
Four SIRS	204	37.0	76	37.3	95	47.3	121	49.8	57	47.1	69	57.0

[a] $p<0.001$ for both ICU and hospital mortality according to the number of SIRS criteria

Table 6 Predictors of hospital mortality in a multivariate logistic regression analysis (*OR* odds ratio, *CI* confidence interval)

	No sepsis		All sepsis categories		Only sepsis		Severe sepsis and septic shock	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age[a]	1.02 (1.01–1.03)	< 0.001	1.04 (1.03–1.05)	< 0.001	–	–	1.04 (1.03–1.05)	< 0.001
Male gender	–	–	0.67 (0.49–0.92)	0.012	–	–	0.62 (0.44–0.88)	0.007
Medical admission	2.81 (1.98–3.98)	< 0.001	1.75 (1.26–2.43)	0.001	–	–	1.64 (1.15–2.33)	0.006
Cancer	–	–	2.15 (1.4–3.3)	< 0.001	–	–	2.53 (1.53–4.17)	< 0.001
COPD	–	–	1.78 (1.17–2.72)	0.007	–	–	1.07 (1.06–2.74)	0.029
Haematological cancer	–	–	3.75 (1.62–7.84)	0.002	–	–	5.92 (2.28–15.36)	< 0.001
Cirrhosis	–	–	2.43 (1.14–5.19)	0.022	–	–	–	–
SAPS II score[b]	1.04 (1.03–1.05)	< 0.001	1.01 (1.01–1.02)	0.046	1.06 (1.02–1.09)	0.001	–	–
Mean SOFA score[b]	1.54 (1.44–1.64)	< 0.001	1.47 (1.38–1.56)	< 0.001	–	–	1.51 (1.41–1.61)	< 0.001
ICU acquired infection	–	–	–	–	–	–	1.64 (1.11–2.42)	0.012
Septic shock	–	–	–	–	–	–	1.48 (1.04–2.09)	0.029
Respiratory infection	–	–	–	–	2.81 (1.18–6.66)	0.019	–	–
SIRS counts[b]	–	–	1.67 (1.04–1.8)	0.025	–	–	–	–

[a] Odds ratio per 1-year increase, [b] Odds ratio per point increase

95% CI 2.0–3.4, $p < 0.01$; sensitivity 72.8%, specificity 49.0%, positive predictive value 17.5%, negative predictive value 92.4%) and septic shock (OR 3.7, 95% CI 2.4–5.8, $p < 0.01$; sensitivity 80.0%, specificity 47.9%, positive predictive value 8.5%, negative predictive value 97.7%). In infected patients the presence of more than two SIRS criteria was not associated with a higher risk of subsequent progression to either severe sepsis or septic shock.

There was an overall increase in organ system failure in infected and non-infected patients as the number of SIRS criteria increased from two to three but not to four. There was no specific organ that failed more with increasing SIRS criteria in infected patients, but there was more cardiovascular, respiratory, CNS and coagulation system failure in non-infected patients. Table 6 shows the predictors of hospital mortality utilizing a multivariate logistic regression analysis. The presence of more SIRS criteria was associated with an increase in the mortality in infected patients but not non-infected patients or patients with sepsis, severe sepsis or septic shock.

Discussion

The present study is the first large, prospective, multicentre study evaluating SIRS criteria and the progression from one stage of sepsis to another in infected and non-infected patients, especially in non-infected patients. It documents the fact that SIRS criteria are very common and yet non-specific. ICU outcome did not differ according to individual SIRS criteria at admission, and the maximum number of SIRS criteria did not differ according to the site of infection or stage of sepsis. There was, however, a higher frequency of three or four SIRS criteria vs. two SIRS criteria in infected then in non-infected patients. Interestingly, all infected patients had at least two SIRS criteria. Although it is difficult to conclude that all infected patients should have at least two SIRS criteria and non-infected patients less than two, it is perhaps a useful finding to keep in mind when assessing patients with suspected infection. Another larger, multicentre study has reported that 16% of infected patients did not have SIRS [17]. Differences in results may be related to different definitions. The Alberti et al. [17] study included only first infections (all infections here), different definitons for organ failure were used, and patients were followed for a year (2 weeks here). In addition, the SOAP population may represent a different case mix as the incidence of infection and severe sepsis with septic shock are higher than in the Alberti et al. study (37% vs. 27% and 79% vs. 54%). The different case mix with a higher incidence of severe forms of sepsis and different definitions for organ failure could explain the absence of infection without SIRS.

The present study supports suggestions that the number of SIRS criteria has important prognostic implications. Previous studies have demonstrated that the presence of two or more SIRS criteria is an independent predictor of infection, length of stay and outcome in various groups of patients [7, 8, 9, 10, 11, 12, 13, 17, 18]. In addition, it has been shown that as patients develop more SIRS criteria, the incidence of sepsis increases [19, 20]. The present study demonstrates that in non-infected patients the presence of

more than two SIRS criteria is associated with a higher risk of subsequent progression to either severe sepsis or septic shock, but that this was not the case in infected patients. In fact, the progression to severe sepsis and septic shock were slightly higher (12.9% and 5.3%, respectively) in non-infected than infected patients (9.4% and 3.7%, respectively). Alberti et al. [21] demonstrated a similar progression in 11% of septic patients to severe sepsis but a greater incidence of 13% to septic shock. As noted above, the Alberti et al. [21] and present studies differed in the definitions used. A previous study with a smaller number of patients found that 93% of ICU patients had SIRS, and that the diagnosis of SIRS was not helpful in predicting severe sepsis or septic shock [22]. In the present study an increasing number of SIRS criteria was accompanied by increasing mortality. As the number of SIRS criteria at the time of admission increased, mortality increased in patients without infections and also for those patients with infections at the various grades of sepsis. The studies of Alberti et al. [17, 21] demonstrated a higher mortality with increasing SIRS criteria, but the mortality differences disappeared after the stratification for the severity of sepsis stage [17]. In the present study the presence of more SIRS criteria was an independent predictor of hospital mortality in infected patients. The increased mortality was probably related to the increased organ system failure noted with increasing SIRS criteria.

Some have argued that the SIRS criteria have also been helpful in clinical trials. In the only positive studies of adjunctive therapy for severe sepsis or septic shock the presence of three SIRS criteria was required for patient enrolment [23, 24]. Others have argued that the SIRS criteria are too unspecific and have therefore contributed to the negative findings of many sepsis interventions [14].

In discussing the controversy surrounding SIRS it is important to look back and determine the reasons for the creation of the concept of SIRS and its persistent use at the 2003 consensus conference [14]. The ACCP/SCCM consensus conference [1] identified several problems regarding nomenclature for septic patients. First, many patients who looked "septic" did not have documented infection, and a term other than sepsis seemed to be needed. Second, many patients with infection were not diagnosed correctly or in a timely fashion. It was believed that the concept "systemic inflammatory response syndrome", or SIRS, would cover the many infectious and non-infectious pathological causes of the inflammatory response [1]. In addition, a more sensitive indicator was needed to diagnose infected patients earlier. The criteria for SIRS were therefore drafted as common tests easily and quickly available at the bedside with broad and very inclusive criteria so that infected patients would not be missed and hopefully diagnosed earlier. The rationale for the concept of SIRS has not changed.

It can be argued that the SIRS criteria are so sensitive and are present in so many ICU patients that their value in identifying infected patients is not great. Those patients who have two or more SIRS criteria, however, should be closely evaluated for infection. There may be additional tests such as interleukin 6, procalcitonin or C-reactive protein [15] that may be more specific, but more work will have to be done before these tests become routine at the bedside. When SIRS was first suggested, it was stated that further work is required to characterize the clinical and prognostic significance and associated sequelae [1]. It is clear from this study and others that SIRS has a great prognostic importance in predicting infections, length of stay, severity of disease, organ failure and outcome.

The strengths of this study are the large number of patients from multiple centres, the prospective inclusion of all patients admitted to ICUs with and without infections, analysis of the progression to different stages of sepsis over time and quality assessment for entered data. Weaknesses include the possibility of over-diagnosing infection using a definition of clinical infection with antibiotic therapy, using SOFA scores for organ failure without the failure necessarily being caused by the infection, the lack of quality evaluation of original entered data, the lack of a clinical evaluation committee to assess clinical diagnoses, no analysis by ICU or country and the fact that ICUs participated on a voluntary basis and therefore that patients may not be representative of all ICU patients in other ICUs. It should be noted that most of these weaknesses are found in other large epidemiological studies [17, 21, 25]. The large number of patients, however, most likely makes the findings relevant to most ICU patients.

In conclusion, SIRS is an established term which has prognostic implications for the development of infection, organ failure and mortality. Future studies should seek to compare the easily measured SIRS criteria with other known prognostic and diagnostic markers.

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