

Original Article

Clinical and epidemiological characteristics of children admitted with fever in emergency department with or without sepsisMariana Costa de Santana¹, Caroline Duarte Mello Amoedo², Cristiana Maria Nascimento-Carvalho^{1,2}¹ School of Medicine, Federal University of Bahia, Salvador, Brazil² Department of Pediatrics, School of Medicine, Federal University of Bahia, Salvador, Brazil**Abstract**

Introduction: Sepsis is a major cause of childhood death worldwide. In developing countries, epidemiological data about sepsis is scarce. This study describes and compares the frequency of etiological agents and initial sites of infection in children with or without sepsis, identifying risk factors and assessing outcomes.

Methodology: Clinical and demographic data from patients < 13 years of age with reported fever in a pediatric emergency department were collected and registered in forms. Patients were classified as with or without sepsis according to Goldstein *et al.*'s criteria [6].

Results: Of 254 patients, 120 (47%) did and 134 (53%) did not meet the sepsis definition. Overall, the median age (IQR) was 1.7 (0.8–3.9) years, and 153 (60%) were boys. Patients with sepsis were older (2.8 [1.1–5.3] versus 1.3 [0.6–2.9] years; $p < 0.001$) and had sickle-cell disease more frequently (7.6% versus 0.8%; $p = 0.007$). By multiple logistic regression, age and sickle-cell disease were independently associated with sepsis. The most frequent initial infections were pneumonia (43.7%), diarrhea (17.3%) and cellulitis/adenitis (13.0%). The frequency of these did not differ when patients with or without sepsis were compared. Etiology was established in 57 (22.4%) patients, 32 (26.7%), and 25 (18.7%) with or without sepsis, respectively. Four (3.3%) patients died in the sepsis subgroup, whereas none died in the other subgroup.

Conclusions: Children who met the 2005 international consensus definition of sepsis showed differences in age and comorbidities (sickle-cell disease) upon admission and were more likely to die.

Key words: pediatric; sepsis; infection; etiology; outcome; mortality.

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Introduction

According to data published by the World Health Organization (WHO), of the 6.3 million children who died in their first 5 years of life in 2013, 51.8% (3.257 million) died of infectious diseases. Pneumonia, diarrhea, and malaria were the leading infectious causes of death [1]. Sepsis represents the progressive underlying inflammatory pathway secondary to any infectious illness, and ultimately is responsible for most infectious disease-related deaths [2].

In immunocompetent children, fever is the earliest clinical sign of infection [3], and, at the same time, it is one of the most common symptoms reported in pediatric emergency departments (EDs) [4]. As such, the early identification of potential septic children by healthcare providers who assist patients with acute febrile illness has decisive importance [5].

In 2005, Goldstein *et al.* established specific sepsis criteria for pediatric patients, based on age-specific norms of vital signs and laboratory data [6]. Though Goldstein *et al.*'s definitions were designed for research

purposes, they are often used clinically in developed nations for identification of children who have life-threatening infections requiring urgent intervention. More importantly, they form the basis for the development of guidelines aimed at treating the various stages of the sepsis continuum [2].

The Surviving Sepsis Campaign established some essential guidelines for reducing the high mortality rates resulting from sepsis in the world. It emphasizes the need to get to know the characteristics of each region [7]. Local epidemiologic studies about pediatric sepsis have been undertaken, most of them in developed countries. However, the important differences between children in developing countries and those in developing ones are clear [8].

This study aimed to describe and compare the frequency of etiologic agents and initial sites of infection, identifying risk factors and assessing outcomes, in pediatric patients admitted with fever, with or without sepsis, by applying Goldstein *et al.*'s criteria [6] in an ED in a developing country.

Methodology

This was a retrospective cohort study. Every patient admitted at the pediatric ED of the Federal University of Bahia Hospital between 1 September 2004 and 28 August 2005 had their medical chart reviewed by one member of the research team. At this ED, children come from the community of their own accord, and those under 13 years of age are seen. Patients who reported fever and had suspected or detected infection were identified, from whom patients with documented fever at physical examination were selected. The inclusion criteria comprised documented fever plus white blood cell count (WBC) collected upon admission plus respiratory rate plus heart rate measured at three or more distinct moments in the absence of fever. Patients with malformations, bronchopulmonary dysplasia, cardiac insufficiency, renal insufficiency, hepatic insufficiency, or medullary aplasia prior to hospital admission were excluded to ensure that vital signs were not abnormal due to underlying ongoing diseases. Demographic and clinical data upon admission and during evolution were registered in standardized forms.

Bacterial infections were searched for by performing blood, urine, and feces culture. Eleven viral causative agents of pneumonia were investigated in nasopharyngeal aspirates (NPA) collected from these patients. Rhinovirus, enterovirus, and human metapneumovirus were searched for by reverse transcriptase polymerase chain reaction (PCR) [9]. Parainfluenza viruses 1, 2, and 3, respiratory syncytial virus, influenza viruses A and B, and adenovirus were investigated by searching for viral antigen in the NPA by performing time-resolved fluoroimmunoassay with monoclonal antibodies. Infection by these respiratory viruses was also investigated by determining specific IgG increase in paired serum samples by enzyme-linked immunosorbent assay (ELISA) [10]. Human bocavirus infection was investigated by quantitative PCR of NPA and serum, by determining IgG increase in paired serum samples and by searching for IgM and IgG avidity by ELISA [11]. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* infections were investigated by determining specific IgG increase tested by ELISA in paired serum samples [12]. PCR in the acute buffy coat was performed for the detection of pneumococcal DNA [13]. *Mycoplasma pneumoniae* infection was investigated by testing either the first or second serum sample for specific IgM by ELISA [14]. *Chlamydia trachomatis* infection was investigated by high IgG level determined by ELISA. IgG increase in paired serum samples or detection of specific IgA and

IgM, all by microimmunofluorescence, were used to investigate *Chlamydia pneumoniae* infection [15].

Serological markers of hepatitis A virus were investigated by determining specific IgM by ELISA [16]. Rotavirus (RV) antigen was searched for in stool specimens by a rapid latex assay (ROTA Rich, Richmond Diagnostics, Barcelona, Spain). *Giardia lamblia* infection was investigated by stool examination on fresh specimens or after preservation with polyvinyl alcohol or 10% formalin [17].

Children were classified as with or without sepsis by Goldstein *et al.*'s sepsis criteria [6]. For this purpose, axillary temperature $> 38.5^{\circ}\text{C}$ was defined as fever and $< 36.0^{\circ}\text{C}$ was defined as hypothermia. Tachypnea was defined as respiratory rate > 50 breaths/minute among children < 1 week of age, > 40 breaths/minute among children 1 week to 1 month of age, > 34 breaths/minute in children 1 month to 1 year of age, > 22 breaths/minute in children between 2 and 5 years of age, and > 18 breaths/minute in children between 6 and 12 years of age. Tachycardia was defined as heart rate > 180 beats/minute among children < 1 year of age, > 140 beats/minute in children between 2 and 6 years of age, and > 130 beats/minute in children 6 to 12 years of age. Bradycardia was defined as heart rate < 100 beats/minute among children 1 week to 1 month of age, and < 90 beats/minute in children between 1 month and 1 year of age. Abnormal WBC was defined as $> 10\%$ of immature neutrophils, or WBC count $> 34 \times 10^3/\text{mm}^3$ among children < 1 week of age, > 19.5 or $< 5 \times 10^3/\text{mm}^3$ in children between 1 week and 1 month of age, > 17.5 or $< 5 \times 10^3/\text{mm}^3$ in children 1 month to 1 year of age, > 15.5 or $< 6 \times 10^3/\text{mm}^3$ in children between 2 and 5 years of age, and > 13.5 or $4.5 \times 10^3/\text{mm}^3$ in children 6 to 12 years of age.

The risk factors studied included age, gender, malnutrition and severe malnutrition, sickle-cell disease, low birth weight, post-natal respiratory distress, and asthma. As part of the analysis, the software Anthro, versions 1.02 and 3.22 (WHO, Geneva, Switzerland), was used to perform the nutritional evaluation in accordance with the National Centre for Health Statistics, United States standard. A z score under -3.00 or -2.00 for the weight-for-age index defined malnutrition and severe malnutrition, respectively [18].

The primary outcome was death. Categorical variables were compared by using Chi-squared or Fisher's exact test as appropriate; continuous variables were assessed using Student's *t* test or the Mann-Whitney U test, taking into account the variable distribution. Multivariate logistic regression analysis by

the enter method was used to assess independent association between sepsis and risk factors that significantly differed in the bivariate analysis. The multivariate analysis was performed in a model adjusted for age. Additionally, multivariate logistic regression analysis by the enter method was used to evaluate independent association between total WBC count sepsis in a model adjusted for age. Then, the receiver operating characteristic (ROC) curve was used to evaluate the ability of total WBC count (predictor variable) to differentiate sepsis from no sepsis (outcome variable). The statistical tests were two tailed, with a significance level of 0.05. The software SPSS version 9.0 (IBM, Armonk, USA) was used for the analysis. The study was approved by the ethics committee of the Federal University of Bahia.

Results

Overall, 681 patients reported fever, of which 290 (43%) had fever detected on physical examination; 3 (1%) did not have either respiratory rate or heart rate or WBC registered in the medical chart; additionally, 33 (11%) met the exclusion criteria. Therefore, this study group comprised 254 patients (Figure 1). The median age (IQR) was 1.7 (0.8–3.9) years (minimum 19 days, maximum 12.6 years), 137 (54%) cases were younger than 1 year of age, and 153 (60%) were boys.

By applying Goldstein *et al.*'s criteria [6], 120 (47%) had sepsis and 134 (53%) patients did not have sepsis. Among children with sepsis, 119 (99.2%) had abnormal WBC: 93 (78.2%) had leukocytosis, 38 (31.9%) had more than 10% of immature neutrophils in the peripheral blood smear, and 12 (10.1%) had leukopenia. One (0.8%) patient had persistent tachypnea in the absence of fever or respiratory disease.

The most frequent diagnoses were pneumonia (43.7%), diarrhea (17.3%), and cellulitis/adenitis (13.0%). All diagnoses are shown in Table 1. Table 2 demonstrates the comparison of each diagnosis frequency between cases with or without sepsis. No significant difference was found. Table 3 compares the frequency of potential risk factors between patients with or without sepsis. Notably, children with sepsis were older and had sickle-cell disease more frequently.

By multiple logistic regression, age was an independent risk factor for sepsis (adjusted OR [95% CI]: 1.2 [1.1–1.3]; *p* = 0.0006). Likewise, independent association between sickle-cell disease and sepsis was found (adjusted OR [95% CI]: 8.8 [1.1–71.2]; *p* = 0.0414). By assessing total WBC count by multiple logistic regression controlled by age, it was possible to observe that WBC count was positively and independently associated with sepsis (adjusted OR [95% CI]: 1.0003 [1.0002–1.0003]). The area under the ROC curve for total WBC count to predict sepsis was 0.84 (Figure 2) when $WBC \geq 17,250/mm^3$ was the cutoff with best performance: sensitivity 72% and specificity 100%.

Overall, etiology was found in 57 (22.4%) cases: 32 (26.7%) with sepsis and 25 (18.7%) without sepsis (*p* = 0.1). The most frequent causative agents were *S. pneumoniae* (*n* = 9; 3.5%), parainfluenza virus (*n* = 9; 3.5%), and respiratory syncytial virus (*n* = 8; 3.1%).

Table 1. Diagnoses of the 254 patients with fever detected upon physical examination.

Diagnosis	Frequency (%)
Pneumonia	111 (43.7)
Diarrhea	44 (17.3)
Cellulitis-adenitis	33 (13.0)
Urinary tract infection	18 (7.1)
Pyodermitis	14 (5.5)
Upper respiratory tract infection	13 (5.1)
Fever without localizing sings	5 (2.0)
Osteoarticular infection	5 (2.0)
Hepatitis	2 (0.8)
Endocarditis	1 (0.4)
Peritonitis	1 (0.4)
Pneumonia + diarrhea	5 (2.0)
Pneumonia + pyodermitis	1 (0.4)
Diarrhea + urinary tract infection	1 (4.0)

Figure 1. Flow-chart of patients enrolled in this study. Patients who had the described comorbidities were excluded to avoid confounding variables: abnormal vital signs and abnormal white blood cell count (WBC) not related to sepsis.

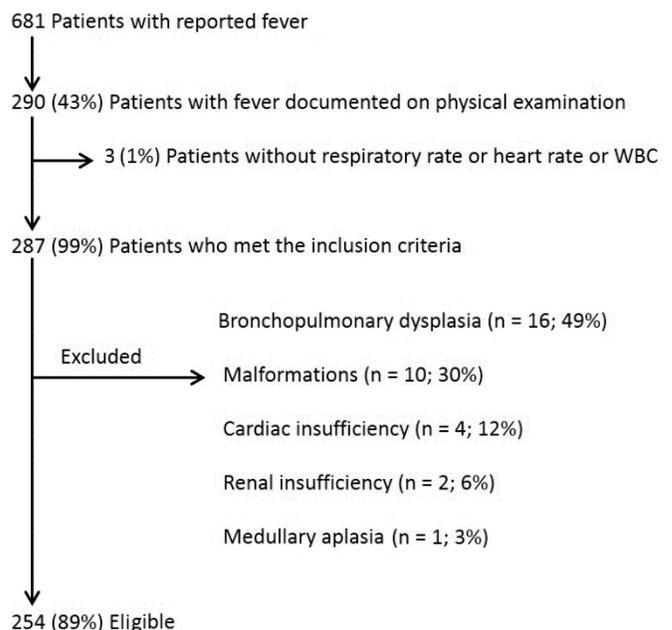


Table 2. Comparison of diagnoses frequency between children with or without sepsis.

Diagnosis	Presence of sepsis		p
	Yes (n = 120)	No (n = 134)	
Pneumonia	61 (50.8)	56 (41.8)	0.1
Diarrhea	19 (15.8)	31 (23.1)	0.1
Cellulitis/adenitis	16 (13.3)	17 (12.7)	0.9
Urinary tract infection	11 (9.2)	8 (6.0)	0.3
Pyodermitis	5 (4.2)	10 (7.6)	0.3
Upper respiratory tract infection	4 (3.3)	9 (6.7)	0.2
Fever without localizing signs	2 (1.7)	3 (2.2)	1.0
Osteoarticular infection	3 (2.5)	2 (1.5)	0.7
Hepatitis	2 (1.7)	0	0.2
Endocarditis	1 (0.8)	0	0.5
Peritonitis	0	1 (0.7)	1

Table 3. Comparison of potential risk factors between children with fever upon physical examination with or without sepsis.

Risk factor	Overall n = 254	Sepsis		p
		Yes n = 120	No n = 134	
Malnutrition ^a	35 (14)	19 (15.8)	16 (11.9)	0.4
Severe malnutrition ^a	14 (5.5)	7 (5.8)	7 (5.2)	0.8
Respiratory distress in neonatal period ^a	15/201 (7.5)	9/107 (8.4)	6/94 (6.4)	0.6
Low birth weight ^a	19/162	9/82 (11)	10/80 (12.5)	0.8
Sickle-cell disease ^a	10/250 (4)	9/118 (7.6)	1/132 (0.8)	0.007
Age ^b		2.8 (1.1–5.3)	1.3 (0.6–2.9)	0.0001
Asthma ^a	5/250 (2)	9/118 (1.7)	3/132 (3)	1

^aResults as proportions n (%); ^bResults as median (interquartile range).

Table 4. Comparison of the etiological agents' frequency among patients with fever upon physical examination with or without sepsis.

Etiological agents	Presence of sepsis		p
	Yes n = 120	No n = 134	
Bacteria			
<i>S. aureus</i>	4 (3.3)	-	0.049
<i>S. pneumoniae</i>	7 (5.8)	2 (1.5)	0.09
<i>E. coli</i>	2 (1.7)	1 (0.7)	0.6
<i>Shigella</i>	1 (0.8)	-	0.5
<i>M. pneumoniae</i>	1 (0.8)	1 (0.7)	1
<i>Streptococcus viridans</i>	1 (0.8)	-	0.5
<i>Salmonella</i>	1 (0.8)	1 (0.7)	1
<i>H. influenzae</i>	-	4 (3.0)	0.1
<i>K. pneumoniae</i>	-	2 (1.5)	0.5
<i>M. catarrhalis</i>	-	1 (0.7)	1
<i>C. trachomatis</i>	-	1 (0.7)	1
Viruses			
Rotavirus	5 (4.2)	2 (1.5)	0.3
Parainfluenza virus	5 (4.2)	4 (3.0)	0.7
Enterovirus	3 (2.5)	1 (0.7)	0.3
Respiratory syncytial virus	2 (1.7)	6 (4.5)	0.3
Rhinovirus	1 (0.8)	3 (2.2)	0.6
Adenovirus	1 (0.8)	3 (2.2)	0.6
Hepatitis A virus ^a	1 (0.8)	-	0.5
Influenza virus	-	2 (1.5)	0.5
Parasite			
<i>G. lamblia</i>	1 (0.8)	-	0.5

^aIgM antibody to hepatitis virus positive, anti-AgHbs and anti-HCV negative.

None of the cases with pneumococcal infection had sickle-cell disease. Table 4 depicts the comparison of the detected etiologies between children with and without sepsis. *S. aureus* infection was significantly more common among children with sepsis. Table 5 depicts the frequency of bacterial agents found by culture in each subgroup and per diagnosis.

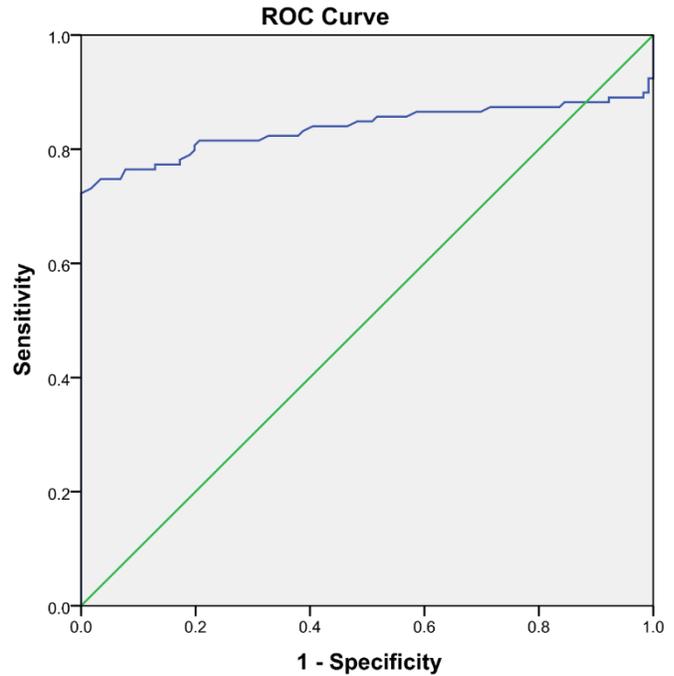
Patients with sepsis stayed longer (days) in the hospital compared with patients without sepsis (median [IQR]: 7 [5–11] versus 5 [3–8]; $p < 0.001$). Four patients died, all of whom had sepsis (3.3%); conversely, none died among patients without sepsis ($p = 0.048$). There were no deaths among septic children with staphylococcal infection.

Discussion

This study demonstrated the high frequency of sepsis (47%) among feverish patients admitted in to a pediatric ED during the enrollment period. This finding is in accordance with Ganjoo *et al.*'s prospective study [19], which detected a frequency around 46% of sepsis among feverish children hospitalized in a tertiary hospital in India by applying the same definitions of Goldstein *et al.* [6]. This high frequency was expected because of the high sensitivity of these sepsis criteria [20]. However, considering that EDs are often the first point of contact for children with sepsis [21], it is important to use objective criteria to identify children at risk. In addition, our study demonstrated that children admitted with fever, which met the early sepsis criteria of Goldstein *et al.* [6], were more prone to die. This is in agreement with Ganjoo *et al.*'s data, which showed a statistically significant higher fatality rate among patients with sepsis [19].

Acute respiratory infections and diarrhea are the most frequent childhood illnesses and causes of attendance at health services in low- and middle-income countries [22]. Pneumonia was the most frequent diagnosis among feverish children in this

Figure 2. ROC curve for blood total WBC count and sepsis in children with documented fever in an emergency room.



Diagonal segments are produced by ties.

study. The high frequency of this disease (43.7%) could be explained because the majority of patients seen were younger than 1 year of age (54%) and pneumonia is highly incident in this age group [1]. Furthermore, it is important to recognize that we analyzed the initial diagnoses performed by assistant pediatricians. Our findings are in accordance with Murphy *et al.*'s data, which detected signs suggestive of pneumonia in 49% of 2,128 children admitted with fever to an ED [23].

In contrast with literature data [24], older age was a significant and independent risk factor for sepsis when risk factors were assessed in the present study. It is important to note that the majority of the sepsis studies were conducted at intensive care units, where patients with severe sepsis and septic shock, and late stages of

Table 5. Bacterial agents identified by culture in patients with or without sepsis.

Diagnosis	Etiologic agent	Biological fluid	
		With sepsis	Without sepsis
Diarrhea	<i>Salmonella</i>	Feces (1)	Blood (1)
	<i>Shigella</i>	Feces (1)	-
Pneumonia	<i>S. pneumoniae</i>	Blood (3)	-
Urinary tract infection	<i>E. coli</i>	Urine (2)	Urine (1)
	<i>K. pneumoniae</i>	-	Urine (2)
Pyodermitis	<i>S. aureus</i>	Blood (1) Secretion (1)	-
Cellulitis	<i>S. aureus</i>	Blood (1)	-
Endocarditis	<i>Streptococcus viridans</i>	Blood (1)	-
Osteoarticular infection	<i>S. aureus</i>	Blood (1)	-

sepsis continuum, were included. Our finding highlights an important difference between these two populations, because in EDs, the vast majority of children present with benign and self-limited viral infections [25]. In addition, in our study, most of the patients were younger than 1 year of age. According to Bertille *et al.*, parents show different attitudes with respect to children's fever. These authors noted that younger children visit pediatricians more frequently than older ones, even if with self-limited viral infections, overusing emergency care providers [26]. It is possible that in our study, older children had been taken to the ED presenting more severe diseases.

Sickle-cell disease was another significant and independent risk factor for sepsis among patients with documented fever. This finding is due to the lack or reduction of spleen function, particularly during the first 6 years of life [27]. We should remember that sepsis may be the initial event in the presentation of as-yet-undiagnosed sickle-cell disease (since the majority of such events occur before 3 years of age) [28,29]. It is possible that the high prevalence of this condition in Brazil [30] highlights this disease as a risk factor for sepsis regionally.

The infection in the two groups had different etiology; *S. aureus* infection was significantly more frequent in septic patients (3.3% versus 0%; $p = 0.049$). It is known that *S. aureus* bacteremia (SAB) is a common and important infection in pediatric patients. The exact incidence of SAB is difficult to ascertain, as prospective population-based surveillance studies are infrequently performed. Age remains one of the most consistent predictors of mortality, with children generally having lower SAB mortality rates than adults [31]. The place of SAB onset influences outcomes, with community-onset episodes having a lower mortality rate, probably secondary to the predominance of skin and soft-tissue infections [32]. There were no deaths among septic children with staphylococcal infection in this study. Interestingly, when the two groups were compared, no difference in the initial site of infection was found.

Methodological constraints in this investigation should be emphasized. This was a single-center study, only reporting data from a subset of the pediatric age group. The data were collected retrospectively, patients were evaluated by different observers, and standardization of evaluations could not be guaranteed. However, strict criteria for enrolling and grouping the cases were used, and those with potential confounding variables were excluded. Moreover, the study was performed in a teaching hospital where the same

standardized procedures for assistance were used over the period of the study.

Conclusions

This study provides evidence that the fulfilment of the formal sepsis criteria is frequent among pediatric patients seen with documented fever in an ED. Furthermore, children with sepsis showed differences in clinical profile; they were older, in contrast to the literature data. Sickle-cell disease was a significant risk factor independently associated with sepsis. Importantly, patients who fulfilled Goldstein *et al.*'s sepsis criteria [6] were more prone to dying. Further studies are necessary to characterize how sepsis presents in developing countries.

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