Reduced mortality after the implementation of a protocol for the early detection of severe sepsis

Glaucio A. Westphal MD, PhD, Álvaro Koenig MD,⁎, Milton Caldeira Filho MD, Janaína Feijó MD, Louise Trindade de Oliveira, Fernanda Nunes, Kênia Fujiwara MD, Sheila Fonseca Martins, Anderson R. Roman Gonçalves MD, PhD

⁎Corresponding author. Rua Plácido Gomes, 500-Bairro Anita Garibaldi, Joinville, SC 89202-050, Brazil.
E-mail address: koenig@netvision.com.br (Á. Koenig).

Keywords:
Septic shock;
Severe sepsis;
Outcomes;
Diagnosis, Hospital
mortality

Abstract
Objective: We evaluate the impact that implementing an in-hospital protocol for the early detection of sepsis risk has on mortality from severe sepsis/septic shock.
Methods: This was a prospective cohort study conducted in 2 phases at 2 general hospitals in Brazil. In phase I, patients with severe sepsis/septic shock were identified and treated in accordance with the Surviving Sepsis Campaign guidelines. Over the subsequent 12 months (phase II), patients with severe sepsis/septic shock were identified by means of active surveillance for signs of sepsis risk (SSR). We compared the 2 cohorts in terms of demographic variables, the time required for the identification of at least 2 SSRs, compliance with sepsis bundles (6- and 24-hour), and mortality rates.
Results: We identified 217 patients with severe sepsis/septic shock (102 during phase I and 115 during phase II). There were significant differences between phases I and II in terms of the time required for the identification of at least 2 SSRs (34 ± 48 vs 11 ± 17 hours; P < .001) and in terms of in-hospital mortality (61.7% vs 38.2%; P < .001).
Conclusion: The early detection of sepsis promoted early treatment, reducing in-hospital mortality from severe sepsis/septic shock.
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1. Introduction

Sepsis is a common clinical condition associated with a high mortality rate among hospitalized patients and constitutes one of the main causes of death worldwide. It is the leading cause of death in noncardiac intensive care units (ICUs) [1-3]. In the United States, between 1979 and 2000, there was an annualized increase of 8.7% in the incidence of sepsis, which represented an increase from about 164 000 cases to nearly 660 000 cases [4]. Later, The Extended Study on Prevalence of Infection in Intensive Care (EPIC) II study showed that the ICU mortality rate of infected patients is more than twice that of noninfected patients (25% vs 11%, P < .001); similar results were obtained for hospital mortality rate (33% vs 15%, P < .001) [2].
In developing countries, this trend seems to be even worse. The Promoting Global Research Excellence in Severe Sepsis study showed a mortality rate due to severe sepsis of 56% in Brazil, contrasting the 45% observed in other developing countries and the 30% in developed ones [1,5,6].

The Surviving Sepsis Campaign (SSC) guidelines issued the following 2 bundle strategy for the management of the septic patient: resuscitation or 6-hour bundle (lactate measurement, blood culture obtained before antibiotic administration, early broad-spectrum antibiotics administration, and early aggressive hemodynamic resuscitation) and the management or 24-hour bundle (steroids, drotrecogin alfa, glycemic control, and low plateau pressure) [7,8]. Subsequently, some studies showed that the implementation of these evidence-based treatment protocols was associated with significant reduction in mortality because of severe sepsis [9-12]. However, despite SSC guidelines implementation in many Brazilian ICUs, sepsis-related mortality remained unacceptably high [13-15]. Aside from organizational and financial problems of many ICUs, one fact became evident: there was a great delay in the detection of the first signs of sepsis and in the proper management of the septic patient. This delay could cause the mortality rates to remain high even after the implementation of the SSC bundles [16-19]. In this study, we aimed to evaluate the impact of an inpatient early-sepsis-risk-detection protocol on sepsis-related mortality rates.

2. Methods

2.1. Design and definitions

A before-and-after study design was used, which consisted of different screening protocols and involved inpatients in the ICUs, hospital wards, or emergency rooms of 2 hospitals both with average to advanced levels of medical care and located in southern Brazil. Epidemiological data, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, hospital sector of diagnosis, ICU and hospital length of stay, and mortality were collected. Patients with end-stage diseases or shock due to noninfectious causes were excluded. The following definitions were used:

- **Clinical signs of infection (CSI):** temperature $>38.5^\circ C$ or $<36^\circ C$; chills; heart rate $>90$ beats per minute; respiratory rate $>20$ breaths/min; systolic blood pressure $<90$ mm Hg or mean arterial pressure (MAP) $<65$ mm Hg; and headache with neck stiffness [18,20].

- **Expanded CSI (ECSI):** the initial CSI, including clinically detectable signs of organ dysfunction: acute encephalopathy (drowsiness, disorientation, confusion, or coma); systolic blood pressure $<90$ mm Hg or MAP $<65$ mm Hg; oliguria; or the need for oxygen supplementation.

- **Signs of organ dysfunction (SOD):** acute encephalopathy; systolic blood pressure $<90$ mm Hg or MAP $<65$ mm Hg; peripheral oxygen saturation $<90\%$; creatinine $>2.0$ mg/dL or hourly urine output $<0.5$ mL/kg for $>2$ hours; bilirubin $>2$ mg/dL; platelet count $<100$ 000 mm$^3$; or serum lactate $>2$ mmol/L [8,9,20].

- **Sepsis:** clinical picture of infection with at least 2 CSI [20].

- **Severe sepsis:** sepsis with at least one sign of organ dysfunction [20].

- **6-hour SSC bundle:** determination of serum lactate levels; collection of at least 2 blood samples from different sites for culture; initiation of appropriate antibiotic therapy within 1 hour after diagnosis; in the event of hypotension or serum lactate $\geq 4$ mmol/L, administration of 20 to 30 mL/kg of crystalloids; administration of a vasopressor if MAP is $<65$ mm Hg after crystalloid infusion; maintenance of a central venous pressure $>8$ mm Hg in patients requiring crystalloid infusion; and maintenance of a central venous oxygen saturation $>70\%$ [8,9].

- **24-hour SSC bundle:** administration of low-dose corticosteroids in accordance with the ICU protocol; administration of recombinant human activated protein C, in accordance with the guidelines of the facility (the institutional policies of the 2 participating hospitals precluded the use of recombinant human activated protein C); maintenance of glucose control with insulin therapy, in accordance with the guidelines of the facility; and, for patients on mechanical ventilation, maintenance of a plateau pressure $<30$ cm H$_2$O [8,9].

2.2. Screening protocols

The before period (phase I) was performed from August 2005 to October 2006 and included all consecutive inpatients with a diagnosis of sepsis or severe sepsis or septic shock using the SSC definitions and protocols [8,9]. Importantly, in this phase, the surveillance for septic patients was based on CSI, and the search occurred only among those with a previous diagnosis of infection.

The phase II period, after the protocol implementation, was performed from November 2006 to November 2007 and differed from phase I by an active surveillance for ECSI in all hospitalized patients. Nursing technicians were trained to identify and report any abnormality of 2 or more ECSI to the ward nurse using a specific formulary (Attachment 1). The ward nurse was called to evaluate the sepsis risk signs, and once risk of sepsis was confirmed, she requested medical evaluation to confirm or rule out the diagnosis of severe sepsis and to initiate the proper management.

The changes proposed for the early-sepsis-risk-detection protocol implementation were mostly operational, and it was not necessary to hire staff or make structural changes.

2.3. Statistical analysis

Continuous data were compared using the Student $t$ test and were expressed as means and SDs. Values of $P < .05$
were considered significant. The differences between groups were evaluated by means of the $\chi^2$ test. Associations between risk factors and mortality were evaluated by logistic regression. All analyses were conducted with the Number Cruncher Statistical System program, version 2000, and the Power Analysis Statistical Software, version 2000 (NCSS, Kaysville, Utah), or the program Statistical Package for the Social Sciences, version 13.0 (SPSS Inc, Chicago, Ill).

### 3. Results

A total of 577 patients were evaluated. During phase I, 119 patients with severe sepsis or septic shock were identified. Of these, 17 were excluded from the present study because they presented with end-stage disease. In phase II, 334 patients were evaluated based on the protocol for the early detection of sepsis. Of these, 115 met the diagnostic criteria for severe sepsis ($n = 49$) or septic shock ($n = 66$). For every 2.7 patients with signs of sepsis risk, at least one presented manifestations of severe sepsis (Fig. 1). Of the 217 patients with severe sepsis or septic shock (phases I and II), 130 (60%) were male. The mean age was $55 \pm 20$ years, and the mean APACHE II score was $21 \pm 8$.

The distribution of sex, age, and APACHE II score was similar between the 2 phases of the study (Table 1). The mean time elapsed between the identification of the first signs of sepsis risk and the detection of sepsis was longer in phase I than in phase II ($34$ vs $11$ hours; $P < .001$). The sepsis-related 28-day mortality rate and the total in-hospital mortality rate were also significantly lower during phase II ($P < .001$). The Kaplan-Meier analysis showed that the reduction in mortality was significant from the beginning of the treatment onward (Fig. 2). A similar reduction in mortality was observed in patients with an APACHE II score $\geq 25$ ($P < .02$).

The length of ICU stay was similar for all patients; however, the length of hospital stay was longer during phase II than during phase I (Table 1).

Mean age, mean APACHE II score, the proportion of males, and the prevalence of septic shock were higher among the nonsurvivors than among the survivors (Table 2). The total length of hospital stay was longer for the survivors, although the length of ICU stay was similar between the 2 groups (survivors and nonsurvivors). The time elapsed between the identification of the first sign suggestive of infection and the detection of sepsis was longer in the nonsurvivors.

Logistic regression was performed to evaluate the association between clinically significant variables (age, APACHE II score, study phase, presence of septic shock, and compliance with the 6-hour bundle) and the risk of death. This association was significant for the APACHE II score (1.16; 95% confidence interval, 1.09-1.22; $P < .001$) and inclusion in phase I (2.26; 95% confidence interval, 1.18-4.35; $P < .02$) of the study.

### 4. Discussion

The present study showed that an institutional strategy of active, systematic surveillance for sepsis-related clinical signs can result in early suspicion and diagnosis of severe sepsis or septic shock, leading to prompt treatment and, most impressively, to reduced mortality associated with severe sepsis.

This finding is especially relevant because sepsis-related mortality in phase I of this before-after study was extremely high (61.7%), although compliance with the 6-hour bundle was 32%. This mortality rate was similar to that reported in other studies conducted in Brazil, in which the reported mortality due to severe sepsis and septic shock ranged from 34.4% to 47.3% and from 52.2% to 65%, respectively [1,5].
In Brazil, despite the implementation of the SSC protocols, the sepsis-related mortality remained higher than 50%, contrasting with the worldwide sepsis-related hospital mortality rate that decreased from 37% to 30.8% over 2 years [14]. One reason could be the low compliance rate of only 9% with the 6-hour bundle in Brazilian ICUs. Even in private hospitals, where compliance with the protocol has been slightly better (10.5%), the mortality rate has remained at 52%, which is unacceptably high [15]. In the present study, compliance with the SSC protocols was better in phase I than in phase II. Nevertheless, the mortality rate was quite high, especially in phase I, which raises doubts about the effect of such compliance. In addition, in a recent study conducted in Spain, the implementation of the SSC protocol promoted a significant reduction in the mortality rate (from 44% to 39.7%), although compliance with the 6-hour bundle was only 10%, a rate similar to that observed in Brazil [21]. Hence, it is likely that severe sepsis-related mortality does not depend exclusively on protocol compliance but rather on the time interval required to implement them into practice. Aggressive fluid resuscitation aims to treat global tissue hypoxia in the early management of sepsis to revert the supply-dependent VO2 status before the development of organ dysfunction [22,23]. Late recognition of septic shock might hinder the achievement of this objective.

Admission to the ICU after the development of organ failure (i.e., late ICU admission) has a significant impact on outcome [16,22-25]. One study showed that the time from the onset of organ dysfunction to diagnosis was strongly correlated with mortality rates; these ranged from 33.3% when treatment was initiated within the first 24 hours after onset to 84.5% when treatment was delayed for 2 or 3 days. The risk of death was 8.73 times greater when severe sepsis was identified more than 48 hours after the onset of organ dysfunction.

### Table 1  Demographic, epidemiological, and clinical data for phases I and II

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase I (n = 102)</th>
<th>Phase II (n = 115)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (n [%])</td>
<td>68 (66.6)</td>
<td>62 (53.9)</td>
<td>.07</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55.2 ± 20</td>
<td>55.4 ± 20.6</td>
<td>.94</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>22 ± 8</td>
<td>21 ± 7.5</td>
<td>.34</td>
</tr>
<tr>
<td>Infectious source (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>43 (42.1)</td>
<td>44 (38.2)</td>
<td>.56</td>
</tr>
<tr>
<td>Urinary</td>
<td>12 (11.7)</td>
<td>4 (3.5)</td>
<td>.03</td>
</tr>
<tr>
<td>Abdominal infection</td>
<td>21 (20.6)</td>
<td>31 (26.9)</td>
<td>.27</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2 (1.9)</td>
<td>9 (7.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>11 (10.8)</td>
<td>10 (8.7)</td>
<td>.95</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>4 (3.9)</td>
<td>6 (5.2)</td>
<td>.65</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (8.8)</td>
<td>10 (8.7)</td>
<td>.97</td>
</tr>
<tr>
<td>Septic shock (n [%])</td>
<td>70 (67.6)</td>
<td>66 (57.4)</td>
<td>.09</td>
</tr>
<tr>
<td>Original hospital ward (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>35 (34.3)</td>
<td>54 (47)</td>
<td>.07</td>
</tr>
<tr>
<td>ICU</td>
<td>67 (65.7)</td>
<td>61 (53)</td>
<td>.07</td>
</tr>
<tr>
<td>6-h bundle compliance (%)</td>
<td>33 (32.3)</td>
<td>33 (28.7)</td>
<td>.55</td>
</tr>
<tr>
<td>24-h bundle compliance (%)</td>
<td>52 (50.2)</td>
<td>55 (47.8)</td>
<td>.64</td>
</tr>
<tr>
<td>Length of ICU stay (d)</td>
<td>16 ± 28</td>
<td>14 ± 13</td>
<td>.49</td>
</tr>
<tr>
<td>Length of hospital stay (d)</td>
<td>31 ± 34.1</td>
<td>40 ± 33</td>
<td>.05</td>
</tr>
<tr>
<td>T-DSR (h)</td>
<td>34 ± 48</td>
<td>11 ± 17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>28-d mortality (n [%])</td>
<td>48 (47)</td>
<td>28 (24.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>In-hospital mortality (n [%])</td>
<td>63 (61.7)</td>
<td>42 (36.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mortality APACHE II &gt;25 (n [%])</td>
<td>26/34 (76)</td>
<td>21/42 (50)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are presented as mean ± SD. T-DSR indicates time required for the detection of sepsis risk.

![Probability of survival in patients with severe sepsis or septic shock](image)

**Fig. 2**  Probability of survival in patients with severe sepsis or septic shock during Phase I (dotted line) and Phase II (solid line), according to the time elapsed after the detection of sepsis (P < .001).
dysfunction, even if antibiotic therapy and fluid resuscitation were started immediately after diagnosis [16].

The findings of the present study underscore the idea that an early warning system [26] based on early identification of sepsis signs is a crucial tool for the effective management of severe sepsis and septic shock. Early warning systems based on physiological parameters may provide an early warning system [26] based on early identification of severe sepsis and septic shock. Early warning systems based on physiological parameters may provide “timely recognition of patients with potential or established critical illness regardless of their location, and timely and aggressive management of these patients” [27]. Medical emergency teams, initially instituted in Australia, patients at risk teams in the United Kingdom, and rapid response teams in the United States have been established to prevent deterioration of septic ward patients [28-30]. The model proposed in this study is, to some extent, an adaptation of early warning systems and medical emergency teams with the specific aim of early identification of patients at risk for sepsis. By adopting this model, we observed that the mean time required to detect a patient at risk dropped from 34 to 11 hours. This reduction resulted in a significant reduction in sepsis-related mortality, which allowed us to speculate that the high mortality rate observed in phase I may be associated with the late detection of sepsis.

These findings indicate that organizational and cultural aspects, more than structural problems of the ICUs in developing countries, are key factors in the struggle to reduce sepsis-related mortality. There are simple and inexpensive measures that can be adopted even if financial resources are limited. For the implementation of an inpatient early-sepsis-risk detection protocol, the nursing staff of the hospital needs to be trained, and a nurse must be assigned to the protocol. To change the routine of the treatment team in phase II, it was necessary to emphasize the importance of changes in vital signs as a marker of severity as well as the need to initiate treatment before admission to the ICU. In addition, it was necessary to remove certain barriers, such as the limited knowledge of the staff regarding this topic, lack of staff training, negative perception of the process, and organizational resistance to change [17-19,31].

Considering its great benefit in mortality reduction, such a program seems to be very cost-effective, even in developing countries. Patients who died in phase II were significantly older than those in phase I, meaning that mortality rate reduction was greater among younger patients after the protocol implementation. Such findings may have social-economic implications because reducing the number of productive years of life lost due to sepsis would reduce the indirect cost of sepsis to society. Future studies should investigate this hypothesis.

It is important to consider the low accuracy of the diagnostic criteria for systemic inflammatory response syndrome (SIRS) and sepsis, as stated in an international consensus: “although SIRS remains a useful concept, the diagnostic criteria for SIRS are overly sensitive and nonspecific” [20,31-33]. Consistent with the idea that an expanded list of signs and symptoms of sepsis can result in a better clinical response to infection [31-33], we adjusted our program of sepsis screening by including clinical manifestations indicative of organ dysfunction (oliguria, need for oxygen supplementation, and altered level of consciousness). In addition, the strategy of systematically monitoring for signs of SIRS or organ dysfunction in all wards underscores the importance of patient care, the importance of each professional involved in that care, and the importance of changes in vital signs as a warning [17].

Our study has some limitations. Although we had 1 year of follow-up before and after the protocol implementation, the comparison of these 2 distinct groups of patients is subject to biases and reduces the degree of certainty of the results. Further studies with a more prolonged follow-up and a greater number of patients are needed to confirm the benefits of the early detection of the septic patient.

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### Table 2 Data related to survivors and nonsurvivors, by study phase

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase I (n = 39)</td>
<td>Phase II (n = 73)</td>
<td>Phase I (n = 63)</td>
</tr>
<tr>
<td>Male(n [%])</td>
<td>17 (43.6)</td>
<td>41 (56.1)</td>
<td>58 (51.8)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.2 ± 22</td>
<td>50.2 ± 19</td>
<td>47 ± 20</td>
</tr>
<tr>
<td>APACHE II</td>
<td>19 ± 6</td>
<td>18.4 ± 6</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>Compliance</td>
<td>6 h (n [%])</td>
<td>14 (36)</td>
<td>22 (30)</td>
</tr>
<tr>
<td></td>
<td>24 h (n [%])</td>
<td>14 (36)</td>
<td>37 (50.7)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>20 (51.3)</td>
<td>38 (52)</td>
<td>58 (51.8)</td>
</tr>
<tr>
<td>ICU stay (d)</td>
<td>21 ± 42</td>
<td>15 ± 13</td>
<td>16 ± 29</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>43 ± 41</td>
<td>43 ± 32</td>
<td>44 ± 37</td>
</tr>
<tr>
<td>T-DSR (h)</td>
<td>18.7 ± 22</td>
<td>12.4 ± 20</td>
<td>13.6 ± 19</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are presented as mean ± SD. T-DSR indicates time required for the detection of sepsis risk.

* P < .05 for survivors vs nonsurvivors during phase I.
† P < .05 for phase I nonsurvivors vs phase II nonsurvivors.
‡ P < .05 for survivors vs nonsurvivors during phase II.
5. Conclusion

The results of the present study show that, more than structural problems, organizational and cultural aspects are of utmost importance.

To establish the diagnosis of sepsis in wards as early as possible, we must observe simple operational aspects, such as the monitoring and interpretation of vital signs. In this direction, nurses should promptly report changes in vital signs to physicians, who should give those changes the necessary attention. The use of this strategy not only reduced the time required to detect sepsis risk but also reduced mortality related to severe sepsis and septic shock.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jcrc.2010.08.001.

References