

# Sepsis in the Intensive Care Unit: Etiologies, Prognostic Factors and Mortality\*

## *Sepse na Unidade de Terapia Intensiva: Etiologias, Fatores Prognósticos e Mortalidade*

Fernando Zanon<sup>1</sup>; Jairo José Caovilla<sup>2</sup>; Regina Schwerz Michel<sup>3</sup>; Estevan Vieira Cabeda<sup>3</sup>; Diego Francisco Ceretta<sup>3</sup>; Graziela Denardin Luckemeyer<sup>4</sup>; Cássia Beltrame<sup>4</sup>; Naiana Posenatto<sup>4</sup>

### SUMMARY

**BACKGROUND AND OBJECTIVES:** Sepsis is the main cause of death in patients treated in intensive care units (ICU). The aim of this study was to evaluate etiology, prognostic factors and mortality of septic patients treated in ICU of Passo Fundo, Brazil.

**METHODS:** Out of 971 consecutive patients prospectively evaluated from August 2005 to February 2006, 560 were selected due to presence of systemic inflammatory response syndrome (SIRS) and followed for 28 days or until discharge or death. Patients were categorized according with the etiology of SIRS and further classified as having SIRS, sepsis, severe sepsis and septic shock. Prognosis was assessed by means of APACHE II and SOFA. Mortality was compared in different etiologies of sepsis, APACHE II and SOFA scores, parameters.

**RESULTS:** Of the 971 patients admitted to the ICU, 560

developed SIRS (58%). The most frequent cause of internation was neurological disease (28.9%), the most frequent site of infection was the respiratory tract (71.6%), and the most prevalent pathogens were gram-negative bacilli (53.2%). Mean APACHE II score was  $18 \pm 9$ , and mean SOFA score was  $5 \pm 4$ . Median ICU stay was 6 (3-11) days and overall mortality rate was 31.1%: 6.1% for non-infectious SIRS, 10.1% for sepsis, 22.6% for severe sepsis, and 64.8% for septic shock.

**CONCLUSIONS:** Sepsis is an important health problem that leads to an extremely high mortality rate in the ICU of Passo Fundo, Brazil.

**Key Words:** epidemiology, sepsis, septic shock, severe sepsis, systemic inflammatory response syndrome.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** Sepse é a principal causa de morte em pacientes tratados em unidade de terapia intensiva (UTI). O objetivo deste estudo foi avaliar etiologia, fatores prognósticos e mortalidade de pacientes sépticos tratados nas UTI de Passo Fundo, Brasil.

**MÉTODO:** Foram avaliados 971 pacientes consecutivos prospectivamente, entre agosto de 2005 e fevereiro de 2006, 560 foram selecionados pela presença de síndrome da resposta inflamatória sistêmica (SIRS) e acompanhados por 28 dias ou até a alta ou óbito. Os pacientes foram classificados de acordo com a etiologia da SIRS e adicionalmente classificados como tendo SIRS, sepse, sepse grave e choque séptico. O prognóstico foi avaliado por meio dos escores APACHE II e SOFA. A mortalidade foi comparada em diferentes etiologias de sepse e parâmetros APACHE II e SOFA.

**RESULTADOS:** Dos 971 pacientes admitidos nas UTI, 560 desenvolveram SIRS (58%). A causa mais frequente de internação foi doença neurológica (28.9%),

1. Specialist in Intensive Care, Associação de Medicina Intensiva Brasileira.

2. Professor, Medical Clinics, Universidade de Passo Fundo.

3. Resident, Department of Medical Clinics, Hospital da Cidade de Passo Fundo.

4. Resident, Department of Medical Clinics, Hospital São Vicente de Paulo, Passo Fundo.

\*Received from Hospital da Cidade de Passo Fundo (HCPF), Hospital Pronto-clínica (HP) and Hospital São Vicente de Paulo (HSVP), Passo Fundo, RS

Presented in February 19, 2008

Accepted for publication in April 13, 2008

Address for correspondence:  
Fernando Zanon, M.D.  
Rua Paissandu, 488/402 - Centro  
99010-101 Passo Fundo, RS, Brazil  
Phone: +55-54-30457217  
E-mail: zanoncti@hotmail.com

©Associação de Medicina Intensiva Brasileira, 2008

o mais freqüente local de infecção foi o trato respiratório (71,6%), e os germes mais prevalentes foram os bacilos gram-negativos (53,2%). O escore APACHE II médio foi  $18 \pm 9$  e o escore SOFA médio foi  $5 \pm 4$ . O tempo médio de permanência foi 6 (3-11) dias e a taxa de mortalidade foi 31,1%: 6,1% para SIRS não infecciosa, 10,1% para sepse, 22,6% para sepse grave e 64,8% para choque séptico.

**CONCLUSÕES:** Sepse é um importante problema de saúde que leva a uma taxa extremamente alta de mortalidade nas UTI de Passo Fundo, Brasil.

**Unitermos:** choque séptico, epidemiologia, sepse, sepse grave, síndrome da resposta inflamatória sistêmica

## INTRODUCTION

Sepsis is an important cause of hospitalization and the main cause of death in intensive care unit (ICU)<sup>1-3</sup>. In 1990, the Center for Disease Control and Prevention (CDC) estimated an incidence of 450 thousand cases of sepsis per year and over 100 thousand deaths in the United States<sup>4</sup>. In 2001, Angus et al.<sup>5</sup> studied over six million records of hospital discharges in seven states in the US and found an estimate of 751 thousand cases of severe sepsis per year, with a mortality rate of 28.6%. Martin et al.<sup>6</sup> reviewed data on hospital discharges for 750 million admissions in the US in 22 years, and found more than 10 million cases of sepsis and an increase in frequency to 82.7/100000 inhabitants in 2000. Studies conducted in Europe, Australia and New Zealand reported that the prevalence rate of sepsis in ICU ranged from 5.1% to 30%<sup>7-11</sup>. The Brazilian Sepsis Epidemiological Study (Bases Study), conducted in five ICU, found mortality rates of 11%, 33.9%, 46.9% and 52.2% in patients with SIRS, sepsis, severe sepsis and septic shock<sup>12</sup>. Another study conducted in Brazil analyzed data from 75 ICU in different regions, and found mortality rates of 16.7% for sepsis, 34% for severe sepsis, and 65.3% for septic shock<sup>13</sup>. Overall mortality rates for sepsis have decreased, but, at 20% to 80%, are still unacceptably high<sup>14</sup>. The incidence of sepsis has increase because of population ageing, more invasive procedures, the use of immunosuppressive drugs and increased prevalence of HIV infection, and this trend is expected to accelerate in the future<sup>5,6</sup>. Few studies investigated the epidemiology of sepsis in ICU in the state of Rio Grande do Sul, where Passo Fundo is located. This study evaluated epidemiologic data and mortality rates of patients with sepsis in the ICU of three hospitals in Passo Fundo, Brazil.

## METHODS

This prospective multicenter observational cohort study included patients at the time of diagnosis of SIRS (time zero). It was conducted from August 2005 to February 2006, in Passo Fundo (population, 180,000), a city in the State of Rio Grande do Sul, Brazil, whose hospitals provide care to the population living in the northern area of this state and in the western region of the neighboring state of Santa Catarina. The general ICU studied are located in three hospitals: Hospital da Cidade de Passo Fundo (HCPF), Hospital ProntoClínica (HP) and Hospital São Vicente de Paulo (HSVP). The three are tertiary general hospitals, and two of them are university hospitals affiliated with the Universidade de Passo Fundo (UPF) and the Brazilian Health System (SUS). They have from 90 to 550 hospital beds, and 9 to 22 ICU beds. This study was approved by the Ethics in Research Committee of UPF, and all patients or their legal guardians signed an informed consent term.

Patients were included if they were 18 years or older and developed systemic inflammatory response syndrome (SIRS)<sup>17</sup> while in the ICU. Exclusion criteria were: ICU stays shorter than 24 hours; and pregnancy. Each new admission was classified as a new patient in this study.

A questionnaire was used to collect data and to keep uniform records for the three ICU. A manual with detailed information about how to fill out the questionnaire and definitions of all variables was handed out to all researchers. The patients were followed up until discharge from ICU, death, or the 28th day after inclusion in the study. Demographic data, the cause of admission, immunosuppression, APACHE II score, SOFA score, and source of infection were collected. APACHE II scores were calculated in the first 24 hours of hospitalization according to the Knaus method<sup>15</sup>, and the SOFA scores<sup>16</sup> were calculated daily during ICU stay. When a variable was absent, it was classified as normal and a value of zero was entered for that variable. The use of antibiotics, predisposing factor for infection, laboratory culture results, ICU length of stay, and ICU mortality rate were also used for the analyses. Patients were classified according to 4 stages: non-infectious SIRS, sepsis, severe sepsis, and septic shock, according to the definitions established by the consensus of the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) in 1991<sup>17</sup>. Patients could change from one severity stage to the other, but did not go back to a previous stage; therefo-

re, their data might be entered in more than one stage. The authors did not play any role in the decisions made by the patients' attending physicians.

Clinical concepts and criteria introduced in the last decade to define SIRS established a more accurate classification of inflammatory events in patients in ICU. SIRS, sepsis, severe sepsis and septic shock were defined according to the consensus of the ACCP/SCCM. Infection was defined as the presence of pathogenic microorganisms in any sterile medium (blood, cerebrospinal fluid, and ascetic fluid) or the clinical suspicion of infection treated with antibiotics or not<sup>17</sup>.

### Statistical Analysis

Data are presented as mean  $\pm$  SD, median (interquartile range) and percentages. The Student *t* test was used to analyze normally distributed variables; the Mann-Whitney test, for no normal variables; and the Fisher Exact test, for categorical variables. To evaluate the discriminatory power of APACHE II scores for mortality, a receiver operation characteristic curve (ROC) was used, and values between 0.7 to 0.8 for area under the curve were classified as good discrimination and, between 0.8 and 0.9, as excellent<sup>18-20</sup>. The level of statistic significance was set at  $p < 0.05$  (two-tailed). The SPSS 13.0 for Windows (Chicago, US) software was used for statistical analyses.

## RESULTS

This study was conducted in the general ICU of three hospitals in Passo Fundo Brazil. Percentages of total number of admissions were 50.7%, 36.6% and 13% for HSVP, HCPF and HP. The two teaching hospitals affiliated with the Brazilian Health System (SUS) had 87% of all admissions (Table 1). During the study, 971 patients consecutively admitted to the ICU were evaluated, and 560 met inclusion criteria, which corresponds to a prevalence rate of 58%. Mean age was  $60.7 \pm 18.6$  years, and 56.8% of the patients were older than 60 years; 55.5% were men. Four hundred eleven patients (42%) were excluded because they did not develop SIRS, where younger than 18 years, stayed in the ICU for less than 24 hours, or data were missing from their records (Figure 1). Patients were admitted to the ICU due to neurologic (29.8%), respiratory (24.3%) or surgical (17.1) problems; clinical causes were found for 76.1% of all cases. Non-infectious causes were responsible for 28.7% of all cases of SIRS, and infectious causes, for 71.3%; sepsis, se-

vere sepsis and septic shock were found in 36.4%, 27.8% and 35.8% of the cases of infectious SIRS. The most frequent symptoms of SIRS were tachycardia (82.3%) and tachypnea (80%). Overall mean APACHE II score was  $18 \pm 9$ ; for survivors, it was  $15 \pm 8$ ; and for no survivors,  $24 \pm 9$  ( $p < 0.001$ ). According to the receiver operating characteristic (ROC) curve, a cut-off point of 18.5 was established as the value to obtain good sensitivity (67.6%) and specificity (67.1%); area under the curve was  $0.734 \pm 0.02$  (Figure 2). Mean SOFA scores for SIRS, sepsis, severe sepsis and septic shock were 3.99, 2.65, 4.90 and 8.12. Overall mean SOFA score was  $5.4 \pm 3.5$ . Mean first and last SOFA scores of patients that survived was statistically different from mean first and last SOFA score of no survivors ( $p < 0.001$ ) (Figure 3). System or organ failures were most common in the respiratory (60.4%), neurologic (42.1%) and renal (37.1%) systems. Failure in 3 or more organs was found for 36.4% of the patients; mortality rate ranged from 14.6% for patients with fewer than 3 organ failures to 59.8% in patients with 3 or more organ failures ( $p < 0.001$ ). Of all study patients, 414 (73.9%) developed infection; cultures were made for 340 (60.7%) and were positive in 50.3% of the cases. Nosocomial infection was found in 53.8% of the cases, and the most frequent sites of infection were the lungs (71.6%), urinary tract (4%) and surgical wound (3.0%). Positive cultures were most frequently obtained from sputum (23%), urine (18.8%) and blood (12.7%). The most frequent pathogens were gram-negative bacilli (*Escherichia coli*, *Pseudomonas aeruginosa*, *Enterobacter sp* and *Acinetobacter sp*) in 53.2% of the cases, and gram-positive cocci (Coagulase-negative *Staphylococcus* and *Staphylococcus aureus*). More than one pathogen was identified in 2.8% of the cases, and fungi, in 1.3%. The antibiotics used most frequently were cephalosporin (48.4%), antianaerobic agents (36.3%) and beta-lactamic antibiotics (26.4%). Only one antibiotic was used in 26.1% of the cases; 2, in 28.6%; three or more, in 24% of the patients. The most important infection risk factors were urethral catheter in 87% of the cases; nasogastric catheter in 73%; central venous catheter in 61%; and mechanical ventilation in 51%. Overall median number of days in the ICU was 6 (3-11), and median ICU stay of patients classified according to stages was 6 (2-14). Overall ICU mortality was 31.1%, and on the 28th day after inclusion in the study, 34.6%. Mortality for non-infectious SIRS, sepsis, severe sepsis, and septic shock was 6.1%, 10.1%, 22.6% and 64.8% (Table 2).

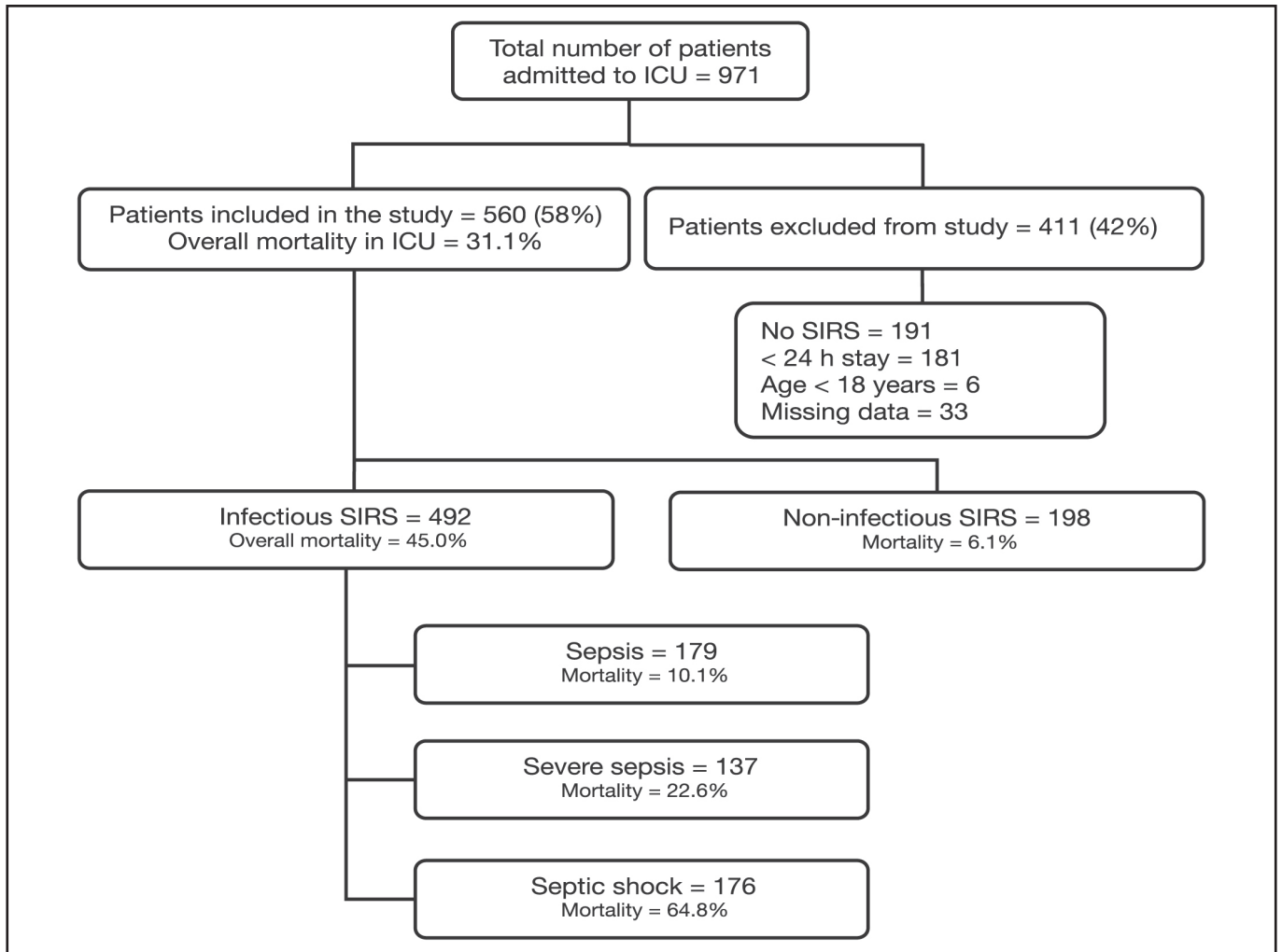


Figure 1 – Patients Admitted to the Three ICU and Mortality Rates.

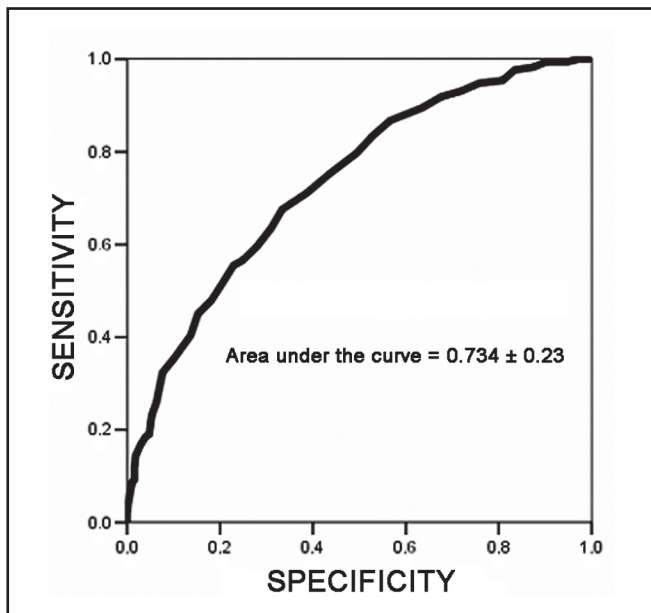


Figure 2 – APACHE II Score: ROC Curve for ICU Mortality.

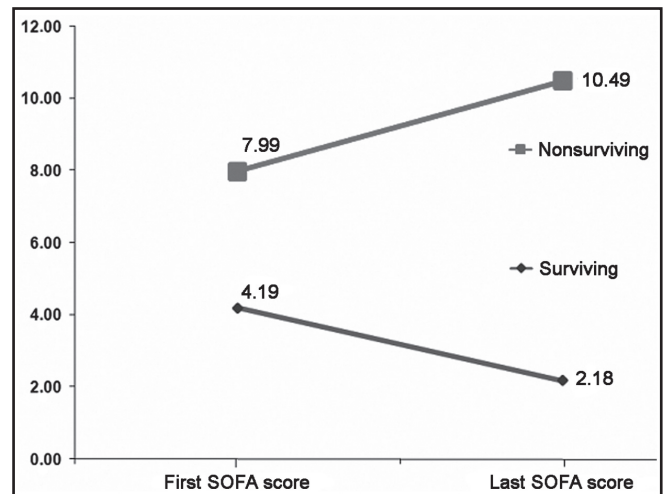


Figure 3 - Comparison of Mean First and Last SOFA Scores of Surviving and Non-Surviving Patients.

Table 1 – Demographics and General Data.

Variables	General
Total number of patients (n)	560
HSVP <sup>a</sup> (patients)	50.7
HCPF <sup>a</sup> (patients)	36.3
HP <sup>a</sup> (patients)	13.0
Age (mean ± SD)	60.7 ± 18.6
Male sex <sup>a</sup>	55
Infectious SIRS <sup>a</sup>	71.3
Non-infectious SIRS <sup>a</sup>	28.7
Sepsis <sup>a</sup>	32.0
Severe sepsis <sup>a</sup>	24.5
Septic shock <sup>a</sup>	31.4
Nosocomial infection <sup>a</sup>	53.8
Community infection <sup>a</sup>	46.2
Infection site <sup>a</sup>	
Lung	71.7
Urinary tract	4.0
Surgical wound	3.0
Pathogens <sup>a</sup>	
Gram negative	53.2
Gram positive	30.4
Length of ICU stay <sup>b</sup>	6.0 (3-11)
Overall mortality in ICU <sup>a</sup>	31.1
Mortality on 28th day <sup>a</sup>	34.6
Non-infectious SIRS mortality <sup>a</sup>	6.1
Sepsis mortality <sup>a</sup>	10.1
Severe sepsis mortality <sup>a</sup>	22.6
Septic shock mortality <sup>a</sup>	64.8

<sup>a</sup>Percentage.

<sup>b</sup>Median and interquartile range.

Table 2 – Data of Patients that Survived and Patients that Died.

Variables	Survivals	Deaths	p
Number of patients (%)	386 (68.9)	174 (31.1)	
Mean age (years)	59.3 ± 19.3	63.8 ± 16.6	0.008a
APACHE II	15 ± 8	24 ± 9	< 0.001a
First SOFA score	4 ± 2	8 ± 4	< 0.001 a
Last SOFA score	2 ± 2	10 ± 5	< 0.001 a
Greatest SOFA score	5 ± 4	12 ± 5	< 0.001 a
Mean number of organ failures	1.0 (0-2)	3.0 (2-4)	< 0.001c
Organ failures (%)			
≤ 2	85.4	14.6%	
≥ 3	40.2	59.8%	< 0.001b
Length of ICU stay (days)	6.0 (4-6)	5.0 (3-5)	< 0.001c

a Student t test.

b Fisher exact test.

c Mann-Whitney test.

## DISCUSSION

This is the first prospective study in our region to analyze the occurrence of sepsis in patients ad-

mitted to the ICU. Sepsis remains a global medical challenge and one of the main causes of death in ICU. This study found a high frequency of sepsis, an overall ICU mortality rate of 31.1% and a rate of 34.6% on the 28th day after inclusion in the study ( $p = 0.237$ ). Studies in Europe and the US with patients with sepsis reported general mortality rates that ranged from 13.5% to 53.6%<sup>1,21-23</sup>. Brazilian studies found a general ICU mortality rate of 21.8% and 46.4%<sup>12,13</sup>. When patients were divided into groups of non-infectious SIRS, sepsis, severe sepsis or septic shock, ICU mortality rates were 6.1%, 10.1%, 22% and 64.8%. Rangel-Frausto et al.<sup>24</sup> and Salvo et al.<sup>10</sup> found mortality rates of 7% and 26.5% for non-infectious SIRS, 36% and 16% for sepsis, 20% and 52% for severe sepsis, and 46% and 82% for septic shock. The SOAP study<sup>21</sup>, conducted in 198 ICU in Europe, found a mortality rate of 32.2% for severe sepsis and of 54.1% for septic shock. Brazilian studies reported mortality rates of 11.3% for non-infectious SIRS, of 16.7% to 33.9% for sepsis, 34.4% to 46.9% for severe sepsis, and 52.2% to 65.3% for septic shock<sup>12,13</sup>. Our overall mortality rates and rates according to sepsis stages were similar to those reported in the literature<sup>25,26</sup>. Overall mean APACHE II score was  $18 \pm 9$ ; for survivors, it was  $15 \pm 8$ , and for no survivors,  $24 \pm 9$ , and the difference was statistically significant ( $p < 0.001$ ). APACHE II scores were significantly associated with death, and a greater score was associated with greater likelihood of death. A cut-off point of 18 was found using the ROC curve, a value that was adequate to obtain good sensitivity (67.6%) and specificity (66.6%); area under the curve was  $0.734 \pm 0.02$ <sup>20</sup> (Figure 3). The use of the APACHE II score as a predictor of mortality is controversial. Some studies reported that it successfully predicted outcome for their patients<sup>19,20,26</sup>, but Lundeborg et al.<sup>27</sup> failed to demonstrate the efficacy of APACHE II as a predictor of mortality of patients with sepsis. The SOFA score was associated with overall mortality in our study. The comparison of means, of the first and last SOFA scores of survivors and no survivors revealed a statistically significant difference ( $p < 0.001$ ) (Table 2), results that are similar to those reported in Brazilian and European studies<sup>14,16</sup>. In our study, patients with two or fewer organ failures had a mortality rate of 14.6%, and those with three or more, 59.8% ( $p < 0.001$ ). These findings are similar to those reported in a study conducted by Vincent et al.<sup>21</sup>,

in which patients without any organ dysfunction had a mortality rate of 6%, whereas those with 4 or more organ dysfunctions had a rate of 65%. In this study, gram-negative bacteria were found in 53.2% of the cases, gram-positive bacteria, in 30.4%, and fungi, in 1.3%. Martin et al.<sup>6</sup> studied the epidemiology of sepsis in the US and reported that gram-positive bacteria were the most frequent in the ICU. The most frequent site of infection was the lungs (71.6%), which is in agreement with findings in the literature<sup>12,13,21</sup>. The mortality rate in the group of patients on mechanical ventilation or immunosuppressed patients was significantly greater than that of patients not on ventilation or immunosuppressed (47.6% and 18.2%  $p < 0.001$ ; 40.9% and 28.7%,  $p = 0.018$ ). Vincent et al.<sup>21</sup> also found a significantly greater mortality rate for patients on mechanical ventilation or immunosuppressed. Median length of ICU stay was 6<sup>3,4-10</sup> days, similar to those reported in the literature<sup>5,8,28</sup>.

One of the limitations of this study was that it was conducted in a period of 6 months (August to February). As the prevalence of infections may be affected by season, this study may have failed to demonstrate the actual prevalence of germs that cause such infections or even of sites of infection<sup>29,30</sup>. Another limitation was that patients were followed up only up to the 28th day after inclusion in the study, and data may have failed to demonstrate actual middle- and long-term morbidity and mortality. Moreover, the study was conducted in only 3 ICU in the city of Passo Fundo, which receives patients only from parts of two Brazilian states. However, few studies investigated the epidemiology of sepsis in Brazil before, and this is the first study on the epidemiology of sepsis in this region.

This study described the epidemiologic profile of patients with sepsis in ICU in the city of Passo Fundo, Brazil, and found a high prevalence of sepsis and an unacceptable high mortality rate in the region. Future studies should include a larger number of patients and ICU to better understand and treat patients with sepsis.

## ACKNOWLEDGEMENTS

We are grateful to the statisticians of the Graduate Research Group of Hospital de Clínicas de Porto Alegre for the help provided in the analysis of data.

## REFERENCES

- Engel C, Brunkhorst FM, Bone HG, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. *Intensive Care Med*, 2007;33:606-618.
- Marshall JC, Vincent JL, Guyatt G, et al. Outcome measures for clinical research in sepsis: a report of the 2nd Cambridge Colloquium of the International Sepsis Forum. *Crit Care Med*, 2005;33:1708-1716.
- Alberti C, Brun-Buisson C, Goodman SV, et al. Influence of systemic inflammatory response syndrome and sepsis on outcome of critically ill infected patients. *Am J Respir Crit Care Med*, 2003;168:77-84.
- Centers for Disease Control - Increase in national hospital discharge survey rates for septicemia, United States, 1979-1987. *JAMA*, 1990;263:937-938.
- Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*, 2001;29:1303-1310.
- Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*, 2003;348:1546-1554.
- Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med*, 2002;28:108-121.
- Finfer S, Bellomo R, Lipman J, et al. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. *Intensive Care Med*, 2004;30:589-596.
- Padkin A, Goldfrad C, Brady AR, et al. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. *Crit Care Med*, 2003;31:2332-2338.
- Salvo I, de Cian W, Musicco M, et al. The Italian SEPSIS study: preliminary results on the incidence and evolution of SRIS, sepsis, severe sepsis and septic shock. *Intensive Care Med*, 1995;21:(Suppl2):S2-44-S249.
- Harrison DA, Welch CA, Eddleston JM - The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care*, 2006;10:R42.
- Silva E, Pedro Mde A, Sogayar AC, et al. Brazilian Sepsis Epidemiological Study (BASES study). *Crit Care*, 2004;8:R251-R260.
- Sales Junior JA, David CM, Hatum R, et al. Sepsis Brasil: estudo epidemiológico da sepse em unidades de terapia intensiva brasileiras. *Rev Bras Ter Intensiva*, 2006;18:9-17.
- Annane D, Aegerter P, Jars-Guincestre MC, et al. Current epidemiology of septic shock: the CUB-Rea Network. *Am J Respir Crit Care Med*, 2003;168:165-172.
- Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*, 1985;13:818-829.
- Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*, 1996;22:707-710.
- Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*, 1992;101:1644-1655.
- Hosmer DW, Taber S, Lemeshow S - The importance of assessing the fit of logistic regression models: a case study. *Am J Public Health*, 1991;81:1630-1635.
- Teres D, Lemeshow S - Using severity measures to describe high performance intensive care units. *Crit Care Clin*, 1993;9:543-554.
- Arabi Y, Al Shirawi N, Memish Z, et al. Assessment of six mortality prediction models in patients admitted with severe sepsis and septic shock to the intensive care unit: a prospective cohort study. *Crit Care*, 2003;7:R117-R122.
- Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*, 2006;34:344-353.
- Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*, 2001;344:699-709.

23. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*, 2001;345:1368-1377.
24. Rangel-Frausto MS, Pittet D, Costigan M, et al. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA*, 1995;273:117-123.
25. Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. *JAMA*, 1995;274:968-974.
26. Cardoso LTQ, Matsuo T, Bonametti AM, et al. Avaliação do risco de mortalidade através do APACHE II para o CTI de um hospital escola público. *Rev Bras Ter Intensiva*, 2002;14:85-94.
27. Lundberg JS, Perl TM, Wiblin T, et al. Septic shock: an analysis of outcome for patients with onset on hospital wards versus intensive care units. *Crit Care Med*, 1998;26:1020-1024.
28. Brun-Buisson C, Meshaka P, Pinton P, et al. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med*, 2004;30:580-588.
29. Sundararajan V, Macisaac CM, Presneill JJ, et al. Epidemiology of sepsis in Victoria, Australia. *Crit Care Med*, 2005;33:71-80.
30. Karlsson S, Varpula M, Ruokonen E, et al. Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. *Intensive Care Med*, 2007;33:435-443.