Epidemiology of Sepsis and Multiple Organ Dysfunction Syndrome in Children

François Proulx, MD; Michael Fayon, MD; Catherine Ann Farrell, MD; Jacques Lacroix, MD; and Marie Gauthier, MD

Study objectives: To determine the cumulated incidence and the density of incidence of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) in critically ill children; to distinguish patients with primary from those with secondary MODS.

Design: Prospective cohort study.

Setting: Pediatric ICU of a university hospital.

Patients: One thousand fifty-eight consecutive hospital admissions.

Interventions: None.

Measurements and results: SIRS occurred in 82% (n=869) of hospital admissions, 23% (n=245) had sepsis, 4% (n=46) had severe sepsis, 2% (n=25) had septic shock; 16% (n=168) had primary MODS and 2% (n=23) had secondary MODS; 6% (n=68) of the study population died. The pediatric risk of mortality (PRISM) scores on the first day of admission to pediatric ICU were as follows: 3.9±3.6 (no SIRS), 7.0±7.0 (SIRS), 9.5±8.3 (sepsis), 8.8±7.8 (severe sepsis), 21.8±15.8 (septic shock); differences among groups (p=0.0001), all orthogonal comparisons, were significant (p<0.05), except for patients with severe sepsis. The observed mortality for the whole study population was also different according to the underlying diagnostic category (p=0.0001; p<0.05 for patients with SIRS and those with septic shock, compared with all groups). Among patients with MODS, the difference in mortality between groups did not reach significance (p=0.057). Children with secondary MODS had a longer duration of organ dysfunctions (p<0.0001), a longer stay in pediatric ICU after MODS diagnosis (p<0.0001), and a higher risk of mortality (odds ratio, 6.5 [2.7 to 15.9], p<0.0001) than patients with primary MODS.

Conclusions: SIRS and sepsis occur frequently in critically ill children. The presence of SIRS, sepsis, or septic shock is associated with a distinct risk of mortality among critically ill children admitted to the pediatric ICU; more data are needed concerning children with MODS. Secondary MODS is much less common than primary MODS, but it is associated with an increased morbidity and mortality; we speculate that distinct pathophysiological mechanisms are involved in these two conditions.

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Key words: child; critical care; incidence; intensive care units; multiple organ failure; prospective study; septicemia; severity of illness

Recent advances in the understanding of the pathophysiology of organ dysfunctions have generated an attractive conceptual framework with which to approach the problem of sepsis and multiple organ dysfunction syndrome (MODS), with a view to developing innovative therapies. New definitions for sepsis and MODS have recently been suggested by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Urging further studies, experts proposed diagnostic criteria for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock as well as conceptual guidelines to distinguish between primary and secondary MODS. It is expected that standardizing the terminology could enhance the quality of assessment of new therapeutic interventions.

Mortality in critically ill children is highly associated with MODS. Pediatric MODS usually presents acutely with a simultaneous onset of organ dysfunctions, and death frequently occurs early after diagnosis. Contrary to observations in the adult population, sepsis may not significantly increase the risk of mortality among children with MODS. Epidemiologic data on sepsis and MODS remain meager in critically ill patients. There are remarkably little data concerning children with progressive or sequential organ dysfunctions. The purpose of this study was first to determine the cumulated incidence and the density...
of incidence of SIRS, sepsis, severe sepsis, septic shock, and MODS in critically ill children admitted to the pediatric ICU. Secondly, we aimed to distinguish patients with primary MODS from those with secondary MODS according to their epidemiologic characteristics.

**Materials and Methods**

From July 1, 1991, to July 31, 1992, all children aged between 0 and 18 years, admitted to the pediatric ICU at Sainte-Justine Hospital, were studied prospectively. Sainte-Justine’s pediatric ICU is a 22-bed multidisciplinary unit in a tertiary care pediatric university teaching hospital. The study was approved by the ethics committee of Sainte-Justine Hospital who waived the need for informed consent.

Time zero was defined as the time of admission to the pediatric ICU and the study of a case ended with discharge from ICU or with death, whichever came first. All patients who were readmitted to the ICU were considered as new cases if the time elapsed between ICU discharge and readmission was more than 72 h; otherwise, days were added as if it was a single pediatric ICU stay. All pediatric ICU admissions, age, sex, final diagnoses, pediatric risk of mortality (PRISM) score on ICU admission, worst PRISM score, positive cultures from any site during ICU stay, occurrence of organ dysfunctions, length of stay, and ICU mortality were noted. Patients with SIRS, sepsis, severe sepsis, and septic shock were identified by looking at the following data: temperature, respiratory rate, heart rate, arterial BP, urine output, Glasgow Coma Score, arterial blood gas values, serum lactate level, WBC count, and inotropic/vasopressor agents.

Diagnostic criteria for SIRS, sepsis, severe sepsis, and septic shock were those suggested by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, with adjustments for age according to reference values. SIRS was defined by the presence of at least two of the following criteria: (1) temperature more than 38°C or less than 36°C; (2) WBC count greater than 12×10⁹/L or less than 4×10⁹/L; (3) lactate level more than 2 mmol/L; (4) heart rate more than 90th percentile for age; (5) tachypnea with a respiratory rate more than 90th percentile for age or hyperventilation, as indicated by PaCO₂ less than 32 mm Hg; (6) BP greater than 120/80 mm Hg or less than 90/50 mm Hg; (7) urine output less than 0.5 mL/kg/h for 2 consecutive hours measured with a urinary catheter. Septic shock occurred in the presence of hypotension with two distinct measurements of blood pressure less than the third percentile for age, after administration of 20 mL/kg or more of crystalloid or colloid plus (1) the requirement of inotropic or vasopressor support (excluding dopamine ≤5 μg/kg/min) or (2) any of the previously defined diagnostic criteria for severe sepsis.

MODS was defined as the simultaneous occurrence of two organ dysfunctions. We modified slightly the criteria suggested by Wilkinson et al. Any item within each category was considered diagnostic. Cardiovascular System: (1) Systolic BP less than 40 mm Hg for patients younger than 12 months or less than 50 mm Hg for patients 12 months or older; (2) heart rate less than 50 or more than 220 beats/min for patients younger than 12 months or less than 40 or more than 200 beats/min for patients aged 12 months or older; (3) cardiac arrest; (4) serum pH less than 7.2 with a normal PaCO₂ value; and (5) continuous IV infusion of inotropic agents to maintain BP and/or cardiac output (dopamine ≤5 μg/kg/min was excluded). Respiratory System: (1) Respiratory rate more than 90 breaths/min for patients younger than 12 months or more than 70 breaths/min for patients 12 months or older; (2) PaCO₂ more than 8.7 kPa (>65 mm Hg); (3) PaO₂ less than 5.3 kPa (<40 mm Hg), in the absence of cyanotic congenital heart disease; (4) mechanical ventilation (for >24 h in a postoperative patient); and (5) PaO₂/ fraction of inspired oxygen less than 200, in the absence of cyanotic congenital heart disease. Neurologic System: (1) Glasgow Coma Score less than 5; and (2) fixed dilated pupils. Hematologic System: (1) Hemoglobin level less than 50 g/L (<5 g/dL); (2) WBC count less than 3×10⁹/L (<3,000 cells per cubic millimeter); (3) platelet count less than 20×10⁹/L (<20,000 cells per cubic millimeter); and (4) D-dimer more than 0.5 mg/mL with prothrombin time more than 20 s or partial thromboplastin time more than 60 s. Renal System: Serum urea nitrogen value of 36 mmol/L or more (≥100 mg/dL); (2) serum creatinine concentration of 177 μmol/L or more (≥2.0 mg/dL), in the absence of preexisting renal disease; and (3) dialysis. Hepatic System: Total bilirubin level more than 60 mmol/L (>3 mg/dL), excluding icterus due to breast feeding. GI System: Gastrointestinal bleeding and one of the following criteria believed to be the result of gastrointestinal bleeding by the treating physician: (1) drop in the hemoglobin level of 20 g/L or more (≥2 g/dL) over 24 h; (2) blood transfusion; (3) hypotension with BP less than third percentile for age; (4) gastric or duodenal surgery; and (5) death. Primary MODS was defined as the occurrence of two simultaneous organ dysfunctions within the first week after pediatric ICU admission, without subsequent evidence of sequential organ dysfunctions as defined below. Secondary MODS was defined as either one of the following: (1) appearance of MODS more than 7 days after admission to pediatric ICU or (2) diagnosis of MODS 7 days or less after ICU admission in the presence of sequential organ dysfunctions defined as an interval longer than 72 h between the time of MODS diagnosis and the attainment of the maximum number of simultaneous organ dysfunctions. Secondary MODS must have occurred in the context of SIRS.

The cumulated incidence was defined as the number of new cases divided by the population at risk during the entire study period. Density of incidence corresponds to the number of new cases per unit person-time (1,000 patient-days) under risk in a given time interval. Density of incidence was used to calculate the risk of acquiring SIRS, sepsis, severe sepsis, septic shock, and MODS for each day after admission to pediatric ICU, according to the following formula: Risk = 1 - e⁻ⁿ, where n is the number of days at risk.

Descriptive statistics are presented as mean ± SD or median and range. Comparative analyses were done using the χ² test for categorical data. Odds ratio and 95% confidence interval are presented for significant result only. Unpaired bilateral Student’s t test was used for continuous data with a normal distribution and the Mann-Whitney U test if the distribution was abnormal. All cases were classified into the following independent diagnostic categories: no SIRS, SIRS, sepsis, severe sepsis, or septic shock, according to the worst state present during stay in pediatric ICU. These groups were compared using analysis of variance for nonrepeated measurements; orthogonal comparisons were done using the Scheffe F test; statistical significance was reached at 0.05.

**Results**

From July 1, 1991, to July 31, 1992, there were 1,058 admissions to the pediatric ICU among 916 children.
There were 657 (62%) male and 401 (38%) female patients; 570 (54%) and 488 (46%) children were admitted in surgical and medical services, respectively. The median age was 35 months (range, 0 to 216 months), and the median length of ICU stay was 2 days (range, 0 to 296 days).

The cumulated incidence of SIRS was 82% (n=869); it was 23% (n=245) for sepsis, 4% (n=46) for severe sepsis, and 2% (n=25) for septic shock. Five percent of the subjects (n=52) had at least one positive blood culture. The worst diagnostic category presented by patients during their pediatric ICU stay was as follows: no SIRS in 18% (n=193) of the study population, SIRS in 60% (n=627), sepsis in 18% (n=192), severe sepsis in 2% (n=21) and septic shock in 2% (n=25). The PRISM scores on the first day of admission to pediatric ICU were as follows: 3.9±3.6 (no SRS), 7.0±7.0 (SIRS), 9.5±8.3 (sepsis), 8.8±7.8 (severe sepsis), and 21.8±15.8 (septic shock); differences among groups (p=0.0001), all orthogonal comparisons, were significant (p<0.05), except for patients with severe sepsis. The worst PRISM scores during pediatric ICU stay were as follows: 3.9±4.4 (no SIRS), 7.8±8.8 (SIRS), 10.6±9.8 (sepsis), 11.1±10.1 (severe sepsis), and 25.7±16.8 (septic shock); differences among groups (p=0.0001), all orthogonal comparisons, were signifi-
cant (p<0.05), except for patients with severe sepsis. The observed mortality for the whole study population was also different according to the underlying diagnostic category (p=0.0001; p<0.05 for patients with SIRS and those with septic shock, compared with all groups). The density of incidence of SIRS, sepsis, severe sepsis, septic shock, and MODS is shown in Figure 1. The risk over time of acquiring SIRS, sepsis, severe sepsis, septic shock, and MODS is presented in Figure 2.

MODS was identified among 18% (n=191) of the study population; 4% of patients with MODS had been readmitted to the ICU, 6 children had been readmitted once, and 2 children had been readmitted twice. The time elapsed between discharge from pediatric ICU and readmission was more than 2 months in five patients and it was 8, 9, 10, 10, and 15 days, respectively, in the remaining five children. Forty-five percent (n=96) of children who presented with MODS had a maximum of two organ dysfunctions, 31% (n=59) had three, 13% (n=24) had four, 7% (n=13) had five, 3% (n=6) had six, and 1% (n=3) had seven organ dysfunctions. There were 68 deaths, accounting for 36% of patients with MODS and 6% of the study population. Among children with MODS, we observed a trend (p=0.057) toward distinct mortality rates according to the underlying diagnostic category: patients without SIRS (1/8, 12%), those with SIRS (44/111, 40%), sepsis (9/41, 22%), severe sepsis (2/8, 25%), or septic shock (12/23, 52%).

There were 168 children with primary MODS and 23 patients with secondary MODS; these patients accounted for 16% and 2% of the study population, respectively. Diagnostic criteria for secondary MODS were met after the first week of pediatric ICU admission in 47% (11/23) of patients and 53% (12/23) of patients with secondary MODS reached diagnostic criteria within 7 days of ICU admission. Comparative analysis between patients with primary or secondary MODS showed a worse PRISM score, a longer duration of MODS, a prolonged ICU stay, and a higher mortality rate among those children with secondary MODS (Table 1).

### Table 1—Characteristics of Critically Ill Children With Primary or Secondary Multiple Organ Dysfunction Syndrome (MODS)

<table>
<thead>
<tr>
<th>Primary MODS</th>
<th>Secondary MODS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=168)</td>
<td>(n=23)</td>
</tr>
<tr>
<td>Age, mo</td>
<td>48.8±61.7</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>115/168 (68)</td>
</tr>
<tr>
<td>PRISM score (1st day)</td>
<td>17.0±11.8</td>
</tr>
<tr>
<td>Worst PRISM score</td>
<td>20.1±13.0</td>
</tr>
<tr>
<td>No SIRS</td>
<td>8/8</td>
</tr>
<tr>
<td>SIRS</td>
<td>99/111</td>
</tr>
<tr>
<td>Sepsis</td>
<td>36/41</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>8/8</td>
</tr>
<tr>
<td>Septic shock</td>
<td>17/23</td>
</tr>
<tr>
<td>Positive blood culture (%)</td>
<td>26/168 (15)</td>
</tr>
<tr>
<td>Duration of MODS, d</td>
<td>3.6±3.7</td>
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<tr>
<td>Length of stay in ICU after MODS diagnosis, d</td>
<td>7.9±14.2</td>
</tr>
<tr>
<td>Death (%)</td>
<td>51/168 (30)</td>
</tr>
</tbody>
</table>

*Analysis of variance: p=0.158.

**Odds ratio (95% confidence interval) for death: 6.5 (2.7 to 15.9).**

**Discussion**

This study was conducted in a single pediatric ICU; there were few children with major burns and no bone marrow transplant patients, a group clearly at risk of developing sepsis and sequential MODS.15,16 This selection bias precludes making inferences from our data to these different subpopulations. However, the age distribution, the relative proportion of medical and surgical cases, and the incidence of sepsis and MODS among our patients were similar to those previously reported,3,4,7 suggesting that our study population was representative of that of a typical pediatric ICU.

SIRS was noted to be the most frequent worst pathologic diagnostic category. Conceptually, SIRS represents endothelial inflammation occurring after various insults, such as trauma or pancreatitis.17 By definition, virtually all patients with a significant infection display evidence of SIRS, but the converse is not true.17 Severe sepsis and septic shock supposedly represent more advanced stages in the continuum of events leading to MODS. We found decreasing cumulated incidences of SIRS, sepsis, severe sepsis, and septic shock. However, we observed an appreciable gap between the frequency of SIRS, that of sepsis, and those of severe sepsis/septic shock. The validity of the definitions proposed by the consensus conference on sepsis and MODS has been previously questioned by
some authors since, for example, many children with streptococcal pharyngitis could be identified as having sepsis using current diagnostic criteria. Moreover, in the adult population, the risk of mortality associated with SIRS has been shown to be highly variable. The utility of these definitions relies on a demonstration that different pathophysiologic stages are being defined, each comporting its own prognostic value. We showed that diagnostic categories were associated with distinct PRISM scores and observed mortality rates with respect to the whole study population. When considering only children with MODS, statistical analysis did not reach significance. Patients with MODS and SIRS had a 40% mortality rate, which is close to the rate of 52% found among those with MODS and septic shock. The relatively small number of patients within each class may have limited the power to detect any difference.

Cumulated incidence is a valuable measure of risk and probability of disease. Density of incidence, also called the incidence rate, allows the assessment of rapidity of disease occurrence. We observed an initial peak in the density of incidence of SIRS, sepsis, severe sepsis, septic shock, and MODS on the day of admission to pediatric ICU; the density of incidence declined rapidly to be followed by a subsequent increase. These observations may result in part from a rapid decrease over time in the number of patients remaining in pediatric ICU.

We stratified patients with organ dysfunctions into those with primary and secondary MODS. Early acute organ system failure is now recognized in the adult literature. Primary MODS is usually considered as the direct result of a well-defined insult in which organ dysfunctions occur early and can be directly attributed to the insult itself; secondary MODS may be the consequence of the host’s response and is identified in the context of SIRS. An accurate distinction between these entities may be difficult to make clinically. We recognize that the 7-day cutoff point used in this study to distinguish between primary and secondary MODS is somewhat arbitrary, although it is supported by our data, showing a trend toward an increasing density of incidence of MODS around the end of the first week of pediatric ICU admission. We found that only 12% of children with MODS had secondary MODS. The duration of MODS and the length of stay in pediatric ICU after MODS diagnosis were longer among children with secondary MODS, providing indirect evidence of an increased morbidity among these patients. The risk of mortality was 6.5 times higher among children with secondary MODS. Distinct risks of morbidity and mortality may suggest that different pathophysiologic mechanisms are involved in children with primary and secondary MODS. Studies at the cellular and the molecular levels may provide a strong basis for the rational use of innovative therapies in critically ill children with MODS.

**REFERENCES**