MINISTRY OF EDUCATION AND TRAINING MINISTRY OF HEALTH
NATIONAL INSTITUTE OF HYGIENE AND EPIDEMIOLOGY

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EPIDEMIOLOGICAL, CLINICAL, MICROBIOLOGICAL CHARACTERISTICS AND FACTORS ASSOCIATED WITH MORTALITY IN PEDIATRIC PATIENTS WITH SEPSIS AGED 1 MONTH TO UNDER 15 YEARS TREATED AT THE NATIONAL CHILDREN'S HOSPITAL, 2018-2020

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LIST OF PUBLICATIONS RELATED TO THE THESIS

1. **Hoàng Văn Kết, Trần Minh Điển, Nguyễn Thị Thùy Dương, Lại Thị Minh, Lê Hồng Nga, Nguyễn Thúy Quỳnh, Lê Anh Tuấn, Bùi Thanh Thúy, Trần Đại Quang (2023).** *"Some epidemiological, clinical, and laboratory characteristics of sepsis in children aged 1 month to under 15 years at the National Children's Hospital, 2018-2020." Journal of Preventive Medicine, Special Issue for the 2023 Scientific Conference of the National Institute of Hygiene and Epidemiology.*
2. **Hoàng Văn Kết, Tống Thị Hà, Trần Huy Hoàng, Phạm Duy Thái, Nguyễn Hoài Thu, Trần Minh Điển, Nguyễn Thị Thùy Dương, Trần Diệu Linh, Hoàng Thị Bích Ngọc, Nguyễn Hiệp Lê Yên (2020)**. *"Antibiotic resistance and genotypic relationships of bacterial strains causing sepsis in children aged 1 month to under 15 years treated at the National Children's Hospital, 2018-2020." Journal of Preventive Medicine, Issue 10, 2020.*

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated body response to infection. Sepsis in children is a significant concern due to challenges in prevention and treatment. The causative agents of sepsis can include bacteria, viruses, parasites, or fungi; however, bacteria remain the primary cause.

Globally, treating sepsis, particularly severe sepsis and septic shock in children, remains difficult even in developed countries. According to World Health Organization (WHO) statistics, sepsis ranks 9th among causes of death in children over 1 year of age, 7th in children aged 1-4 years, and is a leading cause of death in intensive care units. In Vietnam, a study by Vu Van Soat and colleagues showed that the mortality rate from severe sepsis leading to septic shock in the Pediatric Intensive Care Unit of the National Children's Hospital was 85.1%. Another study by Pham Van Thang and Tran Minh Dien reported a mortality rate of around 80%. These alarming figures highlight the severe impact of sepsis in medical facilities.

Although there have been many scientific studies, research projects, and conferences on pediatric sepsis, several issues remain unresolved. Addressing these challenges is critical for improving treatment outcomes. Therefore, we conducted the study titled *"Epidemiological, Clinical, Microbiological Characteristics and Factors Associated with Mortality in Pediatric Patients with Sepsis Aged 1 Month to Under 15 Years Treated at the National Children's Hospital, 2018-2020"* with the following objectives:

1. To describe the epidemiological and clinical characteristics of pediatric patients with sepsis aged 1 month to under 15 years treated at the National Children's Hospital from 2018 to 2020.
2. To determine the distribution, antibiotic resistance patterns, and genotypic characteristics of bacterial strains isolated from pediatric sepsis patients treated at the National Children's Hospital from 2018 to 2020.
3. To analyze factors associated with mortality in pediatric patients with sepsis treated at the National Children's Hospital from 2018 to 2020.

Scientific Innovations and Practical Value of the Study

The thesis contributes several scientific innovations and practical values:

1. Scientific Innovations

- This is a comprehensive study covering multiple aspects conducted at the largest pediatric research and clinical practice center in the country. Therefore, the thesis provides a thorough perspective on the status of pediatric sepsis, along with clinical, epidemiological, and bacterial factors, as well as treatment outcomes and factors associated with mortality.

- This is the first study in Vietnam to provide scientific evidence on the genotypic relationships of bacterial pathogens causing pediatric sepsis. The research results warn of the rapid increase in the risk of bacterial strain transmission, especially antibiotic-resistant bacteria, within the hospital environment.

2. Scientific Value:

- The study employs modern techniques such as bacterial identification using MALDI-TOF, pulsed-field gel electrophoresis (PFGE), and genotypic analysis to provide reliable data on the risk of bacterial transmission and cross-infection in hospitals.

- The research process involved collaboration between the National Institute of Hygiene and Epidemiology and the National Children's Hospital, utilizing techniques meeting ISO 2022 standards, ensuring high accuracy and reliability of the results.

3. Practical Value:

Treating sepsis remains challenging and costly, with high mortality rates despite modern resuscitation facilities. Therefore, it is necessary to study early diagnosis, timely treatment, identify mortality risk factors, and apply scientific advancements to reduce mortality rates in pediatric sepsis. This is an up-to-date and essential research topic.

Structure of the Dissertation

The dissertation is 129 pages long: Introduction (2 pages), Chapter 1: Literature Review (34 pages), Chapter 2: Subjects and Research Methods (18 pages), Chapter 3: Research Results (31 pages), Chapter 4: Discussion (41 pages), Research Limitations (1 page), Conclusion (2 pages), Recommendations (1 page). The dissertation contains 22 tables, 12 figures, and 1 diagram. It includes 189 references, with 22 in Vietnamese and 167 in English.

Chapter 1: LITERATURE REVIEW

1. Definitions in Infections

1.1. Systemic Inflammatory Response Syndrome (SIRS):

The presence of at least 2 out of 4 criteria, with at least 1 mandatory criterion being abnormal body temperature or white blood cell count:

- Central body temperature > 38.5°C or < 36.0°C.
- Tachycardia exceeding 2 standard deviations (SD) for age.
- Respiratory rate exceeding 2 SD for age or the need for mechanical ventilation.
- White blood cell counts increased or decreased according to age.

1.2. Infection:

Suspected or confirmed infection by any agent: positive blood culture, fresh smear staining, PCR, or clinical syndrome highly suggestive of infection. Evidence of infection includes clinical signs, imaging, or laboratory results.

1.3. Sepsis: SIRS + suspected or confirmed infection.

1.4. Severe Sepsis: Sepsis with one of the following signs: circulatory failure, acute respiratory distress syndrome, or dysfunction of 2 or more organs.

1.5. Septic Shock: Sepsis + circulatory failure.

2. Epidemiology of Sepsis in Children

2.1. Characteristics of Age and Gender

Sepsis in children can occur in any age group but is most common in those under 1 year old. Watson L.S. and colleagues conducted a study on the epidemiology of pediatric sepsis in 7 states in the United States and found that the highest incidence rate was in children under 1 year old (69.7%). The incidence of sepsis also varies by gender, with studies consistently showing higher rates in boys than girls. Watson L.S. reported an incidence rate of 0.56% for boys and 0.44% for girls. Tran Minh Dien's study at the National Children's Hospital (2010) found a male-to-female ratio of 59.5/40.5.

2.2. Incidence of Sepsis in Children Globally and in Vietnam

According to Hartman’s study, in 2005, the United States recorded 720,000 hospitalizations related to sepsis, of which 75,255 were children. The number of diagnosed sepsis cases increased annually (from 0.56 to 0.89 cases per 1,000 children). In developing countries, the incidence of sepsis in children is higher. Jaramillo-Bustamante and colleagues found that among 1,051 children aged 1 month to 17 years diagnosed with sepsis, 25% had severe sepsis and 4.8% had septic shock. A recent multinational study conducted on 6,925 children in 128 intensive care units reported a sepsis rate of 8.2%, with regional differences ranging from 6.2% in Europe to 23.1% in Africa.

2.3. Mortality Rates from Pediatric Sepsis

According to the World Health Organization, in 2017, there were 6.3 million deaths in children under 5 years old, with over 50% related to infectious diseases. In developed countries, the mortality rate for pediatric sepsis has significantly decreased (5% - 20%). However, in developing countries, the mortality rate remains as high as 40%. Wang Yue’s study reported a pediatric sepsis mortality rate of 34.6% in China. In Vietnam, Tran Minh Dien’s study indicated that mortality from septic shock reached 65.7%.

3. Clinical Features

Sepsis is a complex condition with variable clinical presentations. Symptoms can differ among patients, depending on the site of infection and the causative agent. Therefore, no single clinical or laboratory feature is definitive for diagnosis. Currently, pediatric sepsis diagnosis still follows the criteria from the 2005 Pediatric Sepsis Consensus Conference.

4. Microbiological Characteristics of Sepsis

The bacteria responsible for sepsis depend on the primary infection site and the timing of diagnosis. Recent studies show an increasing prevalence of Gram-positive bacteria. In the United States, a study from 1979 to 2004 noted that Gram-negative bacteria were the primary cause from 1979 to 1987. However, from 1987 to 2003, Gram-positive bacteria became more prevalent, increasing by 26.3% annually. By 2000, Gram-positive bacteria accounted for 52.1% of sepsis cases, Gram-negative bacteria for 37.6%, and other causes for the remaining cases. The specific bacteria causing sepsis vary by country, region, age, and immune status of patients.

5. Risk Factors Associated with Mortality

Blood lactate is an indicator of tissue hypoperfusion and helps predict sepsis outcomes. Tran Minh Dien’s study found that an arterial lactate level above 6.5 mmol/L was a risk factor for mortality in children with septic shock. Kana Ram Jat’s research indicated that children with lactate levels above 5 mmol/L were at higher risk of mortality from septic shock.

The Pediatric Risk of Mortality (PRISM) score is a reliable tool for predicting mortality in pediatric intensive care units. Multiorgan dysfunction is also a significant mortality risk factor. Graciano AL’s study found that mortality was below 5% in children with 1 or no organ dysfunction but exceeded 80% in those with multiple organ failure. The Vasoactive-Inotropic Score (VIS) is now an effective tool for predicting mortality in septic shock patients. AH AQUE’s study demonstrated a linear relationship between VIS and mortality in children with septic shock.

Chapter 2: RESEARCH METHODS

2.1. Participants:

The study includes all patients aged 1 month to 15 years who were admitted to the inpatient departments of the National Children’s Hospital, diagnosed with sepsis, and had blood cultures performed to identify the causative agent.

2.1.1. Inclusion Criteria

- Patients meeting the criteria for systemic inflammatory response syndrome (SIRS) caused by bacteria.
- Evidence of infection.
- Positive blood culture results.

2.1.2. Exclusion Criteria

- Neonates or children over 15 years of age.
- Families who did not consent to participate in the study.

2.2. Research Methods

2.2.1. Research Design

Objective 1: Descriptive epidemiological study (case series of sepsis patients at admission or during treatment).

Objective 2: Descriptive study with laboratory analysis to determine bacterial characteristics, antibiotic resistance, and genetic relationships of bacterial strains.

Objective 3: Descriptive study with analysis to identify factors associated with mortality in sepsis patients.

2.2.2. Sample Size and Sampling Method

The sample size was calculated based on the proportion of sepsis cases with positive blood cultures.

The formula for calculating sample size:

$$n = \frac{z^2_{1-\alpha/s} P(1-P)}{d^2}$$

The minimum sample size required was 323 patients. In practice, we collected data from 327 patients.

2.3. Research Content and Variables

2.3.1. Research Content

Objective 1:

- Epidemiological characteristics of patients.
- Clinical characteristics at admission.
- Laboratory characteristics at admission.

Objective 2:

- General characteristics of isolated bacteria.
- Antibiotic resistance patterns.
- Genotypic relationships of the 5 most common bacterial species.
- Transmission of 5 bacterial pathogens within the hospital environment.

Objective 3:

- Epidemiological factors.
- Clinical factors.
- Laboratory factors.

2.3.2. Research Variables

Objective 1: To describe the epidemiological and clinical characteristics of pediatric patients with sepsis aged 1 month to under 15 years treated at the National Children's Hospital from 2018 to 2020.

Table 2.1. Variables/Indicators for Objective 1

Variable/Indicator	Definition	Classification	Data Collection Method
Gender	Male or female	Binary	Medical examination
Age	Distribution of sepsis by age group: - Group 1: 1 month to under 12 months - Group 2: 12 to 24 months - Group 3: Over 24 months to 5 years - Group 4: Over 5 years to under 15 years	Qualitative	Based on age classification for SIRS in children
Region	Divided into 3 groups: Urban, rural, or mountainous	Categorical	Medical records
Nutritional Status	Divided into 2 groups: Presence or absence of malnutrition	Binary	Based on weight-for-age, WHO reference values
Underlying Disease	Pre-existing medical conditions before sepsis diagnosis	Categorical	Medical history, medical records

Vaccination History	Divided into 2 groups: Fully vaccinated or Not vaccinated/incomplete vaccination	Binary	Interview
Pre-hospital Treatment	Divided into 2 categories: ≤ 5 days, > 5 days	Binary	Medical history
Infection Site	Primary infection site leading to sepsis	Qualitative	Clinical examination, medical records
Clinical Manifestations	Clinical and laboratory signs of sepsis, combined with the 2005 SIRS criteria for children	Composite Variable	Medical records

Objective 2: Identify the distribution, antibiotic resistance patterns, and genotypes of bacterial strains causing sepsis in patients aged 1 month to under 15 years treated at the National Children's Hospital, 2018-2020.

Table 2.2: Variables/Indicators for Objective 2

Variable/Indicator	Definition	Classification	Data Collection Method
Bacterial Groups Isolated	The proportion of Gram-negative and Gram-positive bacterial strains in the study	Binary	Bacterial culture results
Bacterial Identification Results	The frequency of bacterial strains identified through blood culture	Ratio Variable	Bacterial culture results
Antibiotic Resistance Characteristics of Isolated Strains	The number of bacterial strains sensitive or resistant to each tested antibiotic, based on the minimum inhibitory concentration (MIC) of common bacteria	Qualitative	Antibiotic susceptibility test results
Bacterial Genotype	Determination of the genotypes of isolated bacterial strains	Qualitative	Pulsed-field gel electrophoresis (PFGE)

Objective 3: Analyze factors associated with mortality in pediatric sepsis patients aged 1 month to under 15 years treated at the National Children's Hospital, 2018-2020.

Table 2.3: Variables/Indicators for Objective 3

Variable/Indicator	Definition	Classification	Data Collection Method
Mortality Rate	(Number of sepsis patient deaths × 100%) / Total number of sepsis patients	Dependent	Calculated using SPSS software
Age	Age divided into two groups: ≤1 year and >1 year	Independent	Birth certificate
Gender	Male or female child	Independent	Clinical examination
Underlying Disease	Divided into two groups: with underlying disease and without underlying disease	Independent	Medical records and patient interviews

Hospital-Acquired Infection (HAI)	Divided into two groups: with HAI and without HAI	Dependent	According to the criteria of the Microbiology Department, National Children's Hospital
Clinical Symptoms	Collection of clinical symptoms through examination, interviews, and medical records	Independent	Clinical examination and medical records
Laboratory Indicators	Collected from medical records	Independent	Medical records
Multiple Organ Dysfunction	Multiple organ dysfunction defined as ≥2 organ failures	Dependent	Based on the diagnostic criteria for MODS
Severity Factors at Admission	Assessed within 24 hours of diagnosing sepsis or septic shock	Dependent	Pediatric Risk of Mortality Score (PRISM III)

2.4. Data Processing and Analysis Techniques

Data entry and analysis were conducted using SPSS 20 statistical software. The steps for analysis and data presentation were carried out according to the research objectives, including descriptive statistics and data analysis. PFGE results were analyzed using Bionumerics 6.6.11 software to generate phylogenetic trees.

2.5. Bias Control

Random errors were controlled by ensuring the number of patients recruited met at least the calculated minimum sample size. Systematic errors were minimized by applying clear inclusion and exclusion criteria for patient selection. If any inconsistencies were identified during verification, the subject was excluded from the study. Data entry and processing were performed twice to cross-check the results.

2.6. Ethical considerations

The study was conducted with permission and approval from the Board of Directors of the National Children's Hospital and accepted by the Scientific Council of the National Children's Hospital under Decision No. 391, signed on March 22, 2019. All patient information collected was used solely for research purposes.

Chapter 3: RESEARCH RESULTS

3.1. Epidemiological, Clinical, and Laboratory Characteristics of the Study Population

After analyzing 327 patients who were admitted with a diagnosis of sepsis and met the inclusion and exclusion criteria, we obtained the following results:

3.1.1. Epidemiological Characteristics of Pediatric Sepsis Patients

Children under 12 months accounted for the highest proportion, 48.9%. Male children made up 55%, and 25.1% had poor nutritional status. The percentage of patients who were fully vaccinated was relatively low, at 30%.

The primary infection sites were the respiratory tract (25.7%) and the digestive tract (19%). Community-acquired sepsis accounted for 64.4%, and the rate of septic shock was 18.7%.

Among children with sepsis, 43.4% had comorbid conditions, with the most common being digestive diseases (25.4%), cardiovascular diseases (19.0%), and cancer (14.8%).

3.1.2. Clinical Characteristics

The proportion of patients with respiratory failure was 35.8%, of whom 9.8% required intubation. Patients showed cardiovascular abnormalities, including weak pulse (9.2%), mottling (22.0%), and cold extremities (20.8%).

Neurological dysfunction was observed in 33.9% of patients, with a low proportion of patients in a coma (1.8%). Most patients had normal renal function, while 16.8% experienced renal failure.

3.1.3. Laboratory Characteristics

The average white blood cell count was 17,800 ± 10,600/mm³, with 11.9% of patients having a low white blood cell count (<5000/mm³). The average platelet count was 287.2 ± 189.8/mm³, and 11.6% of patients had a platelet count below 50,000/mm³. CRP levels were very high, with an average of 153.8 ± 85.8 mg/L.

The average pH was 7.4 ± 0.1, with 2.1% of patients showing severe metabolic acidosis (pH <7.2) and 29.6% experiencing compensated metabolic acidosis. The average lactate level was 1.9 ± 1.9 mmol/L, with 24.4% of patients having elevated lactate levels (>2 mmol/L).

3.2. Characteristics of Bacteria Causing Sepsis in Children

3.2.1. General Characteristics and Distribution of Bacteria

Gram-positive bacteria accounted for 52% in the study, which was higher than Gram-negative bacteria at 48%. Among Gram-negative bacteria, Escherichia coli had the highest proportion at 16.2%. Among Gram-positive bacteria, Staphylococcus aureus had the highest proportion at 39.4%.

3.2.2. Genotypic Relationships of Bacteria

We conducted a genotypic analysis of 183 bacterial strains across 5 species: *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae,* and *Acinetobacter baumannii*. The results are as follows:

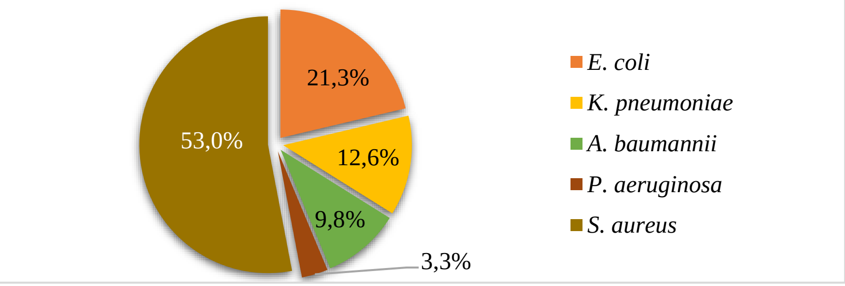

Figure 3.2. Percentage of Bacterial Strains Analyzed for Genotyping

Comments:

Among the total of 183 bacterial strains analyzed for genotyping, *Staphylococcus aureus* accounted for the highest number with 97 strains (53.0%), followed by *E. coli* with 39 strains (21.3%), *K. pneumoniae* with 23 strains (12.6%), *A. baumannii* with 18 strains (9.8%), and *Pseudomonas aeruginosa* with the lowest number of 6 strains (3.3%).

3.2.2.1. Genotypic Relationships of E. coli

Groups E1-E4 exhibited genotypic similarity of ≥80%. The common characteristic of these four groups is that they consist of bacterial strains isolated from different departments at different times (Figure 3.3).

Group E1 and E3 each consisted of 2 strains isolated in the same year but from two different departments.

The 2 strains in Group E3 were isolated from the Oncology Department and the Hepatobiliary Department in 2020, showing >95% genotypic similarity.

Group E2 consisted of 7 strains isolated from different departments, including 2 strains from the Infectious Disease Center that exhibited >95% genotypic similarity.

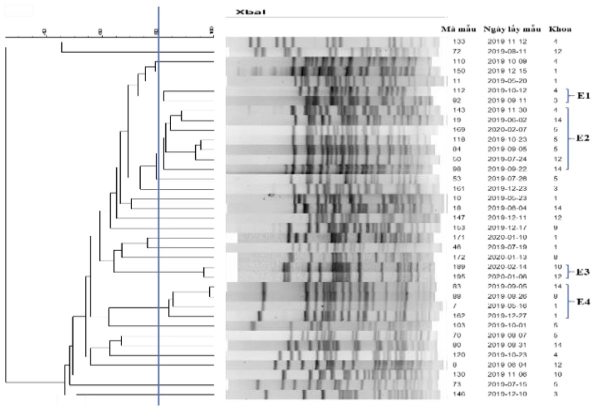

Figure 3.3. Genotypic Classification Tree of *E. coli* Strains

Legend for Departments: 1: Nephrology Center; 2: Cardiology Center; 3: Gastroenterology Department; 4: Intensive Care Unit (ICU); 5: Infectious Disease Center; 7: Allergy - Immunology Department; 8: Private Services Ward; 9: Surgery Ward; 10: Oncology Department; 11: Respiratory Center; 12: Hepatobiliary Department; 13: Hematology Department; 14: Emergency Department.

3.2.2.2. Genotypic Relationships of K. pneumoniae

The *K. pneumoniae* strains showed limited genotypic relationships, with only one genotype group, K1, exhibiting ≥80% similarity. This group consisted of 2 strains isolated from the PICU (Pediatric Intensive Care Unit) in 2019 (Figure 3.4).

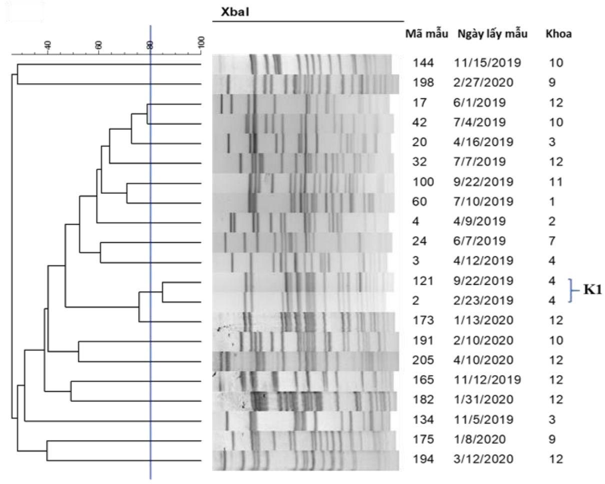

Figure 3.4. Genotypic Classification Tree of *K. pneumoniae* Strains

Legend for Departments: 1: Nephrology Center; 2: Cardiology Center; 3: Gastroenterology Department; 4: Intensive Care Unit (ICU); 5: Infectious Disease Center; 7: Allergy - Immunology Department; 8: Private Services Ward; 9: Surgery Ward; 10: Oncology Department; 11: Respiratory Center; 12: Hepatobiliary Department;

3.2.2.3. Genotypic Relationships of A. baumannii

The A. baumannii strains exhibited very high genotypic similarity (≥80%). All strains belonged to genotype group A1 and were diverse in terms of the departments where the blood cultures were taken (spanning 8 different departments). Notably, strains 26 and 54, isolated from the Cardiology Center, showed nearly 100% similarity (Figure 3.5).

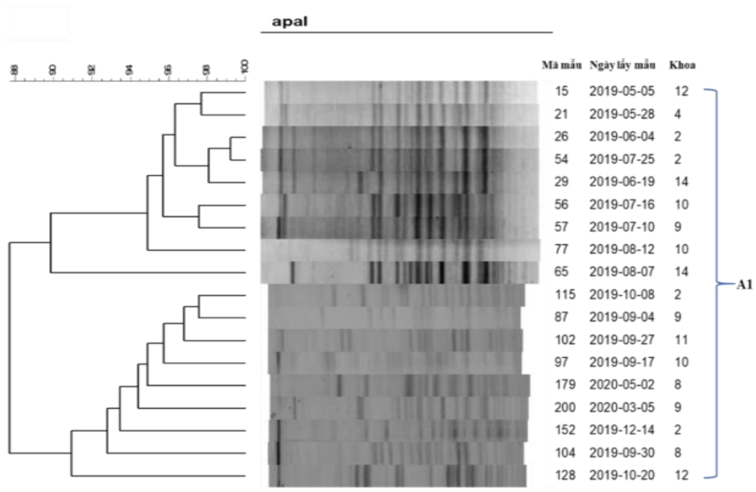

Figure 3.5. Genotypic Classification Tree of *A. baumannii* Strains

Legend for Departments: 2: Cardiology Center; 4: Intensive Care Unit (ICU); 8: Private Services Ward; 9: Surgery Ward; 10: Oncology Department; 11: Respiratory Center; 12: Hepatobiliary Department; 14: Emergency Department.

3.2.2.4. Genotypic Relationships of Pseudomonas aeruginosa

Although the number of Pseudomonas aeruginosa strains was relatively small (6 strains), 5 strains exhibited genotypic similarity of ≥80% (genotype P1). These strains were isolated from 4 different departments, all within the year 2019 (Figure 3.6).

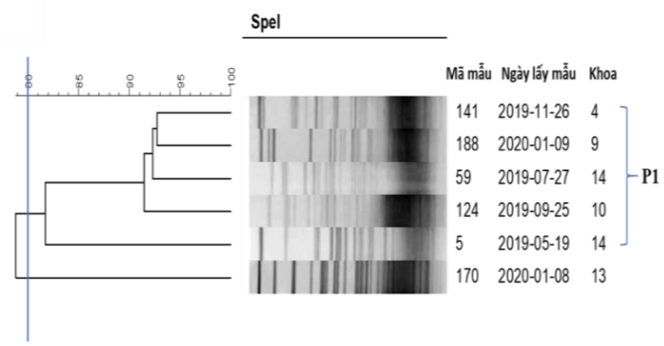

Figure 3.6. Genotypic Classification Tree of *Pseudomonas aeruginosa* Strains

Legend for Departments: 4: Intensive Care Unit (ICU); 9: Surgery Ward; 10: Oncology Department; 13: Hematology Department; 14: Emergency Department

3.2.2.5. Genotypic Relationships of S. aureus

Two strains in group S2 showed genotypic similarity of ≥90%, both isolated from the Infectious Disease Center in 2020. In group S4, some strains displayed up to 100% genotypic similarity, including 2 clusters:

- Cluster 1 (strains 37, 38) isolated from the Intensive Care Unit and the Emergency Department on the same day.
- Cluster 2 (strains 6, 22, 25) isolated from the Allergy - Immunology Department and the Emergency Department.

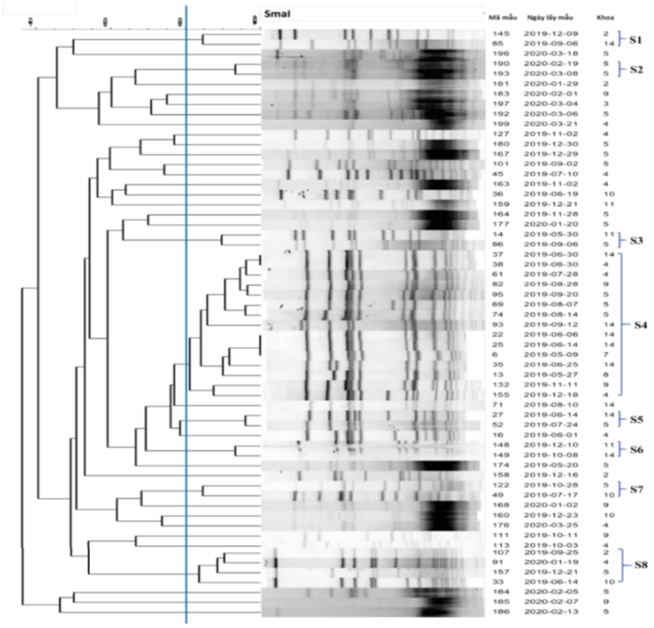

Figure 3.7. Genotypic Classification Tree of *S. aureus* Strains

Legend for Departments: 1: Nephrology Center; 2: Cardiology Center; 3: Gastroenterology Department; 4: Intensive Care Unit (ICU); 5: Infectious Disease Center; 7: Allergy - Immunology Department; 8: Private Services Ward; 9: Surgery Ward; 10: Oncology Department; 11: Respiratory Center; 12: Hepatobiliary Department; 13: Hematology Department; 14: Emergency Department.

Table 3.12. Characteristics of Antibiotic Resistance in Bacterial Strains

Antibiotic	**Số lượng chủng kháng**					**Total**	**Percentage (%)**
	***E. coli* (n=39)**	***K. pneumoniae* (n=23)**	***A. baumannii* (n=18)**	***P. aeruginosa* (n=6)**	***S. aureus* (n=97)**		
Aminoglycosides Group							
Gentamicin	13	11	5	1	13	43	23.5
Fluoroquinolones Group							
Levofloxacin	17	6	4	0	7	34	18.6
Sulfonamides Group							
Trimethoprim / sulfamethoxazol	26	12	1	-	2	41	22.4
Second-Generation Cephalosporins Group							
Cefoxitin	9	15	-	-	76	100	54.6
Third-Generation Cephalosporins Group							
Ceftazidime	21	12	8	2	79	122	66.7
Carbapenems Group							
Imipenem	3	10	6	0	77	96	52.4
Meropenem	3	9	7	0	77	96	52.4
Penicillins Group							
Oxacillin	-	-	-	-	76	76	41.5

Comments:

- The antibiotic with the highest resistance rate is Ceftazidime (66.7%), while the lowest resistance rate is Levofloxacin (18.6%).
- The antibiotic with the highest resistance rate varies among different bacterial strains: *K. pneumoniae* has the highest resistance to Cefoxitin with 15/23 (65.2%). *E. coli* has the highest resistance to Trimethoprim/Sulfamethoxazole with 26/39 (66.7%).

A.baumannii and *P. aeruginosa* have the highest resistance to Ceftazidime, with 8/18 (44.4%) and 2/6 (33.3%), respectively.

- 76/97 strains of *Staphylococcus aureus* are resistant to Methicillin, accounting for 78.3%.
- The overall resistance rate of bacterial strains to the Carbapenem group is 52.4%.

3.3. Factors Associated with Mortality

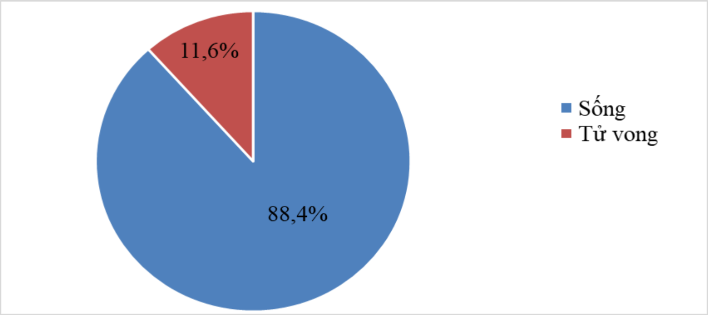

Figure 3.8. Treatment Outcomes of Patients with Sepsis

Comments: The number of deaths in the study was 38 cases, accounting for 11.6%.

Table 3.16. Relationship Between Circulatory Indicators and Mortality Risk

Factor	**Survived** n (%)	**Died** n (%)	**OR (95% CI)**	**p**
Huyết áp: Normal: Low:	15 (44.1%) 19 (55.9%)	10 (32.3%) 21 (67.7%)	1.658 (0.60-4.56)	0.326[a]
Cold Extremities: No: Yes:	8 (23.5%) 26 (76.5%)	2 (6.5%) 29 (93.5%)	4.46 (0.87-22.94)	0.073 [a]
Refill: <3 seconds: ≥3 seconds:	1 (2.9%) 33 (97.1%)	0 31 (100.0%)	-	-
Mental Status:: A+V: P+U:	2 (5.9%) 32 (94.1%)	0 31.0%)	-	-
Urine Output: Normal: Reduced:	17 (50.0%) 17 (50.0%)	13 (41.9%) 18 (58.1%)	1.39 (0.52-3.69)	0.515 [a]
Fluid Resuscitation: < 40ml/kg: ≥40 ml/kg:	12 (35.3%) 22 (64.7%)	10 (32.3%) 21 (67.7%)	1.15 (0.41-3.21)	0.796 [a]
Vasoactive Drugs: ≤2 drugs: >2 drugs:	23 (67.6%) 11 (32.4%)	6 (19.4%) 25 (80.6%)	8.71 (2.77-27.37)	**<0.001**

[a]*Chi-square test;* [b]*Fisher's exact test*

Comments: The use of vasoactive drugs is significantly associated with mortality. Patients who required more than 2 vasoactive drugs had a mortality risk 8.71 times higher compared to those who used 2 or fewer drugs (p < 0.001; OR = 8.71; 95% CI: 2.77–27.37).

Table 3.17. Relationship Between Vasoactive Drugs and Mortality Risk

Factor	**Survived** n (%)	**Died** n (%)	**OR (95% CI)**	**p**

Dopamin: No: Yes:	18 (27.7%) 16 (24.6%)	9 (13.8%) 22 (33.8%)	2.75 (0.99-7.68)	0.051[a]
Adrenalin: No: Yes:	10 (15.4%) 24 (36.9%)	0 31 (47.7%)	-	**0.001[b]**
Noradrenalin: No: Yes:	19 (29.2%) 15 (23.1%)	8 (12.3%) 23 (35.4%)	3.64 (1.27-10.42)	**0.014[a]**
Dobutamin: No: Yes:	30 (46.2%) 4 (6.2%)	20 (30.8%) 11 (16.9%)	4.13 (1.15-14.79)	**0.023[a]**
Mirli: No: Yes:	25 (38.5%) 9 (13.8%)	21 (32.3%) 10 (15.4%)	1.32 (0.45-3.86)	0.608[a]

Comments:

- Among cases with circulatory failure, the percentage of patients using Dopamine, Adrenaline, Noradrenaline, Dobutamine, and Milrinone was 58.4%, 84.6%, 58.5%, 23.1%, and 29.2%, respectively.
- Patients who required Noradrenaline and Dobutamine had a mortality risk 3.64 times and 4.13 times higher, respectively, compared to those who did not use these drugs (p = 0.014 and p = 0.023).

Table 3.20. Multivariate Step 2 Analysis of Mortality Risk Factors

Factor	p	OR	95% CI
Circulatory Failure	<0.001	14.02	5.22-37.65
Coagulation Disorder	Not significant		
White Blood Cell Count	Not significant		
Lactate > 2,65 mmol/l:	0.001	5.09	2.03-12.75

Comments:

After the multivariate step 2 analysis, the statistically significant factors were:

- Circulatory failure: aOR = 14.02 (95% CI: 5.22–37.65).
- Blood lactate > 2.65 mmol/L: aOR = 5.09 (95% CI: 2.03–12.75).

Table 3.21. Relationship Between Organ Failure and Mortality Risk

	Died		**Survived**		**OR (95%CI)**	**p-value**
	n	**%**	**n**	**%**		
Organ Failure						
Yes	37	11.3	139	42.5	1	
No	1	0.3	150	45.9	39.9 (5.4-294.9)	**<0.001*[b]***
Number of Organ Failures						
≤ 2 Organs	4	2.3	105	59.7	75.0 (20.1-280.3)	**0.001[c]**
3-4 Organs	13	7.4	27	15.3	5.9 (2.0-17.6)	**0.001[b]**
≥ 5 Organs	20	11.4	7	4.0	1	

[b] *Chi-square test*

Comments:

- Multiorgan failure is associated with patient mortality ($p < 0.0001$).
- Patients with ≥5 organ failures had a mortality risk 5.9 times higher than those with 3-4 organ failures (95% CI: 2.0–17.6) and 75 times higher than those with ≤2 organ failures (95% CI: 20.1–280.3).

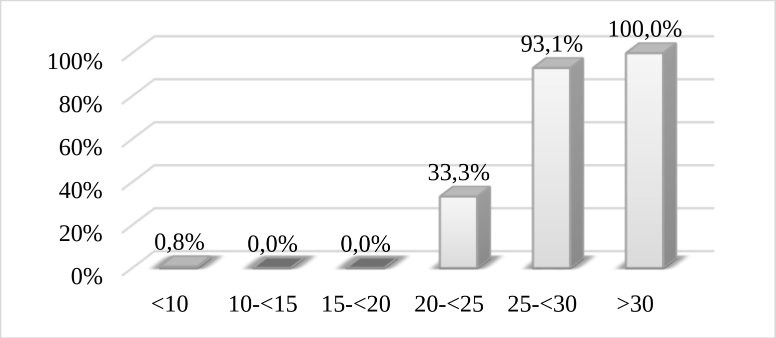

Figure 3.11. Distribution of Mortality Rate by PRISM Score (N=233)

Comments:

- The mortality rate increases with higher PRISM scores.
- For patients with a score below 20, there were almost no deaths.
- For scores between 20-25, the mortality rate was 33.3%; for scores between 25-30, it was 93.1%; and for scores above 30, the mortality rate was 100%.

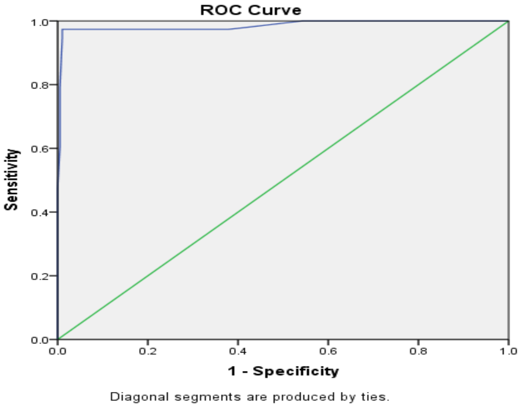

Figure 3.12. ROC Curve of PRISM Score and Treatment Outcome (N=233)

Comments:

- The area under the ROC curve was 0.99 (95% CI: 0.96–1.00) with $p < 0.001$.
- The cutoff point between survival and mortality was 22.5, with a sensitivity of 0.97 and a specificity of 0.99.

Table 3.22. Prognostic Value of PRISM Score for Mortality Risk

PRISM Score	**Died**		**Survived**		**p-value**
	n	**%**	**n**	**%**	
>22,5 Points	37	15.9	2	0.9	**<0.001** [b]
≤22,5 Points	1	0.4	193	82.8	
Total	**38**	**16.3**	**195**	**83.7**	

[b] *Chi-square test*

Comments:

- A PRISM score above 22.5 is closely associated with mortality ($p < 0.001$).

- Of the 38 deaths, 37 cases (97.4%) had a PRISM score above 22.5.

Chapter 4: DISCUSSION

4.1. Epidemiological Characteristics of Children with Sepsis

4.1.1. Age and Gender Characteristics

In our study, the highest incidence of sepsis was in the group under 1 year old, with 160 cases accounting for 48.9%; the lowest incidence was in the group over 5 years old, accounting for 15%. According to Hartman's study, in 2005 alone, there were 75,255 children hospitalized with sepsis, of which nearly 65% were infants under 1 year old. In Vietnam, studies by Trần Minh Điển, Phùng Nguyễn Thế Nguyên, and Bùi Quốc Thắng all concluded that the highest frequency of sepsis in children was in patients under 1 year old.

Currently, many studies have examined the differences in sepsis incidence between genders, and most results show that boys have a higher incidence than girls. Our study yielded similar results to global studies, showing that boys had a higher sepsis incidence, with 180 boys (55%) compared to 147 girls (45%). The male-to-female ratio was 1.2:1. This ratio is consistent with other studies on pediatric sepsis in Vietnam.

4.1.2. Nutritional Status

In our study, 25.1% of children had malnutrition, concentrated mostly in the group under 1 year old. This rate is comparable to the study by Changxue Xiao conducted in Southwest China, which reported a malnutrition rate of 24.12%, where severe sepsis and septic shock accounted for 72.5% of the total malnourished cases. Compared to studies by Desy Rusmawatiningtyas and Dolly Villegas, the malnutrition rates in these studies were 42% and 32.4%, respectively. Thus, the malnutrition rate in our study and Changxue Xiao's study is quite similar but lower than that reported by Desy Rusmawatiningtyas and Dolly Villegas.

4.1.3. Underlying Conditions

Our study recorded that 43.4% of children with sepsis had a history of underlying conditions, with the most common being digestive, cardiovascular, and cancer-related diseases. Other conditions such as neurological, hematological, and immunodeficiency diseases accounted for less than 10%. Our findings are consistent with global research. In the United States, Wasson (2003) reported that 45% of pediatric sepsis patients had comorbidities, with respiratory diseases (19.0%), cardiovascular diseases (17.1%), and chronic lung diseases (16.5%) being the most common in breastfed infants. Weiss SL et al. (2015) indicated that children with severe sepsis and comorbidities, particularly cancer and cardiovascular diseases, had a mortality rate as high as 45%.

4.1.4. Infection Sites

The infection site was determined by the affected organ, which was the primary site leading to sepsis. In our study, most sepsis cases had an identifiable entry point, accounting for 87.5%. The most common infection sites were the respiratory tract (25.7%), skin and soft tissues (23.5%), and the digestive tract (19%). Less common sites included the urinary tract, nervous system, cardiovascular system, and ENT (ear, nose, throat), each accounting for less than 10%. Comparing with other studies, independent research by Watson and Weiss et al. reported that the most common infection site was the respiratory tract (37.2% and 40.2%, respectively), followed by bloodstream infections (25% and 19%, respectively). Thus, our study results are consistent with these findings.

4.1.5. Classification of Sepsis

Nowadays, hospital-acquired sepsis is a major issue affecting treatment outcomes and costs due to its high morbidity and mortality rates. In our study, 113 out of 327 cases (34.6%) were hospital-acquired sepsis, while the remaining 75.4% were community-acquired sepsis. In a study by Guo Yun Su comparing hospital-acquired and community-acquired sepsis in children at Beijing Hospital, the rate of hospital-acquired sepsis was 30.5%, while community-acquired sepsis was 69.5%. Therefore, the hospital-acquired sepsis rate in our study is similar to Guo Yun Su's findings. Similarly, a study in Switzerland (2018) reported a hospital-acquired sepsis rate of 21.5% and a community-acquired sepsis rate of 78.5%. Although hospital-acquired sepsis has a lower incidence than community-acquired sepsis, its consequences are severe, including increased mortality rates, higher antibiotic use, higher rates of antibiotic-resistant bacteria, and increased treatment costs.

4.2. Clinical Characteristics

Regarding respiratory dysfunction in sepsis, our study recorded that 35.8% of children had respiratory failure upon admission, of which 27.4% required intubation, and the remaining 73.6% received oxygen support. Global studies have also reported a high incidence of respiratory failure in children with sepsis. Gurpreet Kaur et al. (2014) found that 42% of pediatric sepsis patients experienced respiratory failure, while Changxue Xiao’s study reported a rate of 76.7%. In Vietnam, Trần Minh Điển's study recorded respiratory failure in 96% of patients, and Bùi Quốc Thắng's study reported a rate of 90.74%.

Regarding circulatory symptoms, our results showed that most patients had relatively stable cardiovascular function upon admission, with cardiovascular abnormalities accounting for a small proportion. There were 61 cases of circulatory failure, making up 18.7%. Gurpreet Kaur's study reported a circulatory failure rate of 30%, while Jaramillo-Bustamante's study reported 48%. Global research indicates that cardiovascular dysfunction often occurs in decompensated septic shock. The most common cardiac dysfunctions in sepsis patients are circulatory failure and cardiomyopathy.

Regarding neurological dysfunction, our study recorded that 33.9% of patients had neurological symptoms such as irritability, lethargy, and coma, with coma cases making up 1.8%. In Teresa Bleakly Kortz's study, 82.8% of patients were fully conscious upon admission, while 4.5% were in a coma. Recently, Jeevan G's study on the clinical characteristics of pediatric sepsis reported that approximately 30.23% of children had varying levels of altered mental status upon admission.

4.3. Bacterial Characteristics

4.3.1. Morphological Characteristics of Bacteria

Among the 327 bacterial strains isolated, 52.0% were Gram-positive, higher than the 48.0% of Gram-negative bacteria. The most common bacteria were Staphylococcus aureus (39.4%), followed by *E. coli* (16.2%), *Klebsiella pneumoniae* (9.8%), *Acinetobacter baumannii* (8.3%), *Streptococcus pneumoniae* (6.1%), and *Pseudomonas aeruginosa* (2.8%). Watson's study reported that 67% of sepsis cases involved cocci, while 33% involved Gram-negative bacteria. Thus, our study results are consistent with those of other international studies.

4.3.2. Genotypic Relationships and Bacterial Transmission

We conducted a genotypic analysis of 183 bacterial strains across five common pathogens: *Staphylococcus aureus, E. coli, K. pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii*. The results are as follows:

The genotypic analysis of *E. coli* strains found that two strains in group E3 were isolated from two different departments, and two strains in group E2 were isolated from the Infectious Disease Center, all with a genotypic similarity of >95%. Similarly, two strains in group E4 showed high similarity but were from two different departments. This suggests the potential for bacterial transmission between departments over time and cross-infection among patients within the same department.

The genotypic analysis of *K. pneumoniae* strains showed low similarity, indicating different sources. In contrast, *A. baumannii* strains showed high genotypic similarity, suggesting transmission between hospital departments, particularly in the Cardiology Center, where two strains isolated in June and July 2019 had nearly 100% similarity. The genotypic analysis of *P. aeruginosa* and *S. aureus* supported the hypothesis of bacterial transmission over different time points within the same department and between different departments. This is the first study in Vietnam to provide molecular-level evidence of genotypic relationships for common bacterial causes of sepsis at the National Children's Hospital.

4.3.3. Antibiotic Resistance Characteristics

In this study, we analyzed the antibiotic resistance of five bacterial types to eight antibiotics from seven commonly used antibiotic groups. The antibiotic with the highest resistance rate across the five bacterial types was Ceftazidime (a third-generation Cephalosporin) at 66.7%, followed by the Carbapenem group at 52.4%. The antibiotic with the highest resistance rate varied by bacterial type. For *E. coli*, the highest resistance was to Trimethoprim/Sulfamethoxazole, with 26/39 cases (66.7%). For *K. pneumoniae*, the highest resistance was to Cefoxitin, with 15/23 cases (65.2%). For *A. baumannii*, *P. aeruginosa*, and *S. aureus*, the highest resistance was to Ceftazidime: 8/18 cases (44.4%), 2/6 cases (33.3%), and 79/97 cases (81.4%), respectively. Notably, according to CLSI 2019 recommendations, screening with Cefoxitin and Oxacillin revealed that 76/97 (78.3%) *Staphylococcus aureus* strains were Methicillin-resistant (MRSA).

4.4. Risk Factors Associated with Mortality

The mortality rate in our study was 11.6%, which is relatively low compared to other studies.

4.4.1. Arterial Blood Lactate

In our study, elevated arterial blood lactate was associated with mortality. The statistically significant cutoff value between the survival and mortality groups was 2.65 mmol/L, with an area under the ROC curve of 0.806 (95% CI: 0.729–0.884). In Vietnam, Bùi Quốc Thắng's study on pediatric sepsis found that lactate levels differed between the survival and mortality groups, with the mortality group having a lactate level of 8.15 ± 4.11 mmol/L compared to 4.97 ± 3.08 mmol/L in the survival group. Similarly, Trần Minh Điển's report on septic shock in children showed that lactate levels above 6.5 mmol/L were associated with mortality. Katherine Bakes' study on pediatric sepsis found that patients with an initial lactate level above 3.9 mmol/L had a higher mortality rate, with a sensitivity of 20% and specificity of 92.3%. Lactate levels can predict mortality rates in sepsis patients and assess treatment effectiveness.

4.4.2. Circulatory Failure and Vasoactive Drug Use

Analysis of mortality risk factors in sepsis for circulatory failure revealed that the intensity of vasoactive drug use was associated with mortality. Specifically, patients who required 3 or more vasoactive drugs had a mortality risk 8.71 times higher (95% CI: 2.77–27.37). In Khyzer B's study on the role of vasoactive drugs in pediatric sepsis, the intensity of vasoactive drug use was also associated with mortality. Mortality increased by 10% with the first vasoactive drug and doubled with the addition of a second drug. Trần Minh Điển's study on mortality predictors in pediatric septic shock found that using 3 or more vasoactive drugs increased the risk of mortality by 6.1 times.

4.4.3. PRISM Score Value

We used the PRISM score to predict mortality. The average PRISM score in our study was 12.6 ± 7.5. Analysis showed that as the PRISM score increased, the mortality rate also increased. Patients with scores below 20 had almost no mortality, while mortality rates rose progressively for scores of 20 or higher, reaching 100% for scores above 30. The area under the ROC curve identified 22.5 points as the cutoff value for distinguishing between survival and mortality ($p < 0.001$). Patients with PRISM scores above 22.5 had a high mortality risk, while those with scores below 22.5 had a lower risk ($p < 0.001$). Our study recorded actual mortality rates corresponding to these scores. Jeevan G et al. (2017) used the PRISM score to evaluate mortality risk in 47 children with septic shock and found that a score of 30 provided the best cutoff for predicting mortality. This score is higher than ours, likely due to differences in sample selection criteria. In Vietnam, Trần Minh Điển's study reported an average PRISM score of 21.9 ± 6.98, with a statistically significant difference between severe and mild cases ($p < 0.0001$). Higher PRISM scores correlated with severe illness and higher mortality, with a survival-mortality cutoff of 20.5 points.

4.4.4. Relationship Between Multiorgan Failure and Mortality

The proportion of patients with organ failure in our study was 53.8%, with 62% having failure of 2 or fewer organs and 15.4% having failure of 5 or more organs. Analysis showed that patients with organ failure had a mortality risk 39.9 times higher than those without organ failure. The more organs that failed, the higher the mortality rate. Patients with 5 or more organ failures had a mortality risk 5.9 times higher than those with 3-4 organ failures and 75 times higher than those with 2 or fewer organ failures. According to epidemiological data on pediatric sepsis in the United States, the trend of multiorgan failure in sepsis patients is increasing, with more organs being identified as failing and higher mortality risks. Mortality risk was 7% with failure of 1 organ compared to 53.1% with failure of 4 organs. Kurade's study supported these findings, showing that although mortality rates in pediatric severe sepsis had declined, mortality remained significantly associated with organ failure. In Kurade's study, 90.69% of patients had multiorgan dysfunction, with failure of 3 or more organs in 32.55% of cases, leading to a mortality risk 6.8 times higher than in patients with failure of fewer than 3 organs.

STUDY LIMITATIONS

- Due to resource constraints, the study only analyzed the genotypic relationships of 183 cases, which did not allow for a complete assessment of the transmission of other bacterial strains.
- The research samples were collected solely from the National Children's Hospital, a tertiary care hospital, meaning most cases were severe. Therefore, the findings do not represent the characteristics of pediatric sepsis nationwide.

CONCLUSION

1. General Characteristics of the Study Group

- The sepsis incidence was highest in children under 1 year old (48.9%), with 25% suffering from malnutrition, 43.4% having underlying conditions, and 70% having incomplete or no vaccination.
- 87.5% of patients had an identifiable infection site, with respiratory infections being the most common (25.7%). Hospital-acquired sepsis accounted for 34.6%, and septic shock occurred in 18.7% of cases.
- 35.8% of patients experienced respiratory failure. 33.9% had neurological dysfunction, with 1.8% in a coma.
- White blood cell counts were elevated, averaging 17,800 ± 10,600/mm^3. 99.4% of patients had CRP levels above 10 mg/L, with an average CRP of 153.8 ± 85.8 mg/L.

2. Characteristics of Bacterial Strains and Genotypic Relationships

- Gram-positive bacteria made up 52.0%, and Gram-negative bacteria made up 48.0%. Among Gram-positive bacteria, Staphylococcus aureus was the most common (39.4%), while among Gram-negative bacteria, E. coli was most frequent (16.2%).
- Bacterial strains exhibited high antibiotic resistance. The highest resistance was to third-generation Cephalosporins (66.7%), followed by Carbapenems (52.4%). 78.3% of Staphylococcus aureus strains were Methicillin-resistant (MRSA).
- The study provided evidence of genotypic relationships between strains of E. coli, K.

pneumoniae, Pseudomonas aeruginosa, and Staphylococcus aureus, suggesting transmission within and between departments.

3. Mortality-Related Factors

- The mortality rate was 11.6%. Patients with hospital-acquired sepsis had a mortality risk 2.65 times higher than those with community-acquired sepsis ($p < 0.05$).
- Patients requiring more than 2 vasoactive drugs had a mortality risk 8.71 times higher than those using 2 or fewer vasoactive drugs.
- The PRISM score was a valuable predictor of mortality. A PRISM score above 22.5 was associated with higher mortality risk ($p < 0.001$).
- The number of organ failures was directly proportional to mortality. Patients with 5 or more organ failures had a mortality risk 5.9 times higher than those with 3-4 organ failures and 75 times higher than those with 2 or fewer organ failures ($p < 0.05$).

RECOMMENDATIONS

Based on the study results, we propose the following recommendations:

1. Early Screening and Control: Implement early screening and control measures for suspected sepsis cases to enable timely diagnosis and treatment.
2. Individualized Treatment: Personalize treatment based on factors such as underlying conditions, nutritional status, infection site, and classification of sepsis (hospital-acquired vs. community-acquired).
3. Infection Control Compliance: Ensure strict adherence to infection control protocols to minimize bacterial transmission within and between hospital departments.
4. Mortality Risk Assessment: Use mortality risk factors to predict outcomes, and identify early prognostic factors to monitor and treat patients with septic shock intensively.