Septic Shock of Early or Late Onset*
Does It Matter?

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Study objectives: To determine possible differences in morbidity and mortality between early and late onset of septic shock in ICU patients.

Design: Systematic data collection.

Setting: Thirty-one–bed, mixed, medicosurgical ICU in a university hospital.

Patients: All 65 patients who acquired septic shock after admission to the ICU between February 1999 and April 2000.

Interventions: None.

Measurements and results: Forty-one of the 65 patients presented with septic shock within 24 h of admission to the ICU (early septic shock [ESS]); the other 21 patients acquired septic shock > 24 h after ICU admission (late septic shock [LSS]). Eleven patients had a second episode (7 patients in the ESS group, and 4 patients in the LSS group), and 1 patient in the LSS group had a third episode of septic shock. Patients with ESS had higher APACHE (acute physiology and chronic health evaluation) II (mean ± SD, 26 ± 6 vs 20 ± 6; p = 0.002) and sequential organ failure assessment (SOFA) scores (11 ± 3 vs 7 ± 3, p < 0.001) on ICU admission, and a higher blood lactate concentration at the onset of shock (median 3.70 mEq/L; interquartile range, 2.6 to 6.6 mEq/L; vs median, 2.50 mEq/L [interquartile range, 1.8 to 4.0 mEq/L], p = 0.03) than patients with LSS. However, the duration of septic shock (median, 42 h [interquartile range, 21 to 97 h] vs median, 93 h [interquartile range, 32 to 241 h], p = 0.058) and the length of ICU stay after the onset of septic shock (median, 75 h; [interquartile range, 38 to 203 h] vs median, 321 h [interquartile range, 96 to 438 h], p = 0.018), was shorter in patients with ESS than patients with LSS. The ICU mortality rate was 63% (26 patients) in the ESS group, and 88% (21 patients) in the LSS group (p = 0.071). At the onset of the first episode of shock, patients with ESS had higher SOFA scores (11 ± 3 vs 9 ± 3, p = 0.045), lower pH (7.24 ± 0.15 vs 7.33 ± 0.12, p = 0.01), and were treated with higher doses of dopamine (median, 20 μg/kg/min [interquartile range, 14 to 20 μg/kg/min] vs median, 12 μg/kg/min [interquartile range, 8 to 20 μg/kg/min], p = 0.028) than patients with LSS.

Conclusions: Septic shock is more severe when of early onset, as reflected by more severe organ dysfunction, greater lactic acidosis, and higher vasopressor requirements, yet the outcome is better, as reflected by a shorter duration of the shock episode, shorter ICU stay, and slightly lower mortality rates. These differences may influence clinical trials of therapeutic agents for sepsis, and should be taken into account when analyzing the results.

(CHEST 2004; 126:173–178)

Key words: blood lactate; length of stay; organ failure; outcome

Abbreviations: APACHE = acute physiology and chronic health evaluation; ESS = early septic shock; LSS = late septic shock; SOFA = sequential organ failure assessment

Septic shock is a common disease process among ICU patients and remains a major cause of morbidity and mortality worldwide. Indeed, the outcome of patients with septic shock has changed little despite advances in supportive therapy. Importantly, the presence of shock independently predicts mortality above that expected from sepsis alone, and rapid identification and effective, early interven-
The ICU. However, development of septic shock in an ICU patient who already has multiple organ failure may portend a very poor outcome, to the extent that vasopressor treatment may become futile.6 The time of onset of septic shock therefore may be very important in determining outcome, yet clinical trials do not usually report this information. The aim of this study was to evaluate the epidemiology and outcome of early vs late-onset septic shock in the ICU.

PATIENTS AND METHODS

The Ethics' Committee waived the need for informed consent, as this was an observational study. We retrospectively analyzed the clinical, hemodynamic, and biological data of all patients consecutively admitted to a 31-bed department of medical-surgical intensive care over a 14-month period (February 1999 to April 2000) who acquired septic shock. Septic shock was defined as hypotension (systolic BP of <90 mm Hg or a drop in systolic BP of >40 mm Hg from baseline), persisting at least 1 h despite administration of fluid for intravascular volume expansion, requiring use of vasopressor drugs to keep the systolic BP of >90 mm Hg, associated with signs of organ dysfunction or hypoperfusion (including, but not limited to, lactic acidosis, oliguria, or acute alterations in mental status), in the presence of a documented infection (as defined by the Centers for Disease Control and Prevention).5

In our institution, the treatment of circulatory shock follows a standard regimen. Resuscitation is based on fluid therapy, primarily colloids, for normalization of stroke volume. In addition, dopamine up to 20 μg/kg/min followed by norepinephrine infusion, when dopamine is inadequate, are administered in cases of hypotension refractory to fluid administration in order to maintain a mean arterial pressure between 65 mm Hg and 75 mm Hg. Dobutamine is added at doses up to 20 μg/kg/min when the cardiac index is <2.5 L/min/m² and/or the mixed venous oxygen saturation is <86% or severe myocardial depression is diagnosed using echocardiography. If, in spite of these drugs, hemodynamic stability is not obtained, epinephrine is added. All patients in shock requiring vasopressor agents are equipped with a pulmonary artery catheter. Adrenergic agents are weaned as early as possible. Repeated fluid challenges are performed according to filling pressure in order to exclude hypovolemia. Broad-spectrum empiric antibiotics are started based on likely pathogens according to the probable source of the sepsis, and adjusted as soon as culture results are available.

The onset of septic shock was considered as the start of vasopressor agents (dopamine, norepinephrine, or epinephrine) after a fluid challenge with crystalloid and/or colloids caused no further increase in cardiac index and pulmonary artery occlusion pressure remained between 10 mm Hg and 18 mm Hg. Patients with hypovolemic or cardiogenic shock who then acquired sepsis were not included due to the difficulty in determining the exact time of onset of shock due to sepsis in such patients.

Septic shock was considered as early when it presented within 24 h of ICU admission (early septic shock [ESS]) and late when it developed >24 h after ICU admission (late septic shock [LSS]). For this study, septic shock was considered to have resolved when the administration of vasopressor agents had been stopped for a period of at least 48 h. The need for further vasopressor support beyond this 48-h period was considered as a new episode of septic shock. All first episodes of shock were analyzed separately for the two groups. The data from all subsequent episodes of shock in the ESS group were assessed as part of the LSS group.

The following data were collected: body temperature, mean arterial pressure, heart rate, respiratory rate (nonventilated or ventilated), oxygenation: alveolar-arterial oxygen pressure gradient or PaO₂, fraction of inspired oxygen, arterial pH, serum sodium, serum potassium, serum creatinine, hemocrit, WBC count, Glasgow coma score, doses of vasopressor agents (dopamine, norepinephrine or epinephrine), platelet count, bilirubin concentration, and serum lactate concentration. For a single missing value, a replacement was calculated using the mean value of the result preceding and the result after the missing value. When more than one consecutive result was missing, it was considered as a missing value in the analysis.

The APACHE (acute physiology and chronic health evaluation) II score9 and the sequential organ failure assessment (SOFA) score11 were calculated on ICU admission in all patients. In patients with LSS, the SOFA score was calculated also on the day of onset of septic shock. The presence at ICU admission of the following risk factors for sepsis was noted: a diagnosis of trauma, surgery (elective or emergency), mechanical ventilation, history of neurologic vascular disease, immunosuppression, nephritis, or cirrhosis. Statistical analysis included a Student t test, x², and Fisher exact test. Nonparametric data were analyzed by a Mann-Whitney rank sum test. Data are reported as mean ± SD, unless stated otherwise; p < 0.05 was considered statistically significant.

RESULTS

There were no significant differences in primary diseases, risk factors, or sources of infection among the 41 patients with ESS and the 24 patients with LSS (Tables 1, 2). At the onset of shock, all patients were treated aggressively with fluids and vasoactive agents as per institution protocol. All patients received empiric antibiotics adjusted according to culture results; the rate of appropriateness of empirical antibiotic therapy was the similar in the two groups (data not shown). In the ESS group, 35 patients were in shock on or within 6 h of ICU admission, 2 patients were in shock within 6 to 12 h of ICU admission, and 4 patients were in shock within 12 to 24 h. In the LSS group, nine patients acquired shock between 24 h and 48 h of ICU admission, six patients between 48 h and 120 h, and nine patients ≥ 120 h after admission. As expected, the APACHE II
score at ICU admission was higher in patients with ESS than in patients with LSS (p = 0.002). The total length of ICU stay was longer in patients with LSS than patients with ESS (p < 0.001), as was the length of ICU stay after the onset of septic shock (Table 1). Of the patients with ESS, 15 survivors and 21 nonsurvivors received mechanical ventilation. Of the patients with LSS, 7 survivors and 16 nonsurvivors received mechanical ventilation. The mortality rate of patients during a first episode of septic shock was 51% (21 of 41 patients) in the ESS group, and 71% (17 of 24 patients) in the LSS group (p = 0.07). Eleven patients had a second episode of septic shock, and one patient had a third episode of septic shock. These patients had a mortality rate of 82% (9 of 11 patients; Fig 1).

Table 3 presents the data for patients during episodes of septic shock. For first episodes of shock, patients with ESS had higher SOFA scores, lower pH, higher blood lactate concentrations, and higher doses of dopamine than patients with LSS. However, when considering all episodes of septic shock, the SOFA score on the day of onset of septic shock was not significantly different in the ESS and LSS groups (p = 0.209). The cardiovascular SOFA scores on ICU admission and on the day of onset of septic shock were higher in the patients with ESS than in the patients with LSS (data not shown). The renal SOFA score on ICU admission was higher in patients with ESS than in patients with LSS (p = 0.011). At
the onset of shock, blood lactate levels were higher in patients with ESS than in patients with LSS (p = 0.03).

**DISCUSSION**

Septic shock, the most severe form of sepsis, is associated with high mortality rates, largely due to the progressive compromise of various organ systems and the development of multiple organ failure. In our study, the mortality rates of 63% (ESS) and 88% (LSS) were higher than those reported in recent clinical trials, likely related to the presence of severe underlying disease (advanced malignancy, cirrhosis, neurologic disease) in many of our patients; such patients are frequently excluded from interventional studies. Interestingly, recent epidemiologic studies in Europe have reported similar septic shock mortality rates of 60%. This highlights an important difference between the mortality rates noted in clinical trials of new therapeutic agents, where specific groups of intensive care patients may be excluded, and the real-life situation.

The time of onset of treatment may play a critical role in outcome in patients with severe sepsis and septic shock. Early and effective antibiotic therapy is associated with reduced mortality rates. Lundberg et al showed a trend toward increased mortality for patients who acquired septic shock on a general ward compared to those who acquired septic shock on the ICU, despite being younger and having lower APACHE scores. These authors suggested that a delay in the administration of vasoactive drugs in general ward patients as opposed to ICU patients may have been responsible for the increased mortality. However, starting strong vasopressor support in already severely compromised patients may be futile. Abid et al showed a relationship between mortality and both the degree

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**Figure 1. Patient classification by episode of septic shock.**
of organ dysfunction and the duration of ICU stay before starting norepinephrine.

The present study shows important differences in the characteristics of early and late episodes of septic shock. Episodes of septic shock presenting early during ICU admission were more severe than those developing later; the APACHE II and SOFA scores were higher in patients with ESS than in patients with LSS, demonstrating higher disease severity and greater organ compromise in these patients. However, the ICU length of stay after the onset of shock was shorter in ESS than in LSS, and the mortality rate was somewhat higher when shock developed late than when it developed early. Thus, ESS appears to be more severe but has a better outcome. In patients with sepsis syndrome, Knaus et al18 also noted that mortality was increased in patients with a longer “lead-time,” ie, a longer hospital or ICU stay before meeting sepsis syndrome criteria. However, Brun-Buisson et al12 found no relation between mortality and the time between ICU admission and development of severe sepsis. These contrasting results may be due to the different definitions of sepsis used.

In our unit, all patients with septic shock are treated according to a strict protocol, so that the differences in length of stay and outcome were not related to different therapeutic regimes. Importantly, there were no differences in risk factors or sources of infection among early and late episodes of septic shock, although there were some differences in the organisms responsible for infection. Infections due to Pseudomonas species were more common in the late-onset group, perhaps not surprising, as nosocomial infections are more common in patients staying longer in the ICU. The principal organism in the ESS group was Streptococcus pneumoniae. The differences in causative organisms may in part explain the differences in mortality, as Pseudomonal infections are associated with higher mortality rates.19 Another possible explanation for the observations is the role of vasopressor agents in the metabolism of cyclic adenosine monophosphate, via adrenergic receptors, modulating the inflammatory response.20,21

In conclusion, despite being similar in terms of risk factors, admitting disease, and source of infection, patients who acquired septic shock early during their ICU stay had a higher degree of illness severity and more severe organ dysfunction, yet outcome was better. Such differences may influence the results of clinical trials and should be taken into account when analyzing clinical trial data.

Table 3—Data From Episodes of Shock*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early Onset</th>
<th>First Episode</th>
<th>p Value vs Early Onset</th>
<th>All Episodes</th>
<th>p Value vs Early Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes, No.</td>
<td>41</td>
<td>24</td>
<td></td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>SOFA score</td>
<td>11 ± 3</td>
<td>9 ± 3</td>
<td>0.045</td>
<td>10 ± 3</td>
<td>0.200</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.24 ± 0.15</td>
<td>7.33 ± 0.12</td>
<td>0.010</td>
<td>7.29 ± 0.15</td>
<td>0.249</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>37.4 ± 10.0</td>
<td>34.7 ± 8.1</td>
<td>0.257</td>
<td>34.3 ± 7.1</td>
<td>0.126</td>
</tr>
<tr>
<td>Lactate, mEq/L</td>
<td>3.7 (2.6–6.7)</td>
<td>2.5 (1.7–3.4)</td>
<td>0.02</td>
<td>2.5 (1.8–4.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No.</td>
<td>41</td>
<td>24</td>
<td></td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Maximum doses, µg/kg/min</td>
<td>20 (14–20)</td>
<td>12 (8–20)</td>
<td>0.028</td>
<td>16 (10–20)</td>
<td>0.094</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No.</td>
<td>20</td>
<td>3</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Maximum doses, µg/kg/min</td>
<td>0.3 (0.1–1.0)</td>
<td>2.1 (0.7–3.3)</td>
<td>0.132</td>
<td>1.8 (1.2–2.7)</td>
<td>0.220</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, No.</td>
<td>3</td>
<td>0</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maximum doses, µg/kg/min</td>
<td>2.6 (1.8–9.5)†</td>
<td>0</td>
<td></td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Shock duration, h</td>
<td>42 (21–97)</td>
<td>89 (32–242)</td>
<td>0.075</td>
<td>93 (32–241)</td>
<td>0.058</td>
</tr>
<tr>
<td>Shock duration in survivors, h</td>
<td>77 (25–152)</td>
<td>59 (34–98)</td>
<td>0.078</td>
<td>77 (44–100)</td>
<td>0.809</td>
</tr>
<tr>
<td>Mortality, No. (%)</td>
<td>21 (51)</td>
<td>17 (71)</td>
<td>0.070</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as median (25–75 percentile) unless otherwise indicated.
†Median (range).

References