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Original Research

Sepsis in Pediatric in Vietnam: A Retrospective Study in Period 2008 to 2018

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ABSTRACT

Background: Sepsis is a life-threatening condition caused by dysregulation of the patient's response to infection. Sepsis is a significant cause of morbidity and mortality worldwide in children.

Methods: This retrospective study was conducted from 2008 to 2018 at Children Hospital N1, Vietnam. The focus was primarily on the epidemiological factors, origin of infection, organ dysfunction, microbiological outcomes, and treatment of sepsis in pediatric patients. Results were recorded at a pediatric intensive care unit (PICU) in Vietnam.

Results: From 2008 to 2018, we had 678 patients diagnosed with sepsis treated at the PICU, with 75% diagnosed with septic shock. Most patients (80%) were under 5 years old and the ratio of male to female children was 1.2/1. The common source of sepsis was infections of the gastrointestinal tract (42%), respiratory tract (31%), skin (7%), and soft tissue (7%). Most pediatric patients had organ dysfunction (77%), and functional disorders of two or more organs accounted for 69% of children assisted with invasive ventilation. The positive blood culture rate was about 38% and was predominantly gram-positive agents (56%). The death rate due to sepsis was quite high, at 37%.

Conclusion: In the past 10 years, sepsis caused by gram-positive agents has become more common, and this is a remarkable change. Sepsis remains the most common cause of death among children at the PICU and has not shown improvement. The severity of sepsis parallels the risk of death.

Keywords: Children, retrospective, sepsis, severe sepsis, septic shock, Vietnam

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INTRODUCTION

Sepsis, and its progression to septic shock, is a serious disease with a high mortality rate. It occurs in almost all ages, but is especially prevalent in children, where the rate continues to increase to about 5–10% per year.[1] Early diagnosis and appropriate treatment can reduce the mortality prognosis, especially in patients with septic shock, while also preventing complications and sequelae. The main treatment at present is active resuscitation, appropriate antibiotic therapy, and supportive treatment of organs.[2] Many clinical studies show that delayed and inappropriate antibiotic treatment increases the risk of death five-fold, especially in patients with septic shock, and every hour of delayed antibiotic treatment reduces the patient's ability to survive by 8%.[3]

Diagnosing sepsis in children is a challenge for clinicians. The Goldstein standard, introduced in 2005, is still widely applied in many resuscitation units.[4] As of 2016, the consensus on Sepsis 3rd (sepsis-3) created a new step in the diagnosis of sepsis, but the application of this standard to children requires more research.[5,6] The Department of Pediatrics and Pediatric Resuscitation in Vietnam has introduced a campaign for the diagnosis and treatment of surviving sepsis, which has made research and treatment more consistent and clearer by virtue of the guidance from this "surviving sepsis campaign".

Sepsis in children is a severe, rapidly progressing disease that requires early diagnosis and prompt treatment. The Pediatric Intensive Care and Toxic Management Department (PICU) at Children Hospital N1 is the last unit for resuscitation in South Vietnam. This unit is the right place to apply and train medical professionals regarding the guidelines for treatment of sepsis in children and to update the current treatment of this pathology in children. Many definitions and standards for sepsis have been established, but none has yet shown an absolute superiority.

METHODS

Study sites and populations

This retrospective study was conducted at one of the leading pediatric hospitals in South Vietnam. Subjects included children with sepsis and septic shock treated in the PICU at Children Hospital N1 from September 2008 to December 2018.

Inclusion criteria

The study was conducted on children under 16 years of age who were diagnosed with suspected sepsis or within 24 hours after being hospitalized with at least 3 criteria for a sepsis diagnosis. The diagnostic criteria included body temperature, heart rate, breathing, and one of the criteria of altered mental status, systolic blood pressure, low oxygen saturation, or leukocytes. Severe cases of sepsis and septic shock that included symptoms of sepsis and clinical symptoms such as cardiovascular, respiratory, or other organs were also included in this study.[4] Interviews were only carried out with the consent of the families of the children studied.

Exclusion criteria

Newborns younger than one month of age treated in Neonatal Intensive Care Unit (NICU) were excluded from the study. Children with fungal infections or with family members with fungal infections were also excluded from this study.

Data analysis

All children admitted to PICU underwent a medical history assessment, examination, treatment, and follow-up until death or discharge. The main data of the study were recorded on a unified data collection form, and statistics were calculated using SPSS 20.0 software. Variables were scaled and quantitative variables were averaged and presented with standard deviations.

Ethical approach

The research protocol was submitted to the hospital's ethics panel for review and approval before the research was conducted. Each patient's family was assured that all

information collected on the pediatric patient was for scientific purposes only.

RESULTS

Table 1. Baseline characteristic of pediatric patients (N= 678)

Value		N	%
Age	< 1 year	277	41
	1 - 5 years	267	39
	> 5 years	134	20
Sex	Male	363	54
	Female	315	46
Diagnosis	Sepsis	169	25
	Septic shock	509	75
Sources of infection	Respiratory	212	31
	GI	285	42
	Skin and soft tissue	48	7
	CNS	48	7
	Other	85	13
Number of Organ failure	1	155	23
	> 1	523	77
Blood culture	Negative	423	62
	Positive	255	38
	Gram (+)	144	56
	Gram (-)	111	44
Mechanical ventilation	Yes	469	69
	No	209	31
Mortality	Dead	251	37
	Survival	427	63

The study included 678 children who met the study criteria between 2008 and 2018. Some characteristics of the children included in research are shown in **Table 1**. The majority of these patients (75%) were diagnosed with septic shock. Sepsis was most common in children under 5 years of age (80%), and the proportion of bacterial infection was higher (1.2/1) for boys than for girls. The origin of sepsis was mainly from foci of infection from the gastrointestinal tract (42%), respiratory tract (31%), skin (7%), and soft tissue (7%), with the remainder arising from central nervous system infections and other foci of infection (13%). All children had at least one organ dysfunction, and 77% had dysfunction of two or more organs. The rate of positive blood cultures was 38%, and gram-positive agents accounted for the majority at about 56%. Overall, 69% of the pediatric patients had intubation for breathing and mechanical ventilation (**Table 1**).

Agents

The proportions of infective agents found in the pediatric patients are listed in **Table 2.** A coagulase negative Staphylococcus result was considered to be positive when it gave a positive response after two cultures and the patient showed clinical manifestations of infection, or when one blood sample and one catheter culture sample were positive under an appropriate clinical situation.

Table 2. The proportion of bacterial infections in pediatric patients

Type of bacteria	N	%
Gram-positive bacteria	**144**	**56**
MRSA	28	19
MSSA	4	3
Staphylococcus coagulase (-)	77	53
Streptococus pneumonia	28	19
Streptococcus spp.	5	3
Staphylococcus saprophyticus	2	1
Gram-negative bacteria	**111**	**44**
Ancinetobacteria spp.	22	20
Pseudomonas aeruginosa	10	9
E. coli	15	14
Stenotrophomonas maltophilia	14	13
Klebsiella pneumonia	9	8
Burkholderia cepacia	6	5
Burkholderia pseudomallei	3	3
Salmonella sp.	6	5
Shigela spp.	2	2
Alcaligenes faecalis	2	2
Cupriavidus pauculus	2	2
Ralstonia pickettii	8	7
Roseomonas gilardii	2	2
Sphingomonas paucimobilis	5	5
Vibrio vulnificus	1	1
Raoultella ornithinolytica	1	1
Enterobacter spp.	1	1
Morganella morganii	2	2

Fluid Therapy

From 2008 to 2011, 46.3% of the cases underwent fluid therapy for 60 minutes. The total volume of treatment was 86.4 ± 41.1 ml/kg. From 2012 to 2016, the average use of therapeutic fluids was 60.6 ± 36.7 ml/kg, and in 2017-2018, the total treatment volume was 47.5 ml/kg. According to the guidelines of Children Hospital N1, fluid is administered at 20 ml/kg/ h to compensate for shock volume. As a result, the patient's total initial fluid intake is often low. We compensate for the lack of fluids because of the danger of these patients suffering from respiratory failure due to an inadequate means of breathing. Children Hospital N1 started applying rapid rehydration (20 ml/kg/5–20 min) according to the SSC guidelines of 2008.[7] However, guidance, training, and application also add to the time for diagnosis and for prompt use to quickly recover the volume. Since 2012, we have applied ultrasound to assist in evaluating the translation responses. The amount of administered fluids has begun to decline, and fluid overload is less of a problem, and has shown significant decreases in 2017–2018 (**Figure 1**).

Inotropes and vasopressors

Before 2008, we used dopamine and dobutamine to support inotropes (**Figure 2, Table 2**). However, after applying SSC 2008[7] in 2012 and especially 2016, the use of adrenaline as the first line of treatment increased. The mortality rate also decreased proportionally across the periods by an average of 37% (**Figure 3**). However, we did not consider the sequelae rates in conjunction with the decreases in mortality rates.

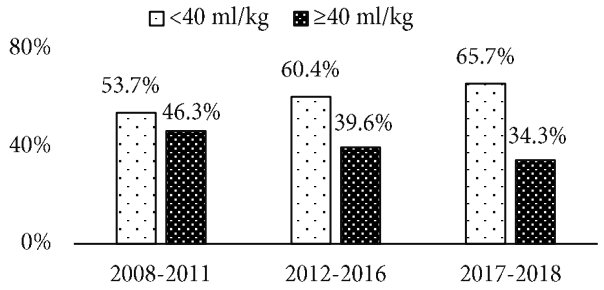

Figure 1. Total fluid infusion during the first one hour

Table 3. Percentage of inotropes and vasopressors

VASOPRESSOR Medicine	2008-2011	2012-2016	2017-2018
Dopamin	42%	33%	28%
Dobutamin	32%	18%	12%
Adrenaline	10%	29%	33%
Noradrenaline	16%	20%	27%

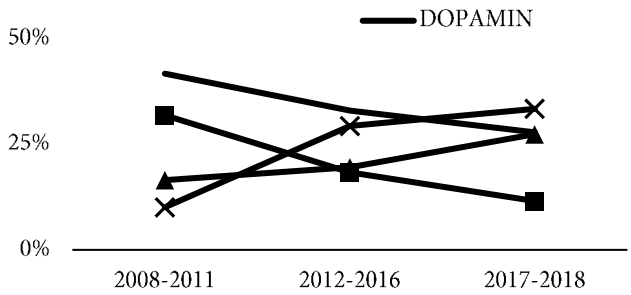

Figure 2. Tendency to use inotropes and vasopressors

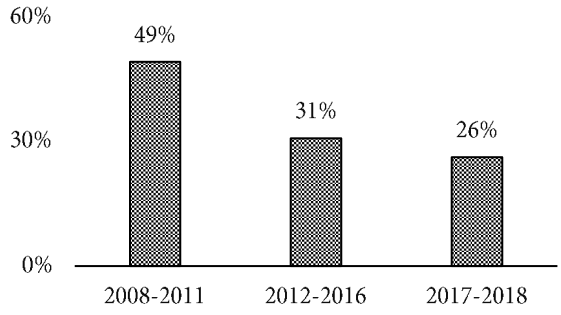

Figure 3. Mortality rate of sepsis

DISCUSSION

Severe sepsis in children in the PICU over the past 10 years has not shown much change, with the highest incidence still in infants. All studies of sepsis in children have shown that rates of sepsis and septic shock are higher in young children than in older children. Although all children have the potential to develop sepsis from small infections, the risk is usually higher in children with very low birth weight, suppressed immune systems, congenital deformities, catheterization, and chronic medical conditions. In most epidemiological studies around the world, sepsis occurs in almost all ages. However, children under five years of age, and especially younger than one year, still account for a higher proportion and their conditions often worsen.[1, 8-12] This may be explained by the fact that in children under five years old, the immune humoral and cellular immunity systems are not completely developed; therefore, young children are more susceptible to infections and older children are more likely to have progression of their infections.[13,14]

The proportion of boys and girls in our study did not differ significantly, in agreement with global statistics. Many epidemiological statistics in the US have also indicated no gender difference in sepsis in children.[1,12] Dannai and Martin also showed no influence of sex on sepsis.[8] The incidence of sepsis in pediatric patients in the United States averages about 42,000 annually, with a mortality rate of 10%.[1,12] Studies from the United Kingdom have shown that 17% of children die from severe sepsis and septic shock in PICUs.[15] Childhood sepsis among PICU patients in developing countries is higher than 50%.[16]

Sepsis progresses through various stages, including systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multi-organ dysfunction syndrome (MODS).[4] All infection sites can be the entry point for sepsis. In the present study, the most common primary foci of infection were from the gastrointestinal tract, followed by the respiratory tract, skin, and soft tissue. The studies in 2013–2015 by Hartman,[17] Mayr,[9] Ruth,[18] and Weiss[19] also showed similar results. Respiration and digestion are the two most common inputs for septicemia agents. The percentage of positive blood cultures is quite high (38%) among positive cases. Gram-positive bacteria account for 56% of these infections and remain the main cause of sepsis; however, even fungi, viruses, and parasites in the urinary tract, lungs, skin, and other tissues can cause sepsis.

Most previous standards consider blood culture as the gold standard for the diagnosis of sepsis. However, at the International Conference on sepsis in children in 2005, criteria for determining infections were added to include blood culture, staining, and blood PCR.[4] Of the available methods, blood culture is still the most commonly used method today. Blood culture is usually done before administration of antibiotics, and at least two samples are cultured. However, the percentage of positive blood cultures in patients with fever is very low, at about 5–15%, and some researchers think that the rate of blood culture positive in patients with suspected sepsis is no greater than 5–30%. In patients already taking antibiotics, the rate of positive culture will be still much lower.[2] A positive culture also depends on the severity and location of the infection. Cases of bacteria growing slowly or having contamination result in lower and longer results. The proportion of patients with severe sepsis and a septic shock-positive transplant rate can be up to 50%.[20] We study noted positive blood culture results in about 38% of our patients, a positive number, but compared to other samples, this rate is still quite low. Therefore, in the current clinical practice, we now apply more blood PCR to identify septic agents, especially in cases of unfavorable progress and poor response to initial antibiotic treatments, as blood cultures can be repeatedly negative. The current blood PCR results are promising, as they show higher accuracy and shorter diagnosis time than blood culture. However, even PCR has disadvantages, such as an inability to assess the sensitivity or resistance of bacteria to antibiotics. The need to create specific primers that help identify bacteria is a further limitation.[10, 21-29] We now recommend a combination of blood cultures and blood PCR to assist in identifying sepsis agents in children in clinical practice.

Previous studies of sepsis at our center have recorded the dominant gram-negative agents, but statistics over the past 10 years have recorded the rise of particular gram-positive agents, including methicillin-resistant *Staphylococcus aureus* (MRSA) and pneumococcal forms.

About 56% of the bacteriostatic agents isolated were gram-positive bacteria, which is a rare rate in many parts of the world. However, some foreign authors have recently recorded similar changes.[30] For example, Shapiro reported a ratio that ranged from 30–60%, while Gray reported a rate of 30.8%,[31] and Martin reported a rate of 52.1%.[1] Staphylococcal agents, especially MRSA, now cause increasingly more sepsis, rapid progression, and high mortality.[32-36] This is quite interesting, and it should be considered when making decisions regarding the appropriate initial antibiotic treatment.

The primary treatment for sepsis is the proper use of antibiotics, but even after providing the appropriate antibiotic therapy, the mortality rate may remain high due to complications of sepsis such as septic shock, organ damage to the lungs, kidney, heart, etc., and especially when the child has MODS. Therefore, close monitoring and timely antibiotic administration, detection, and treatment of complications of sepsis will hopefully reduce mortality.

In the past 10 years, since the application of Goldstein's sepsis diagnostic standards as well as the American Resuscitation Association and the SSC guidelines for the treatment of sepsis in children, we have achieved positive results in our PICU.[2, 37, 38] If infusion is introduced within the first hour, the rate of sepsis is now greatly reduced. The SSC septicemia guidelines from 2008 and 2012 allowed for a maximum of 60 ml/kg of fluid to be recovered in the first hour, or even up to 200 ml/kg.[2] However, in recent years, this has changed. The problem of fluid overload indicates that positive fluid balance is very important in resuscitation and affects mortality, mechanical ventilation time, and the duration of stay in the PICU. Consequently, using a strategy that incorporates early vasomotor to limit the amount of fluid against shock has brought about positive effects. The SSC guidelines of 2016 [37] and of the American Pediatric Resuscitation Association 2017 [38] have been applied by a control center for the past two years. At present, the amount of fluid used in our resuscitation has decreased significantly.

Apart from the changes in anti-shock fluid, vasomotor is also a matter of concern. The pathophysiology of septic shock in children is quite complex. In adults, septic shock is a typical representative of distributional shock (vasodilation), with 90% being warm shock. However, the opposite situation occurs in children, where 50% of the cases are cold shock,[39, 40] and the rate of reduced myocardial contractility in children is about 60%.[41] Therefore, most of the previous guidelines for the treatment of sepsis in children indicated a preference for vasoconstrictors that increase myocardial contractility, with dopamine being the preferred drug.[2,42] However, due to the side effects associated with arrhythmias, the ability to achieve hemodynamic targets is poorer than that achieved with adrenaline, which has, by far, been dopamine-free.

Following the guidelines of the 2017 American Pediatric Resuscitation Association, adrenaline and noradrenaline have now become the preferred options for resuscitation in children with septic shock.[38] Our center has also adopted these same changes. Along with these changes in the treatment, the mortality rates at our center has also decreased over time. This is similar in developed countries. However, compared with the United States and European countries, our mortality rate is still quite high, although it is much lower than many countries with similar economic conditions.[1, 12, 43] Hopefully, with the changes from the Third International Consensus on Sepsis and the application of the American Pediatric Resuscitation Association's guidelines for sepsis–septic shock, updated in 2017, we will see even more positive results in the future.

CONCLUSION

In the past 10 years, sepsis caused by gram-positive agents has become more common. Treatment of sepsis and septic shock in Vietnamese children has improved with the introduction of the SSC guidelines in 2008, which has brought about positive results. Mortality rates are now declining in this patient population in Vietnam.

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CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

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