

Epidemiological study of pediatric severe sepsis in Argentina

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ABSTRACT

Introduction. Severe sepsis (SS) is one of the leading causes of pediatric mortality in Argentina. The objective was to describe the epidemiological characteristics and to analyze risk factors associated with mortality from SS among patients hospitalized in pediatric intensive care units (PICU) in Argentina.

Population and Methods. Observational, prospective cohort study among patients with SS hospitalized in PICUs in Argentina from 8/1/2008 to 9/30/2008.

Results. Two thousand five hundred and fifty nine patients were admitted at 59 PICUs. A total of 315 patients (335 events) were included. Patients' median age was 8 months (1-182). The frequency was 13.8%, and 28-day mortality was 31.6%. Patients with a higher mortality were those who were coming from rural areas, had comorbidities at the time of admission or a history of cancer, had shock or acute respiratory distress syndrome (ARDS), were administered low-dose corticosteroids or vasoactive drugs or more than 60 ml/kg of fluid in the first hour and in the first 6 hours, and had severe malnutrition. Following adjustment by severity using a multivariate logistic regression model, only coming from a rural area, having shock or ARDS remained associated with 28-day mortality. Forty per cent of patients received antibiotics 60 minutes after diagnosis.

Conclusions. SS is an event with a high frequency and mortality in Argentina. In the severity adjusted multivariate analysis, only coming from a rural area, having ARDS and/or shock were associated with higher mortality.

Key words: sepsis, pediatrics, critical care, fluid therapy, mortality.

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INTRODUCTION

Severe sepsis (SS) is one of the leading causes of death among children in Argentina¹ and the main cause among children dying in pediatric intensive care units (PICU) in the world.²⁻⁶

In 2003, Watson et al. estimated the incidence of sepsis in the general pediatric population of the USA to be 0.65/1000 in children and 5.6/1000 in infants (more than 42 000 cases/year and about 4500 deaths/year).² Ten years later, they pointed out that mortality had decreased (from 10.6% to 8.9%), but that the incidence and costs had increased (0.89/1000 children and five billion dollars per year, respectively).⁴

In 2017, the World Health Assembly adopted Resolution 70.7 to "improve the prevention, diagnosis and clinical management of sepsis." The Assembly recognized the scarcity of epidemiological data regarding the entity at an international level and urged Member States to take specific actions to reduce the burden of sepsis on public health and the economy.^{7,8}

In Argentina, no epidemiological studies addressed pediatric SS; therefore, there is no essential information available to implement measures aimed at improving results.

The objective of this study was to describe the epidemiological characteristics and to analyze risk factors associated with mortality from SS among patients hospitalized in PICUs in Argentina.

POPULATION AND METHODS

In 2008, a multicenter, observational, prospective cohort

study of every event of SS was conducted among patients hospitalized in PICUs in Argentina.

Patients between 1 month old and 216 months old who were admitted to the PICU between 8/1/2008 and 9/30/2008 with a diagnosis of SS at the time of admission to the PICU or during their hospitalization were included. Patients who had been admitted to the PICU before 8/1/2008 but remained hospitalized during the study period were excluded. The definition of SS and the main outcome measures met the International Pediatric Sepsis Consensus Conference⁹ (*Annex 1*).

The selection of outcome measures that could potentially predict the course of the condition was initially based on what is reported in the literature on the possible impact of each of these on mortality from SS (*Annex 1*).

Terminally ill patients or patients with exclusive palliative care needs or adjustment of therapeutic effort, patients with a different diagnosis other than SS, patients admitted to the PICU during the study period but who had their first episode after 60 days of hospitalization in the unit; and patients that could not be followed-up after admission to the unit were not included.

In March 2008, the enrollment was conducted by requesting a written informed consent to the head of the Division of each of the 130 PICUs (public and private) in the country¹⁰. For every participating PICU, two coordinators received an Access 1997-2007 database and a chart for each patient (*Annex 2*). Once completed, the chart was returned to the principal investigators for analysis.

All patients admitted to the PICU during the study period were registered and followed-up for up to 60 days after admission (if still hospitalized in the PICU). Those who met the inclusion criteria were followed-up until discharge from the PICU, or their death during hospitalization in the PICU, or after 28 days had elapsed since the start of the event. A new event was considered as such if it was unrelated to the previous event and if there was a time interval of at least 30 days between events.

Statistical analysis

Continuous outcome measures were summarized as mean and standard deviation (SD) or mean and range, depending on the distribution; categorical outcome measures were expressed in percentages. Student's *t* test or Wilcoxon test were used to compare continuous outcome measures, and the χ^2 test for categorical outcome measures.

The association between the possible predicting factors and the primary endpoint (28-day mortality) was assessed using a bivariate and multivariate logistic regression analysis. Initially, a bivariate analysis between each of the independent or predictor variables (*x*) and the dependent variable (*y*), 28-day mortality, was performed. It was analyzed if there was an individual association taking into account the change of crude β coefficients and the Wald test for each of them. The cut-off point of *p* was < 0.1 .

In the multivariate analysis, a parsimonious manual multiple model was designed. The cut-off point for accepting the variable when entering the multivariate model was $p < 0.05$. Overall calibration of the final model: the Hosmer-Lemeshow test was done and a *p* value ≥ 0.05 was established in order not to reject the null hypothesis and to consider that it was globally well adapted to the model.

To limit data recording, categorization and analysis biases, training was provided in the participating PICUs before the start of the protocol. In order to minimize errors, the principal investigators reviewed database consistency, outliers, completeness and treatment of missing data in a standardized manner. Data were processed using the Stata 12.0 statistical package, Statacorp, Texas, USA.

Ethical aspects

Collected data were accessed in accordance with all ethical and legal regulations (Act 25326). Collected data were not used for any other purposes, and the identity of PICUs and patients' was kept confidential by means of dissociation (coded or reversely dissociated data).

This study was approved by the Ethics Committee, and the medical and teaching departments of the participating hospitals. It was conducted in the context of the National Committee of Emergencies and Critical Care of the Sociedad Argentina de Pediatría. No type of funding was received for its execution.

RESULTS

Out of 130 PICUs, 61 accepted to participate, representing 22 of the 24 national jurisdictions; data were sent by 59 PICUs, 14 of which had no cases of SS (*Annex 3*).

During the study period, 2559 patients were admitted to the 59 participating PICUs, 332 of whom had 353 events of SS (frequency: 13.8 %). Seventeen patients with 18 events were not

included (3 events for being admitted before 8/1/08; 7 for not meeting SS criteria; 2 for being admitted before 8/1/08 and not meeting SS criteria; 6 for lack of follow-up). That means that 315 patients with 335 events were analyzed (1 event: 315 patients; 2 events: 19 patients; 3 events: 1 patient) (Figure 1).

Table 1 shows general and patients' outcome data; Table 2, clinical aspects and treatments provided; Table 3, infection data.

Patients' mean age was 8 months (1-182). Nonsurviving patients were younger than survivors (mean: 6 months old vs. 13 months old, respectively). The median length of stay was 11 (1-119 days).

Diagnosis was made at the time of admission at the PICUs for 181 events (54 % versus 46 % after admission); there were no differences in mortality between both groups. 80 % of cases were referred from other hospitals.

There were 106 deaths (31.6 % of events) in the PICUs; four of them among patients who had more than one event. The mortality in patients with one event (32 %) showed no statistical differences with nonsurviving patients who had more than one event (20 %) ($p = 0.24$).

Twelve per cent of patients with microorganism identification did not receive

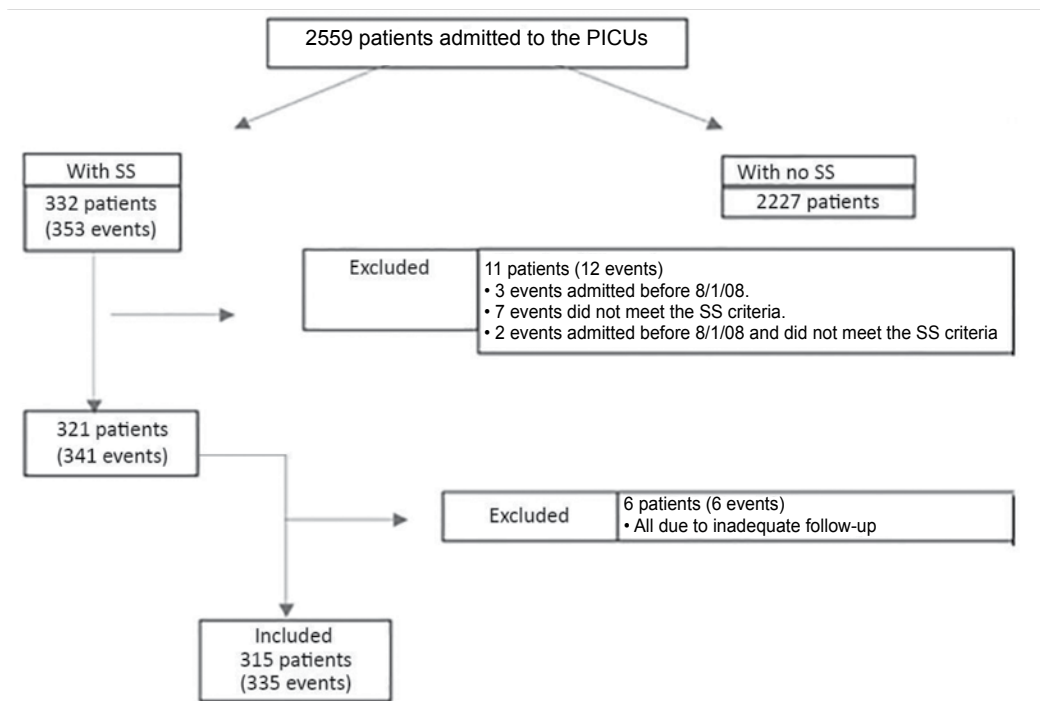
the adequate antibiotic at the time of admission; however, non-identification of the microorganism at the time of admission was not associated with higher mortality ($p = 0.7$).

The patients with higher mortality were those with severe malnutrition, those who came from rural areas, those with comorbidities at the time of admission, those who had a history of cancer, and those with hospital-acquired infections. The presence of comorbidities doubled mortality (OR: 2.1; 95 % CI: 1.3-3.3), and the presence of cancer tripled it (OR: 3.6; 95 % CI: 1.5-8.3) (Table 4).

Patients who received more than 60 mL/kg of fluid administration within the first hour or within the first six hours of treatment had a higher mortality. In addition, the probability of dying doubled in a clinically relevant and statistically significant way (OR: 1.9; 95 % CI: 1.05-3.63; and OR: 1.8; 95 % CI: 1.10-3.06, respectively) (Table 4).

The following outcome measures were included in the multivariate analysis: age, place of residence, nutritional status, severity at admission, concomitant disease, presence of shock, presence of acute respiratory distress syndrome (ARDS), fluids > 60 mL/kg within the first hour, use of vasoactive drugs, treatment with

FIGURE 1. Enrollment of the studied population flowchart



PICU: pediatric intensive care unit; SS: severe sepsis.

TABLE 1. Characteristics of the population (n: 315 patients, 335 events)

	Values
Sex, n (%)¹	
Female	151 (47.9)
Male	164 (52.1)
Age¹ (in months)	X = 35
	M _e = 8 (1-182)
Weight (in kg)	X = 12.6
	M _e = 7.6 (2.5-65)
Nutritional status, n (%)¹	
Adequate	226 (71.7)
Moderate malnutrition	57 (18.1)
Severe malnutrition	32 (10.2)
Place of origin, n (%)¹	
Rural	46 (14.6)
Urban	269 (85.4)
History of surgery, n (%)¹	53 (16.8)
Emergency surgery	24 (7.6)
Elective surgery	29 (9.2)
History of trauma, n (%)¹	15 (4.8)
Concomitant diseases, n (%)^{1,2}	
With concomitant disease	161 (51.1)
Without concomitant disease	154 (48.9)
Neurological disease	21 (6.7)
Heart disease	38 (12.1)
Respiratory disease	41 (13.0)
Renal disease	13 (4.1)
Gastrointestinal disease	21 (6.7)
Hematologic disease (not cancer)	12 (3.8)
Immunologic disease	12 (3.8)
Cancer	25 (7.9)
Metabolic disease	4 (1.3)
Chromosomal/genetic disease	28 (8.9)
Uncategorized, disabling chronic disease	20 (6.3)
Extrinsic immunosuppression	10 (3.2)
Transplant	6 (1.9)
Length of stay in the PICU³	
Mean	16 days
Median	11 days (1-119)
Sequelae, n (%)^{3,4}	
Yes	85 (37.1)
No	125 (54.6)
Unknown	19 (8.3)
Mortality, n (%)³	
<i>In the PICU</i>	
Dead	106 (31.6)
Alive	229 (68.4)
<i>After discharge from the PICU</i>	
Dead	2 (0.6)
Alive	186 (55.5)
Unknown course after discharge from the PICU	41 (12.2)

¹ Data analyzed based on the total number of patients with severe sepsis (315).

² Some patients had more than one concomitant disease or sequela.

³ Data analyzed based on the total number of events of severe sepsis (335).

⁴ Data analyzed based on the total number of survivors discharged from the PICU (total = 229).

X: mean; M_e: median; kg: kilogram; PICU: pediatric intensive care unit.

TABLE 2. Clinical characteristics and treatments provided (number of events: 335)

	Values in n (%) ¹
Presence of hyperthermia	
Yes	296 (88.4)
No	39 (11.6)
PIM²	X □ = 23.6 (1-93), Me = 12
Presence of shock	
Yes	277 (82.7)
No	58 (17.3)
Presence of neurological dysfunction	
Yes	69 (20.6)
No	266 (79.4)
Presence of ARDS	
Yes	196 (58.5)
No	139 (41.5)
Presence of renal dysfunction	
Yes	56 (16.7)
No	279 (83.3)
Presence of hematologic dysfunction	
Yes	103 (30.8)
No	232 (69.2)
Presence of hepatic dysfunction	
Yes	49 (14.6)
No	286 (85.4)
Type of fluids used²	
Saline solution	296 (88.4)
Gelatin	71 (21.1)
Albumin	28 (9.0)
Plasma	18 (5.4)
Other	34 (10.2)
No fluids were used for expansion	4 (1.2)
Use of vasoactive drugs²	
Dopamine	202 (60.3)
Adrenaline	81 (24.2)
Noradrenaline	72 (21.5)
Dobutamine	59 (17.6)
Milrinone	24 (7.2)
Nitroprusside	1 (0.3)
Nitroglycerin	4 (1.2)
Phenylephrine	2 (0.6)
No vasoactive drugs were used	54 (16.1)
AMV requirement²	
Traditional ventilation	307 (91.6)
High frequency ventilation	3 (1.0)
NIV	3 (1.0)
No data	28 (8.4)
Use of renal function replacement therapies²	
Peritoneal dialysis	9 (2.9)
Hemodialysis	3 (1.0)
Hemofiltration	3 (1.0)
Hemodiafiltration	1 (0.3)
No renal function replacement therapies were used	322 (96.1)
Use of specific treatments in the first 72 hours²	
Heparin	1 (0.3)
Albumin	62 (18.5)
Immunoglobulin	15 (4.5)
Insulin	21 (6.3)
Low-dose corticosteroids	57 (17.0)
High-dose corticosteroids	29 (8.7)

¹ Data analyzed based on the total number of events of severe sepsis (total = 335).

² Some patients received more than one drug, type of fluid, type of ARM, renal function replacement therapy, or specific treatment.

x: mean; M_e: median; PIM2: Pediatric Index of Mortality 2; ARDS: acute respiratory distress syndrome; AMV: assisted mechanical ventilation; NIV: non-invasive ventilation.

TABLE 3. Infection data (number of events: 335)

	Values in n (%) ¹
Source of the infection¹	
Hospital -acquired	136 (40.6)
Community-acquired	191 (57.0)
Unknown	8 (2.4)
Microorganism identification¹	
With identification	213 (63.6)
Without identification	122 (36.4)
Method used to identify the microorganism²	
Culture	151 (70.9)
IgM	3 (1.4)
PCR	9 (4.2)
Other	50 (23.5)
Identified microorganism²	
Gram (-) bacillus	69 (32.4)
Gram (-) coccus	9 (4.2)
Gram (+) coccus	68 (31.9)
Fungi	4 (1.9)
Virus	45 (21.1)
Other	18 (8.5)
Resistant microorganisms²	39 (18.3)
Gram (-) bacillus, ESBL+	19 (8.9)
Vancomycin-resistant enterococci	1 (0.5)
Methicillin-resistant staphylococci	19 (8.9)
Time of administration of the first antibiotic dose¹	
Within 60 minutes of diagnosis of SS	195 (58.2)
After 60 minutes of diagnosis of SS	131 (39.1)
No data	9 (2.7)
Adequate antibiotic^{2,3}	
No	25 (11.7)
Yes	140 (65.7)
Unknown	48 (22.5)

¹ Data analyzed based on the total number of events of severe sepsis (total = 335).

² Data analyzed based on the total number of identified microorganisms (total = 213).

³ Antibiotic used at the time of the patient's admission, which was consistent with the antibiogram of the microorganism subsequently identified.

IgM: immunoglobulin M; PCR: polymerase chain reaction; Gram (-): Gram-negative; Gram (+): Gram-positive; ESBL: extended spectrum beta-lactamase; SS: severe sepsis.

low-dose corticosteroids. The final multivariate logistic regression model developed with a parsimonious model is robust and stable, and calibrates and discriminates adequately, with a Hosmer-Lemeshow test value of 0.67 and an area under the ROC (Receiver Operating Characteristic) curve of 0.76 (see Annex 4). This model shows an independent, statistically significant and clinically relevant association between the place of residence, the severity at admission, the presence of shock and ARDS with a higher 28-day mortality (Table 5).

DISCUSSION

To our knowledge, this is the first and only multicenter epidemiological study on pediatric SS in the PICUs of Argentina, with the participation of half of the existing PICUs in the country at that time.

The frequency, which was higher than that reported in other studies, was lower than the 16.3 % value of the South American PICU subgroup that participated in the international Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study.^{6,7}

Mortality was higher than what has been reported in other studies (31.6 % versus 11 % of South American PICUs in SPROUT), although it was consistent with the 30 % mortality estimation of the Global Sepsis Initiative for developing countries.^{6,7,11}

The association between a rural origin and a higher mortality rate, which has also been observed in other critical pediatric entities, may be due to "...disparities in the economic, demographic and cultural realities..."¹²⁻¹⁴

Infant prevalence and the percentage of patients with comorbidities were consistent with previous publications. However, unlike other studies, in this study, the age of the survivors doubled that of nonsurviving patients.^{2,5-7,12,14-16}

The association between a higher mortality and the presence of shock and ARDS has also been reported by Odetola et al., and Landry et al.^{17,18}

Treatments administered were consistent with the clinical practice guidelines (CPGs) recommendations of the time, in which the use of crystalloids, dopamine, and traditional mechanical ventilation prevailed.^{19,20}

Lower mortality was observed with the use of dopamine versus noradrenaline or adrenaline, although it may have only reflected the greater severity of treatment progression compared to patients treated with drugs other than dopamine.^{21,22}

Consistent with recent publications, a higher fluid administration in the first hour and in the first six hours was associated with a greater number of deaths. However, this was not observed in our multivariate analysis following adjustment by severity, among other predictive outcome measures in the final model.²³⁻²⁷

Regarding the association of vasoactive drugs and fluid administration in the first hours with mortality, it is worth noting that this study was not initially designed to identify potential predictive outcome measures.

TABLE 4. Association between the clinical presentation or treatment provided and mortality (number of events: 335)

Outcome measure	Total (N: 335) ¹	Survivors (N: 229) ²	Nonsurviving patients (N: 106) ²	<i>p</i> ³
PIM (mean)	23.6 (95% CI: 20.7-26.6)	18.0 (95% CI: 14.9-21.2)	35.8 (95% CI: 29.8-41.8)	< 0.0001
Nutritional status, n (%)				
Adequate/Moderate malnutrition	302 (90.1)	211 (69.9)	91 (30.1)	
Severe malnutrition	33 (9.9)	8 (54.5)	15 (45.5)	0.07
Place of origin, n (%)				
Rural	48 (14.3)	21 (43.8)	27 (56.2)	
Urban	287 (85.7)	208 (72.5)	79 (27.5)	0.0001
Concomitant disease, n (%)				
Yes	170 (50.7)	103 (60.6)	67 (39.4)	
No	165 (49.3)	126 (76.4)	39 (23.6)	0.002
Cancer, n (%)				
Yes	25 (7.5)	10 (40.0)	15 (60.0)	
No	310 (92.5)	219 (70.6)	91 (29.4)	0.002
Diagnosis of SS at the time of admission at the PICU, n (%)				
Yes	181 (54.0)	121 (66.9)	60 (33.1)	
No	154 (46.0)	108 (70.1)	46 (29.9)	0.5
Source of SS, n (%)				
Hospital acquired	142 (42.4)	87 (61.3)	55 (38.7)	
Community-acquired	193 (57.6)	142 (73.6)	51 (26.4)	0.02
Shock, n (%)				
Yes	277 (82.7)	183 (66.1)	94 (33.9)	
No	58 (17.3)	46 (79.3)	12 (20.7)	0.05
ARDS, n (%)				
Yes	196 (58.5)	121 (61.7)	75 (38.3)	
No	139 (41.5)	108 (77.7)	31 (22.3)	0.0002
Types of fluids, n (%)				
<i>Albumin</i>				
Yes	28 (8.3)	21 (75.0)	7 (25.0)	
No	307 (91.6)	208 (67.8)	99 (32.2)	0.4
<i>Plasma</i>				
Yes	18 (5.4)	7 (38.9)	11 (61.1)	
No	317 (94.6)	223 (70.0)	95 (30.0)	0.006
Fluids in the first hour, n (%)				
≤ 60 mL/kg	286 (85.4)	202 (70.6)	84 (29.4)	
> 60 mL/kg	49 (14.6)	27 (55.1)	22 (44.9)	0.03
Fluids in the first 6 hours, n (%)				
≤ 60 mL/kg	145 (51.8)	109 (75.1)	36 (24.8)	
> 60 mL/kg	135 (48.2)	84 (62.2)	51 (37.8)	0.02
Use of vasoactive drugs				
Yes	281 (84.0)	183 (65.1)	98 (34.9)	
No	54 (16.0)	46 (85.2)	8 (14.8)	0.004
Use of corticosteroids, n (%)				
<i>Corticosteroids in general</i>				
Yes	86 (25.7)	48 (55.8)	38 (44.2)	
No	249 (74.3)	181 (72.7)	68 (27.3)	0.004
<i>Low-dose corticosteroids</i>				
Yes	57 (17.0)	32 (56.1)	25 (43.9)	
No	278 (83.0)	197 (70.9)	81 (29.1)	0.03
<i>High-dose corticosteroids</i>				
Yes	29 (8.7)	16 (55.2)	13 (44.8)	
No	306 (91.3)	213 (69.6)	93 (30.4)	0.11

¹ Data analyzed based on the total number of events of severe sepsis (total = 335).² Data analyzed based on the total number of survivors of severe sepsis events (total = 229) and the total number of nonsurviving patients from severe sepsis events (total = 106).³ *P* calculated from the percentage of nonsurviving patients from the indicated outcome measures.

PIM: Pediatric Index of Mortality; SS: severe sepsis; ARDS: acute respiratory distress syndrome; mL/kg: milliliters per kilogram; CI: confidence interval.

The prevalence of Gram-positive coccus and Gram-negative bacillus among the identified microorganisms might be due to a change in the epidemiological profile of SS after the introduction of the pneumococcal, *Haemophilus influenzae*, and meningococcal vaccines, as pointed by Irvin et al.²⁸

Weiss et al. reported a higher mortality associated with antibiotic administration after the first hour.²⁹ In our study, 40 % of patients received the first antibiotic dose after that time, and no differences in mortality were observed between the group that received it before and those who received it afterwards ($p = 0.15$).

After discharge from the PICU, (respiratory, neurological and renal) sequelae were mildly lower to that reported by Weiss et al. (37 % versus 45 %).⁵

Some comments on the epidemiological study of pediatric severe sepsis in Argentina should be done. Although 10 years have elapsed since its execution, due to the volume of data observed and participating PICUs, it is an important study to establish guidelines on the diagnosis and treatment of SS in the country.

The prevalence and high mortality underscore the importance of the entity in Argentina, where a PICU with more than 10 beds is able to treat at least one patient with SS every day of the year.⁵

Ruth et al., using the International Classification of Diseases, 9th revision (ICD-9) with the modified Angus criteria for PICUs, reported a mortality rate of 26.4 %.⁶ Our data may be more in line with this figure and reflect the inconveniences of Argentina's health system.

Han and Carcillo highlighted that early identification and aggressive resuscitation of newborn infants in septic shock by non-specialist physicians saved lives.³⁰ In our study, 80 % of patients were referred from other hospitals, which made it necessary to extend SS training to staff working outside these units.

When the study was conducted, the treatment paradigm favored an initial aggressive fluid

resuscitation.^{19,20,30,31} Since our initial data contradicted the prevailing paradigm, researchers were cautious about publishing our results, being wary of the possibility of these being biased and therefore invalid; the latter was, however, ruled out by later analysis. Although in the multivariate analysis this information lost relevance, a trend towards a higher mortality was observed in the group that received more than 60 mL/kg of fluids in the first hour and in the first 6 hours, doubling the mortality rate in this group.

Studies conducted in later years challenged such paradigm.²³ Van Paridon et al. reported an association between high fluid volumes in children with SS and an extended length of mechanical ventilation and stay in the PICU.³²

Recent CPGs suggest the need to adequately assess higher fluid administration and infuse antibiotics and vasoactive drugs earlier.³³

In spite of the essentially descriptive nature of this study, it enabled to analyze SS in a large group of PICUs in Argentina. This type of study is useful to improve the quality of care for patients, provide information to improve their care, and facilitate health decision-making based on national data.

CONCLUSIONS

1. Pediatric SS is common in Argentina (13 % of admissions to PICUs), with a mortality rate of 31 %.
2. Most of the patients were infants (median age: 8 months), had previous comorbidities (50 %), came from urban areas (85 %), had a normal weight (71 %), and came from outside the PICUs (80 %).
3. 40 % of patients received antibiotics one hour after the admission to the PICU.
4. Coming from a rural area, the presence of shock, having ARDS, adjusted by severity (estimated according to the Pediatric Index of Mortality 2 [PIM2]), were associated with a higher mortality in the multivariate analysis. ■

TABLE 5. Multivariate analysis

Outcome measure	OR	95% CI	P
PIM2	1.02	1.01-1.03	< 0.0001
Rural area	3.34	1.70-6.57	< 0.001
ARDS	2.56	1.49-4.40	< 0.001
Shock	2.24	1.07-4.70	0.032

OR: odds ratio; CI: confidence interval; PIM: Pediatric Index of Mortality; ARDS: acute respiratory distress syndrome.

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ANNEX 1.

OPERATIONAL DEFINITION OF OUTCOME MEASURES AND DESCRIPTION OF FACTORS THAT WERE CONSIDERED PREDICTORS OF MORTALITY

The pediatric systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, ARDS outcome measures are in accordance with the International Consensus Conference on Pediatric Sepsis.⁹

a. Outcome measures

I. SIRS: nonspecific inflammatory process that occurs after a trauma, an infection, burn injuries, acute pancreatitis, or surgical procedures.

SIRS diagnosis: the presence of at least 2 of the following 4 criteria, one of which must be abnormal temperature or leukocyte count:

- Core temperature of $> 38.5^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$.
- Altered heart rate (HR):
 - Tachycardia: HR > 2 SD above normal for age in the absence of external stimuli, chronic drugs, painful stimuli, or otherwise unexplained persistent elevation during 30 minutes-4 hours.
 - or for children < 1 year old, bradycardia: HR $< 10^{\text{th}}$ percentile, in the absence of vagal stimulus, β blocker drugs, congenital heart disease, or otherwise unexplained depression during more than 30 minutes.
- Respiratory rate > 2 SD above normal for age or mechanical ventilation not related to neuromuscular disease or general anesthesia.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or $> 10\%$ immature neutrophils.

II. Sepsis

SIRS associated with a suspected or proven infection.

III. Severe sepsis

Sepsis plus one of the following:

- Cardiovascular organ dysfunction or
- ARDS or
- 2 or more other organ dysfunctions.

IV. Septic shock

Sepsis and cardiovascular organ dysfunction.

V. ARDS: a severe respiratory failure due to a noncardiogenic pulmonary edema, caused by an increased alveolar-capillary barrier permeability and secondary to an acute lung injury.

- ARDS diagnosis: presence of arterial oxygen partial pressure (PaO_2) < 200 mmHg, bilateral pulmonary infiltrates, acute onset, no signs of left heart failure.

VI. Proven infection: objective pathogen identification through one or more methods, which include the culture of patient's samples, Gram staining, tissue staining, CRP, or other well-known methods.

VII. Suspected infection: a very suggestive clinical presentation, high probability of infection at clinical exam, imaging, laboratory tests. Examples include perforated viscus, chest radiography consistent with pneumonia, petechiae, purpura fulminans, or white blood cells in a normally sterile body fluid.

VIII. Elective surgery: major surgery (other than tracheostomy) within 2 weeks prior to admission.

IX. Emergency surgery: unscheduled surgery within 24 hours of onset of symptoms.

X. Comorbidities: medical conditions that can reasonably last for, at least, a year, unless death occurs, which compromise several organs or a system, severe enough to require specialized medical care or referral to a tertiary care facility. (In Annex 2. Data collection record, point 12 shows different conditions).

XI. PICU-acquired sepsis: sepsis identified at 48 h of PICU admission or later.

XII. Hospital-acquired sepsis: sepsis identified at 48 h of hospital admission or later.

XIII. Vasoactive drugs: defined in *Annex 2*. Data collection record, point 15.

XIV. Adequate nutritional status: indicates a history of weight loss of less than 5 % in the last 6 months (data collected from parents during history taking), but there are recent data showing appetite recovery, with no visible subcutaneous fat loss. (Overall subjective assessment).

XV. Moderate malnutrition: indicates a 5 %-10 % weight loss (data obtained during history taking) without regaining it, low dietary intake, and mild to moderate subcutaneous fat loss. (Overall subjective assessment).

XVI. Severe malnutrition: indicates a weight loss of more than 10 %, with severe loss of subcutaneous fat tissue and muscle wasting; most of the times along with edema. (Overall subjective assessment).

For this analysis, the severe malnutrition outcome measure was dichotomized into “yes” / “no”, considering the adequate and moderate malnutrition categories as lack of severe malnutrition.

b. Factors considered predictors of mortality at the moment of the study design, their identification and hierarchization

The selection of the outcome measures that could be associated with the course of SS was initially based on what is reported in the literature regarding the potential impact of each of these on mortality from sepsis or SS. One example is the delay in the administration of an antibiotic therapy, which was described as an independent factor of an unfavorable clinical course, or the presence of shock.

Other outcome measures reported as relevant in studies of SS in the general population or having some clinical or demographic plausibility were also considered, such as age, previous nutritional status, having a chronic disease at the time of the event, the volume expansion administered during the first hours, or the presence of complications along the clinical course (e.g., ARDS).

Table 4 (Association between the clinical presentation or the treatment provided and mortality) shows a full list of potential predictive outcome measures. The statistical analysis describes the process of identification and hierarchization of outcome measures. The association between potential predictors and the primary endpoint (28-day mortality) was assessed using a bivariate and multivariate logistic regression analysis. Initially, a bivariate analysis between each of the selected independent outcome measures or predictors (x) and the dependent outcome measure (y), 28-day mortality, was done. The existence of an individual association was observed through the change of raw β coefficients and Wald test for each of them. In this stage, the cut-off point of p was < 0.1 .

The following outcome measures were included in the multivariate analysis model: age, place of residence, nutritional status, severity at admission, concomitant disease, presence of shock, presence of ARDS, fluids > 60 mL/kg within the first hour, use of vasoactive drugs, treatment with low-dose corticosteroids, selected based on a p value of > 0.10 .

The final multivariate logistic regression model developed with a parsimonious model was robust and stable, and calibrated and discriminated adequately, with a Hosmer-Lemeshow test value of 0.67 and an area under the ROC (Receiver Operating Characteristic) curve of 0.76.

ANNEX 2. DATA COLLECTION RECORD

1. ID number:

2. Number of event:

3. Age: (in months)

4. Sex: Male

Female

5. Date of admission at the hospital:

//

6. Date of admission at the ICU:

//

7. Regular residence:

Rural

Urban

8. History:

Surgery: Yes No

Elective

Emergency

Trauma: Yes No

9. Weight (grams):

10. Length/Height (centimeters):

11. Nutritional status

(visual impression if 11 and 12 could not be recorded):

Adequate

Moderate malnutrition

Severe malnutrition

12. Comorbidities:

In case of more than one condition, record all of them.

Neuromuscular disease

Cardiovascular disease

Respiratory disease

Renal disease

Gastrointestinal disease

Hematologic disease (not cancer)

Immunologic disease

Extrinsic immunosuppression

Transplant

Cancer

Metabolic disease

Chromosomal/genetic disease

Other uncategorized, disabling chronic disease

None

13. Clinical characteristics of the episode of severe sepsis at the time of diagnosis (according to Tables 2, 3 and 4):

- **SIRS (2 criteria, one of which must be one of the first two criteria)**

	Yes	No
Thermal deregulation	<input type="checkbox"/>	<input type="checkbox"/>
Leukocytosis, leukopenia or > 10% immature neutrophils	<input type="checkbox"/>	<input type="checkbox"/>
Tachycardia at any age or bradycardia in children < 1 year old	<input type="checkbox"/>	<input type="checkbox"/>
Tachypnea or AMV	<input type="checkbox"/>	<input type="checkbox"/>

- **Proven infection:** Yes No
- **Suspected infection:** Yes No
- **Organ dysfunction (Table 4)**

- Cardiovascular
- Respiratory
- Neurological
- Hematologic
- Renal
- Hepatic

- **ARDS:** Yes No

	YES	NO
Pa/Fi < 200		
Bilateral infiltrates		
Acute beginning		
No signs of left heart failure		

- **Diagnosis of severe sepsis:**
- Upon admission to the PICU
- Within the first 24 h
- Between 24 and 48 h
- > 48 h

14. Severity of the disease:

- PIM2

15. Treatment at the ICU (severe sepsis episode-septic shock):

▪ **Resuscitation measures during the first 6 hours**

○ **Expansions:**

- Isotonic saline solution
- Gelatin
- Starch
- Albumin
- Plasma
- Other

Total amount in the first hour (cc/kg):

✓ Unknown:

○ **Total amount in the first 6 hours (cc/kg):**

✓ Unknown:

○ **Vasoactive agents (in the first 6 h):**

(Specify the maximum dose in $\mu\text{g}/\text{kg}/\text{min}$ only for the first 3, if known)

- | | |
|--|--|
| <input type="checkbox"/> Dopamine: $\mu\text{g}/\text{kg}/\text{min}$ | <input type="checkbox"/> Nitroprusside |
| <input type="checkbox"/> Adrenaline: $\mu\text{g}/\text{kg}/\text{min}$ | <input type="checkbox"/> Nitroglycerin |
| <input type="checkbox"/> Noradrenaline: $\mu\text{g}/\text{kg}/\text{min}$ | <input type="checkbox"/> Phenylephrine |
| <input type="checkbox"/> Dobutamine | <input type="checkbox"/> Other: |
| <input type="checkbox"/> Milrinone | |

▪ **Assisted ventilation (in the first 72 h):**

- Traditional AMV
- High frequency
- Non-invasive

▪ **Renal function replacement (in the first 72 h):**

- Peritoneal dialysis
- Hemodialysis
- Hemofiltration

▪ **Specific treatment (in the first 72 h):**

- Heparin
- Albumin
- Intravenous gamma globulin
- Low-dose corticosteroids (replacement)
- High-dose corticosteroids
- Insulin
- Other (specify):

▪ **General treatment**

○ **Antibiotics:**

- Yes
- No

The first dose was administered within the first hour after diagnosis:

- YES
- NO
- Unknown

16. Patient's outcome:

- **Organ dysfunction over time since the start of the episode**

Days of evolution	1	3	7	14
Date				
Cardiovascular				
Respiratory				
Neurological				
Hematologic				
Renal				
Hepatic				

- **Date of discharge from the PICU:**

/ /

Alive Dead

- **Discharged from hospital?**

Alive Dead Unknown

- **Still in the PICU at 28 days after the start of the episode:**

Yes No

- **Patient's death is related to the severe sepsis episode:**

Yes No Unknown

- **Patient's sequelae after discharge from the PICU or at 28 days:**

- **Oxygen-dependent:** Yes No Unknown
- **Severe neurological dysfunction:** Yes No Unknown
- **Chronic kidney injury:** Yes No Unknown
- **Tube feeding:** Yes No Unknown

17. Characteristics of the infection:

- **Origin of the infection**

- Community-acquired
- PICU-acquired nosocomial
- Hospital-acquired nosocomial
- Unknown

- **Primary source of infection**

- Respiratory
- Genitourinary
- Abdominopelvic
- Skin, cell tissue
- Bone, joint
- Central nervous system (CNS)
- Endocarditis
- By devices
- Primary bacteremia
- Other
- Unknown

Microorganism

○ **Specify the name:.....**

- Gram (+) coccus
- Gram (-) coccus
- Gram (-) bacillus
- Virus
- Fungi
- Parasites
- Other

○ **Study of the microorganism:**

- Culture
- CRP
- IgM
- Other

○ **Place found:**

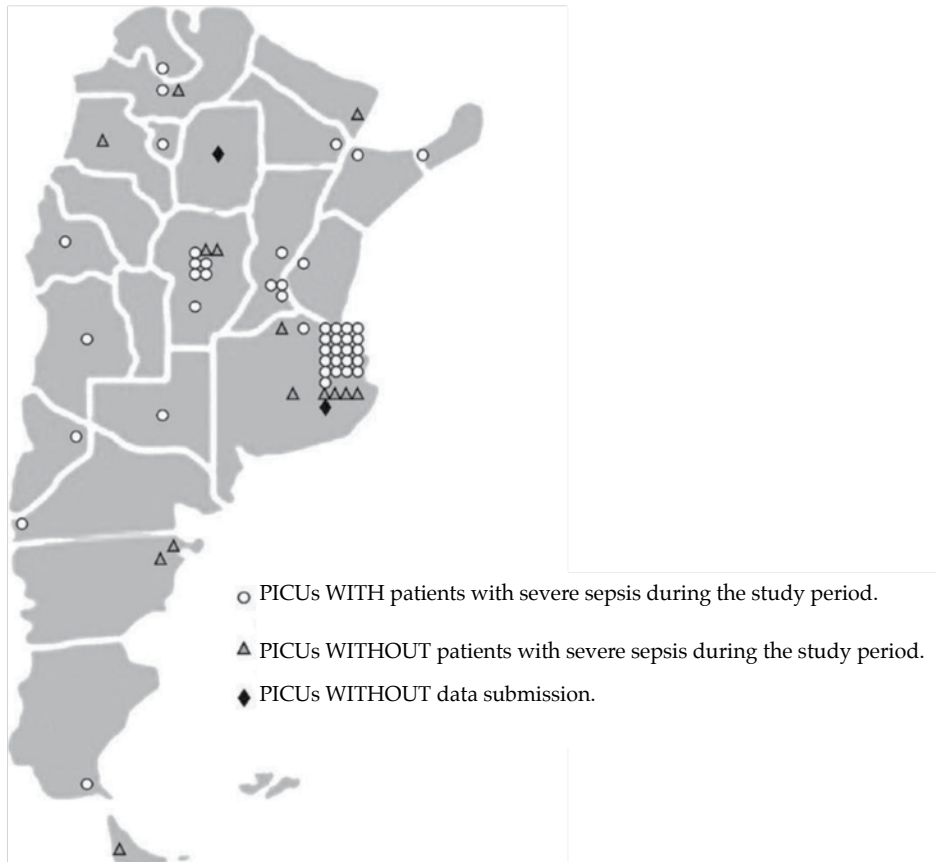
- Blood
- Urine
- Cerebrospinal fluid (CSF)
- Bronchoalveolar lavage (BAL), mini-BAL
- Pulmonary secretions
- Focus puncture
- Pleural fluid
- Devices
- Other

○ **Resistance:**

- Methicillin-resistant staphylococcus
- Vancomycin-resistant enterococcus
- Gram (-) bacilli, ESBL+

- No microorganism identification**

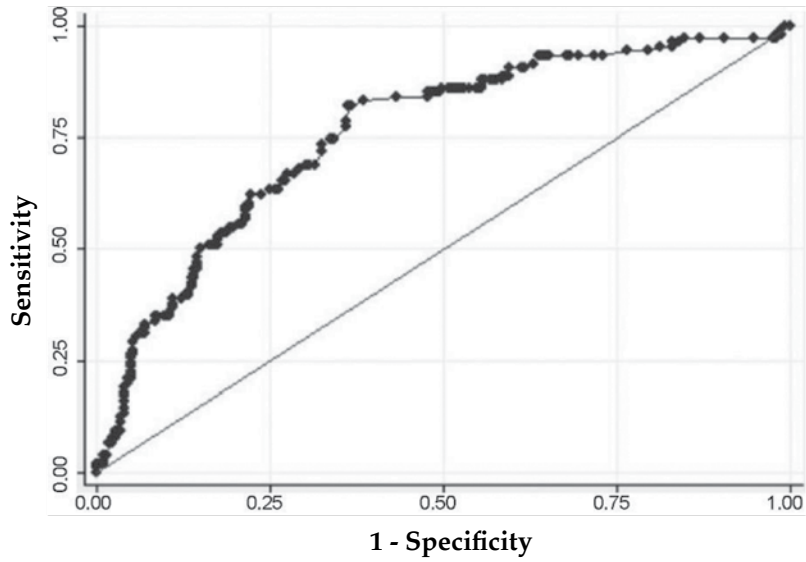
ANNEX 3. DISTRIBUTION OF PARTICIPATING PEDIATRIC INTENSIVE CARE UNITS



PICU: pediatric intensive care unit.

ANNEX 4.

AREA UNDER THE ROC CURVE = 0.76.



Area under the curve = 0.7592