OUR EXPERIENCE IN PEDIATRIC SEPSIS

M Militaru, D Martinovici
2nd Pediatrics Clinic Cluj-Napoca, Romania

Abstract

Despite the existence of an international consensus regarding both pediatric sepsis-related definitions, and the management of this serious condition, there is no detailed analysis of the epidemiology, diagnosis and prognosis of pediatric sepsis in Romania. We sought to determine the influence of age, gender, microbiologic etiology, and underlying condition on the incidence, outcome, and associated hospital resources use of sepsis and its complications in pediatric patients. We analyzed our Clinic's patients' files for the years 2003 and 2004. Of 2876 hospitalizations for an infectious process in children, 248 met the International Pediatric Sepsis Consensus Conference definitions for sepsis, or 124 cases of pediatric sepsis per year. The incidence was highest in infants (12 per 100 infected children) and fell constantly with age. The incidence of sepsis in children did not vary significantly by sex in any of the age groups. One third of the cases had underlying disease (33%). The majority of infections causing sepsis were respiratory (64%). Microbiologic etiology was determined in 25% of all cases, with Gram-negative bacteria being the most important pathogens. Hospital mortality was 5% overall, with a mortality of 53% for the patients presenting with septic shock. The mean length of stay was 12 days. Several factors were significantly associated ($p<0.005$) with a poor outcome: shock, metabolic acidosis, increased serum bilirubin and creatinine levels, the presence of 4 or more organ dysfunctions. The therapy with corticosteroids was found to improve the outcome of pediatric patients with severe sepsis or septic shock. Sepsis is a significant healthcare problem in children and is associated with the use of extensive healthcare resources. We therefore need to make efforts to increase awareness and adopt the existing evidence-based recommendations for the management of sepsis and its complications.

Keywords: sepsis, severe sepsis, septic shock, children, epidemiology, clinical features, treatment, mortality, prognostic factors.

Introduction

The worldwide burden of sepsis in children is tremendous. Latest reports suggest that in the United States alone, there were estimated 4,400 pediatric deaths from sepsis every year, with hospital costs of $ 1,7 billion, and sepsis being the fourth leading cause of hospital admissions. However, most research has focused on adults, and information about sepsis in children is limited.

A description of pediatric-specific definitions for systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome was recently published (1). Still, there is no detailed analysis of the epidemiology, diagnosis, treatment, and prognosis of pediatric sepsis in Romania. We therefore sought to explore our Clinic's sample of pediatric sepsis in more depth. Specifically, we analyzed the impact of age, gender, underlying pediatric disease, and microbiologic etiology on the incidence, mortality, and length of hospitalization of children who develop sepsis; as well as several clinical features occurring in children with sepsis; and the existence of a series of parameters, which could be used as outcome-predicting factors.

Purpose

The main goal of our study was to determine the importance of sepsis and its complications in the general morbidity and mortality in the pediatric population. Secondly, we tried to identify those parameters, which could be used as prognostic factors. And last - we analyzed the results of the various management strategies currently applied in the treatment of sepsis and its complications in our Clinic.

Materials and methods

Data sources

We constructed a patient database for the calendar years 2003 and 2004 based on the analysis of the patients' files. We extracted demographic characteristics (age, gender, social background), principal and all secondary admission and discharge diagnoses, clinical parameters (community/hospital-acquired infection, SIRS criteria, organ dysfunction parameters: respiratory, cardiovascular, digestive, hepatic, neurologic, renal, hematologic, shock), laboratory parameters (erythrocytes sedimentation rate, white blood cells count, hemoglobin, hematocrit, platelets count, fibrinogen, procalcitonin, C-reactive protein, pH and blood gases, serum electrolytes, coagulation parameters, BUN, creatinine, bilirubin, AST and ALT, chest radiograph, other imaging examinations, electrocardiogram, blood cultures and other cultures and antibiogram results), therapeutical measures and duration (antibiotics, fluids resuscitation, inotropics, vasopressors, transfusions, corticosteroids, intravenous immunoglobulin, GM-CSF, oxygen), length of sepsis, length of stay, and hospital discharge status.

Case selection and definitions

We identified cases with sepsis, severe sepsis or septic shock by analyzing all hospitalizations for a bacterial or fungal infectious process from our Clinic within the 2-years period.

We defined children as patients who are 18 years old or less, and divided them into 6 clinically and

physiologically meaningful age groups for age-specific vital signs and laboratory variables to meet the diagnosis criteria, as recommended by the Consensus Panel (1). (Tables 1 and 3).

The diagnosis was based on the current specific definitions of systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, and organ dysfunction for neonates and children (1). (Tables 2 and 4).

Table 1: Pediatric age groups for sepsis definitions

Age-group	Age
Newborn	0 days to 1 month
Infant	1 month to 1 year
Toddler	1 to 3 years
Preschool	3 to 6 years
School age child	6 to 12 years
Adolescent	12 to 18 years

Table 2: Definitions of SIRS, infection, sepsis, severe sepsis and septic shock

SIRS[*]

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- Core[**] temperature of >38.5°C or <36°C.
- Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5-to 4-hr time period OR for children <1 yr old: Bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.
- Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or receipt of general anesthesia.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or >10% immature neutrophils.

Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

Sepsis

SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other dysfunctions (defined in Table 4).

Septic shock

Sepsis and cardiovascular organ dysfunction as defined in Table 4.

[*]See Table 3 for age-specific ranges for physiologic and laboratory variables; [**]core temperature must be measured by rectal, bladder, oral or central catheter probe.

Table 3: Age-specific vital signs and laboratory variables (lower values for heart rate, leukocyte count, and systolic blood pressure are for the 5th and upper values heart rate, respiration rate, or leukocyte count for the 95th percentile).

Age group	HR beats/min		R	Leukocyte Count X 10^3/mm^3	SBP
	↑	↓			
Newborn	>180	<100	>50	>19.5 or <5	<65
Infant	>180	<90	>34	>17.5 or <5	<100
Toddler	>160	NA	>29	>16.5 or <5	<100
Preschool	>140	NA	>22	>15.5 or <6	<94
School age child	>130	NA	>18	>13.5 or<4.5	<105
Adolescent	>110	NA	>14	>11 or <4.5	<117

HR- heart rate; ↑-tachycardia; ↓- bradycardia; RR- respiratory rate; SBP- systolic blood pressure; NA- not applicable.

Table 4: Organ dysfunction criteria

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus ≥ 40 ml/kg in 1 hr:

- Decrease in blood pressure (hypotension) <5th percentile for age or systolic BP < 2 SD below normal for age. OR
- Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) OR
- Two of the following:

Unexplained metabolic acidosis: base deficit>5mEq/l;

Increased arterial lactate >2times upper limit of normal;

Oliguria: urine output <0.5 ml/kg/hr;

Prolonged capillary refill: >5 seconds;

Core to peripheral temperature gap >3°C.

Respiratory

- PaO_2/FiO_2 <300 in absence of cyanotic heart disease or preexisting lung disease; OR

- $PaCO_2$ >65 torr or 20 mmHg over baseline $PaCO_2$; OR
- Proven need of >50% FiO_2 to maintain saturation ≥92%; OR
- Need for nonelective invasive or noninvasive mechanical ventilation.

Neurologic

- Glasgow Coma Score ≤11; OR
- Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline.

Hematologic

- Platelet count < 80,000/mm^3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients); OR
- International normalized ratio >2.

Renal

- Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline level.

Hepatic

- Total bilirubin ≥4 mg/dl (not applicable for newborn); OR
- ALT 2 times upper limit of normal for age.

Surgical cases were not taken into account. We defined cases as surgical if they had a major surgical procedure other than tracheotomy.

Statistical analysis

We constructed the databases and conducted analyses in Microsoft Excel (Microsoft Corp., Redmond, WA). We compared categorical data by chi-square test and continuous data by Student and Anova test as appropriate.

Results

Epidemiology

We identified 248 cases of sepsis within the 2 years. The age- and sex-adjusted annual incidence of sepsis was 8.5 cases per 100 children hospitalized for a bacterial or fungal infection or 124 cases of sepsis per year. The incidence was highest in infants (12 per 100 infected children, 38% of the cases, p=0.001) and fell constantly with age. The mean age was 46 months (median, 24 months). The incidence of sepsis in children did not vary significantly by sex for any of the considered age groups.

One third of all children with sepsis (33%) had underlying comorbidity. Drug-induced conditions (drug-induced Cushing-syndrome or chemotherapy-induced neutropenia) were the most common categories of underlying disease overall (23%), followed by malnutrition (20% of the cases).

Site of infection and microbiologic etiology

The majority of infections causing sepsis were respiratory (64%), followed by digestive and urinary tract infections (18% and 12% respectively). (Table 5).

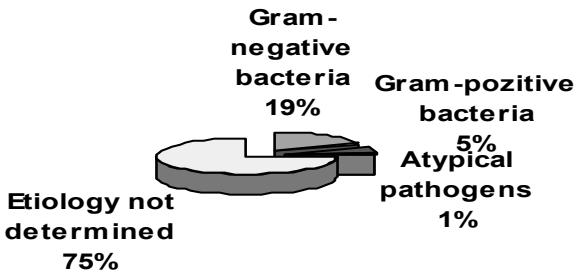
Table 5: The source of infections causing sepsis

Source	Number of cases	%
Respiratory	156	63%
Digestive tract	42	18%
Urinary tract	30	12%
Central nervous system	6	2.4%
Ear/nose	3	1.2%
Central venous or ventricular catheter	3	1.2%
Cutaneous/soft tissues	1	0.4%
Peritonitis	1	0.4%
Undetermined	6	2.4%

Respiratory infections predominated in toddlers (45% of the cases), whereas digestive sepsis was particularly common in infants (36%).

The microbiologic etiology was only determined for 25% of the patients. As shown in Figure 1, Gram-negative bacteria caused the majority of infections that evolved with sepsis.

Figure 1: Microbiologic etiology of infections in patients with sepsis



Enterobacteriaceae caused most of Gram-negative infections (59%), with *Escherichia coli* (56%) and *Klebsiella pneumoniae* (12%) being the most frequent pathogens. *Pseudomonas aeruginosa* (10%) was the third most frequent agent of Gram-negative sepsis. The most common Gram-positive infecting organism was *Staphylococcus aureus* (75%). Atypical pathogens were identified in a minority of patients (4%).

Diagnosis and Clinical Features

Our study showed that only 19 (7.66%) out of the 248 cases of sepsis, which we found, had been correctly diagnosed during the hospitalization period. Other 27 cases (10.8%) were diagnosed as sepsis, septic shock or septicemia without fulfilling the diagnosis criteria or were diagnosed as 'septic- or toxico-septic state'.

Most frequently patients presented with 3 out of the 4 diagnosis criteria (56% of the cases, p=0.00002). The most common were changes in core temperature (either fever or hypothermia) (98% overall); significant changes in the heart rate occurred in 90% of the patients; tachypnea occurred in 38% of the cases; leukocyte count abnormalities were encountered in 95% of our patients.

Children with sepsis were found to present with a large variety of symptoms and signs, or alteration of the laboratory variables. (Table 6)

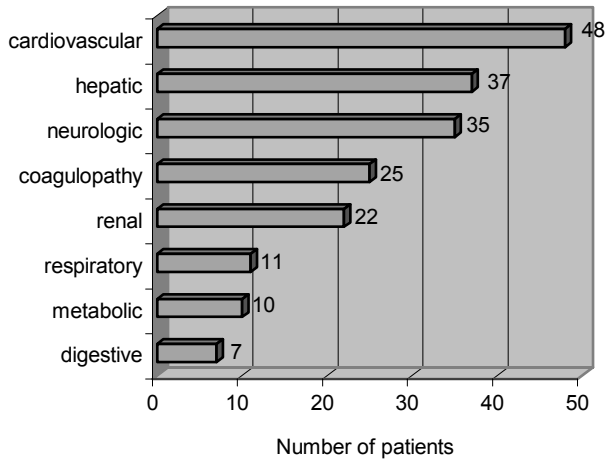
Table 6: Symptoms and signs in pediatric septic patients

Symptoms and signs	No of patients	%
Neurological	35	14%
Cardiovascular	22	9%
Respiratory	11	4%
Digestive	7	3%
Hepatic	25	10%
Renal	20	8%
Cutaneous	20	8%
Coagulopathy	20	8%

Up to 24% of the patients included in our study had a severe evolution: severe sepsis occurred in 17% of all cases, and septic shock affected 7%. The majority of infections causing severe sepsis were either respiratory (48%) or digestive (31%), as well as for the septic shock, which actually occurred only as a consequence of respiratory (65%) and digestive (35%) infections. The incidence of both severe sepsis and septic shock was the highest in infants (31% and 35% respectively).

Most patients with MODS presented with an association of 4 or more organ dysfunctions (35%, p<0.005). As shown in Figure 2, the most common organ dysfunction was the cardiovascular organ dysfunction (occurring in 17% of the children with sepsis).

Figure 2: The organ dysfunctions in children with sepsis



Treatment

The recommendations of the Consensus Conference were followed in less than 5% of all patients.

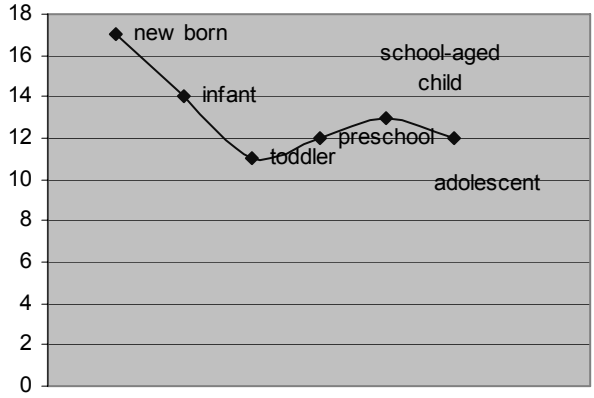
Initial empirical anti-infective therapy included a mean of 2 antibiotics per patient, with a minimum of 1 and a maximum of 7 antibiotics per patient. An antibiogram was performed in only 4% of all patients. The mean duration of anti-infective therapy was 10 days, with a minimum o 1 day and a maximum of 91 days. The most commonly used were 3rd generation Cephalosporins (71%). The most frequently used was Ceftriaxone (30%). The most frequent association of 2 antibiotics was Ceftazidime + Amikacin (39%).

Fluid resuscitation was used for the therapy of 93% of the patients with severe sepsis and septic shock. Inotropic therapy and vasoactive drugs were used in 10% of all patients with severe sepsis and septic shock. A number of 20 patients with severe sepsis and septic shock received intravenous corticosteroids (hydrocortisone), mostly those with sepsis of respiratory origin.

Hospital Resource Use

The mean length of stay (LOS) was 12 days, with a minimum of 1 day and a maximum of 91 days. Forty percent of the total hospital days were incurred by new-borns, who had a higher mean LOS than other children (18 vs. 7 days, p< 0.00001). (Figure 3). Mean LOS was similar between boys and girls. The mean LOS was also high in patients with underlying disease (21 days). Nonsurvivors had a much lower LOS, but higher hospital costs, than survivors (1 vs. 13 days, p< 0.0001).

Figure 3: The age – mean length of stay curve

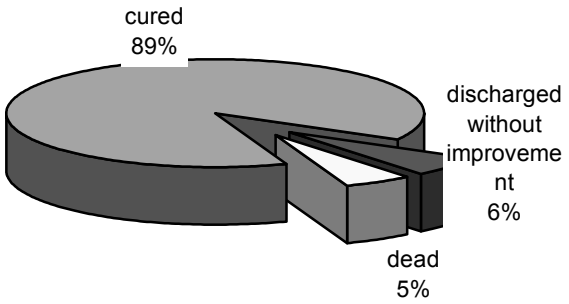


Mortality

Sepsis and its complications were incurred for more than 25% of the general hospital mortality in our clinic.

Of 248 patients with sepsis, 13 died before discharge, and 15 were discharged with no signs of improvement. (Figure 4). The annual age- and sex-adjusted mortality rate was 5 per 100 children.

Figure 4: The outcome of the patients with sepsis



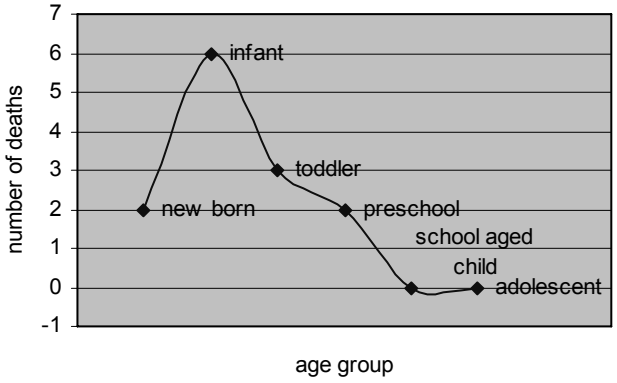
Hospital mortality generally varied little with age, except for the significantly higher rate among infants, who were incurred for 47% of all deaths. Because hospital mortality varied little with age, the number of deaths per population paralleled the incidence rate, with a high rate in infants that fell dramatically in older children. (Figure 6). There was no gender-related difference in hospital mortality.

The mortality rate was significantly increased by the severity of the septic process: among the severe sepsis cases the mortality rate was 5%, whereas among the patents with septic shock it was much higher: 53%.

Hospital mortality was higher in children with underlying disease (11% vs. 1.8%, $p< 0.002$).

More than three quarters of deaths occurred within the first 2 days from admission.

Figure 5: The age- number of deaths curve



Prognostic factors

Several factors were fond to significantly influence the outcome of the pediatric patients with sepsis. First of all there was the presence of changes in core temperature ($p=0.0019$), tachypnea ($p=0.00004$) or tachycardia ($p=0.009$) on admission. Secondly we found the respiratory ($p=0.0003$) or digestive ($p=0.0002$) origin to be associated with a poor outcome. There was also the occurrence of increased serum bilirubin ($p=0.001$) or creatinine ($p=0.0002$) level, or metabolic acidosis ($p=0.003$). The risk of death also increased with increasing number of failing organs, from 3.8% for those with single organ dysfunction to 53.2% for those with four organ systems or more failing ($p=0.0001$).

On our sample of patients, therapy with corticosteroids was found to significantly increase survival in the severe sepsis and septic shock cases ($p=0.0049$).

Discussions

We found sepsis and its complications to be a major health problem in children, with more than 120 cases and 6 associated deaths per year in our clinic only.

Infants were at highest risk. More than any other single factor, age influences the epidemiology of sepsis. Infants and older children are two epidemiologically distinct pediatric populations, with different incidences, underlying diseases, sites of infection, infecting organisms, and organ dysfunctions.

There was no significant gender-related difference in the occurrence and evolution of sepsis.

As with adults, underlying illness was very common in children who develop not only sepsis, but also severe sepsis and septic shock.

These findings are consistent with those of prior studies (2).

In a great majority of cases the microbiologic etiology was not determined, leading to a prolonged duration of the treatment. There are several reasons why it is important to try and make a microbiological diagnosis in septic patients. First, and most important, is to ensure that effective antimicrobial therapy is given. There is strong evidence to support the intuitive belief that patients given appropriate therapy are more likely to survive than those given inadequate or inappropriate treatment (3). Secondly, obtaining microbiological information will contribute to the local epidemiological database, without which logical prescribing is difficult, if not impossible. There are substantial differences between ICUs in the microbial ecology, including the prevalence of methicillin-resistant *Staphylococcus aureus,* and vancomicin-resistant *Enterococcus fecalis.* Antimicrobial resistance patterns also vary widely, for example, penicillin-resistance in *Streptococcus pneumoniae,* and gentamicin-resistance in *Enterobacteriaceae.* Furthermore, these patterns are constantly changing, and an up-to-date awareness of these patterns is obviously essential when considering empirical therapy. Finally, knowledge of the microbial cause may be important in the choice of adjunctive future therapies (for instance- antiendotoxin agents) (3).

In the cases in which a pathogen was identified, the etiology was found to be quite diverse, implying that any preventive strategies must be multifaceted. The predominance of Gram-negative bacteria in the etiology of sepsis is reported in literature for the 70's and the 80's, with an increase of the proportion of infections caused by Gram-positive bacteria (4).

Unfortunately, there still remain a very large number of cases in which sepsis is either not diagnosed, or is recognized very late in the evolution, far beyond the optimal therapeutic moment. Even more, there is still an extensive use of old, outdated language.

Patients' symptoms and signs, as well as the laboratory parameters values, vary a lot, mainly because of the different sites of infection, but also because of the various occurring organ dysfunctions.

Regarding the treatment of sepsis, we found a constant lack of a protocol – not only in the treatment of severe sepsis and septic shock, but also in the use of anti-infective therapy (5).

Children who develop sepsis consumed substantial healthcare resources, with average length of stay in excess of most conditions.

One fourth of the patients with sepsis have a severe evolution, with a significantly higher rate of hospital mortality (53% in our study vs. 9-12% reported in the literature), sepsis being the most important cause of death in our clinic, together with poisonings. We could blame this on the delayed diagnosis, the deficiencies in the laboratory diagnosis, as well as on the lack of therapeutical protocols and of a team specially trained for the treatment of severe sepsis and septic shock.

There were several major limitations of our study, mainly due to the variations in filling patients' files, as well as the absence of a protocol of investigation and surveillance of the pediatric patients with sepsis, which made us therefore unable to select all the required data for our patients. There was also the lack of precise administrative data, making us unable to determine the exact cost of hospitalization for the pediatric patients with sepsis.

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Correspondence to:

Alexandru Pirvan
B.P. Hasdeu Street, No. 73,
Cluj-Napoca 400371,
Romania
Tel 0264439081
pirvanaaa@yahoo.com