ORIGINAL ARTICLE
Bali Medical Journal (*Bali MedJ)* 2022, Volume 11, Number 2: 962-969
P-ISSN.2089-1180, E-ISSN: 2302-2914

Microbial blood culture patterns and antibiotic susceptibility in pediatric febrile neutropenia at Sanglah General Hospital Bali

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Received: 2022-06-02
Accepted: 2022-07-14
Published: 2022-08-22

ABSTRACT

Background: Febrile neutropenia is defined as a fever with a temperature more than or equal to 38.3°C in two measurements within 24 hours and accompanied by severe neutropenia (≤500/µL). Gram-positive bacteria have been the most common cause of febrile neutropenia in children for the previous two decades. However, the contradiction in some studies reported that gram-negative bacteria were the main pathogens causing infection. Because there are differences and shifts in the bacterial spectrum, information on the bacterial pattern and antibiotic susceptibility is critical to reaching the optimal management of febrile neutropenia patients.
Methods: This observational, descriptive study was conducted in Sanglah Hospital, Bali, Indonesia, involving pediatric patients (<18 years old) with febrile neutropenia. Data on antibiotic susceptibility and microbial patterns were collected retrospectively from the blood culture registry taken from febrile neutropenia patients from October 2017 to August 2020. Collected data were analyzed using the SPSS program for Windows, version 21.0. Univariate analysis was conducted, and data with a categorical scale were reported in frequency distribution and percentage, then displayed in a table and graph.
Result: A total of 180 episodes of febrile neutropenia were collected from 89 patients. Among 180 blood cultures, there were found 44 (24.44%) blood cultures with positive results. A higher proportion of gram-negative organisms (33; 75%) is found compared to gram-positive organisms (11; 25%). The susceptibility rates were 100% for Azithromycin, Amoxicillin Clavulanate, Cefoperazone Sulbactam, Meropenem, Linezolid, and Doxycycline, while Cefepime, the previous empirical antibiotic, was susceptible at 79.31% isolates.
Conclusion: Gram-negative bacteria were the most frequent cause of infection among febrile neutropenic patients. Although the research evidence is still weak due to the small sample size, Cefoperazone Sulbactam could be a better option to replace Cefepime as an empirical antibiotic due to its significantly higher susceptibility.

Keywords: *antibiotic susceptibility, blood culture, children, febrile neutropenia*.
Cite This Article: Clearesta, K.E., Gustawan, I.W., Ariawati, K., Fatmawati, N.N.D., Utama, M.G.D.L., Widnyana, A.A.N.K.P., Lastariana, K.A.Y. 2022. Microbial blood culture patterns and antibiotic susceptibility in pediatric febrile neutropenia at Sanglah General Hospital Bali. *Bali Medical Journal* 11(2): 962-969. DOI: 10.15562/bmj.v11i2.3436

INTRODUCTION

Neutropenia is the most frequent complication in immunocompromised patients corresponding with high levels of morbidity and mortality.[1] Severe neutropenia is defined as a condition in which the absolute neutrophil count (ANC) is ≤500/µL.[2] The incidence of neutropenia varies greatly depending on the region of the country.[3] In European countries, the incidence is around 6.2 cases per 1 million population each year, while in the United States is 56.4 cases per 1 million population each year, with the rate of hospitalization reaching 60,000 cases each year.[4-6]

The most common etiology of neutropenia are infection, autoimmune disorders, congenital, malignancy, chemotherapy procedures, and adverse drug reactions.[3] Neutrophils play a critical role in the immune system. In HIV patients, neutropenia is an independent risk factor for bacteremia and increased mortality rate.[7] Studies report that there is a significant association between the severity and the duration of neutropenia to the risk of infection.[8,9] An early sign of infection in neutropenia patients which must be considered is febrile neutropenia.[10]

Febrile neutropenia (FN) is defined as a fever with a temperature more than or equal to 38.3°C in two measurements within 24 hours and accompanied by severe neutropenia. Febrile neutropenia remains a medical emergencies condition that has a high mortality rate; thus, prompt administration of antibiotics is crucial in these patients.[2]

Broad-spectrum antibiotics were introduced 30 years ago with a significant decrease in mortality and morbidity in febrile neutropenic patients due to bacterial infections.[2] The most severe condition in bacterial infections is bacteremia with or without primary infection sites. The Infectious Diseases Group of the European

Organization for Research and Treatment of Cancer (EORTC-IDG) reported a reduction in the rate of bacteremia from 32% in 1973 to 22% in 1994. However, there was a shift in the bacterial spectrum causing the infection. From 1973 to 1978, the distribution of gram-positive and negative bacteria was 71% and 29%, respectively, whereas, in 1992-1994, the proportion changed to 33% and 67%.[11]

According to a study conducted in Israel, gram-positive bacteria have been the most common cause of febrile neutropenia in children for the previous two decades.[2] The same results were also reported in other studies conducted in Malaysia and Pakistan.[10,12] Another study in Turkey also found that gram-positive bacteria caused 56.4% of infections in children with febrile neutropenia, whereas gram-negative bacteria caused 24.7 percent of cases.[11] However, there is a contradiction in a study conducted in the Asia Pacific region which reported that gram-negative bacteria were the main pathogens causing infection.[13]

Because there are differences and shifts in the bacterial spectrum causing infection in children with febrile neutropenia, information on the bacterial pattern and antibiotic susceptibility are critical to reaching the optimal management of febrile neutropenia patients. A study in Brazil reported that the most common isolated bacteria in febrile neutropenic patients were Escherichia coli, while the most commonly and effectively used antibiotics were Cefepime, Vancomycin, and Fluconazole.[14] Until now, the empiric antimicrobial therapy used for febrile neutropenic patients at our center, Sanglah General Hospital, Bali, is Cefepime. The purpose of a study of bacterial patterns and antibiotic susceptibility in pediatric patients with febrile neutropenia at our center is urgently needed to determine whether Cefepime is still viable as an empirical antibiotic for pediatric patients with febrile neutropenia.

METHODS

This observational, descriptive study was conducted in Sanglah Hospital, Bali, Indonesia, involving pediatric patients (< 18 years old) with febrile neutropenia. Data on antibiotic susceptibility and microbial patterns were collected retrospectively from the blood culture registry taken from FN patients from October 2017 to August 2020. Febrile neutropenia is defined as a fever with a temperature more than or equal to 38.3°C in two measurements within 24 hours, accompanied by severe neutropenia, in which the absolute neutrophil count (ANC) ≤500/μL. The inclusion criteria were children under 18 years old, with FN, and who underwent blood cultures. We excluded positive blood culture samples with the same result, which were taken after the initial blood culture occurred in the same episode of FN. The exclusion criteria of this study were the sample of the study, which has been found to be the same sample of bacteria at the same episode of febrile neutropenia. The sample of this study was consecutive sampling.

All patients with severe neutropenia (ANC ≤500/μL), without signs of infection, were given Cefixime orally as prophylaxis. Cefepime 50 mg/kg every 8 hours intravenously was administered to the patient fulfilling the criteria of FN after obtaining two blood culture samples. Blood samples from pediatric patients were drawn from two different sites of peripheral venipuncture and collected in aerobic media (BacT/ALERT®, bioMérieux, France), with a blood volume of 1-2 ml in each culture bottle. Bacterial identification and antimicrobial susceptibility testing of the isolates were performed using an automatic system (VITEK® 2 Compact, bioMérieux, France).

Positive blood culture is defined as when there is positive growth of microorganisms in the 2-sides-blood samples, as febrile neutropenia was considered a significant clinical manifestation in all patients. Length of stay is measured from the first day of admission until the last day of hospitalization. The mortality rate is defined as the number of patients who died among the sample population during hospitalization. Multidrug-resistant (MDR) isolates were defined as isolates that were resistant to at least one antibiotic in three or more drug classes.[15]

Collected data were analyzed using the SPSS program for Windows, version 21.0. Univariate analysis was conducted, and data with a categorical scale were reported in frequency distribution and percentage, then displayed in a table and graph. This study was approved by the Research Ethics Committee of the Faculty of Medicine University of Udayana and Sanglah General Hospital Denpasar. Our study has been certified ethically feasible, with a license number 1534/UN14.2.2.VII.14/LT/2021, which has been published by the Research Ethics Committee Faculty of Medicine, Universitas Udayana/ Sanglah General Hospital.

RESULT

The characteristics of the research subjects

Antibiotic susceptibility data and microbial patterns were collected retrospectively (October 2017 to August 2020) from a blood culture registry taken from FN patients. Table 1 summarizes the characteristics of our research subjects. A total of 180 episodes of febrile neutropenia (FN), collected from 89 patients, were included in this study. Out of those episodes, 110 (61.1%) subjects were male, and the other 70 (38.9%) subjects were female. Our study participants ranged in age from 17 to 226 months and had a median age of 73 months. Acute lymphocytic leukemia (74; 41.11%), acute myeloid leukemia (18; 10%), retinoblastoma (14; 7.78%), and osteosarcoma were the most common underlying illnesses in the patients (13; 7.22%).

Identification of microorganisms with positive blood culture result

Among 180 blood cultures on each episode of FN, we found 44 (24.44%) blood cultures with positive results, three of them were excluded due to the same isolates in the same episode of FN. Therefore, 44 isolates were analyzed. The microbial pattern was categorized into gram-positive and gram-negative microorganisms. We found a higher proportion of gram-negative organisms (33; 75%) compared to gram-positive organisms (11; 25%).

Table 2 explains the detailed microbial pattern among positive blood cultures. *Coagulase-Positive Staphylococcus* (54.54%) was the most common gram-positive bacteria identified, followed by *Coagulase-Negative Staphylococcus* (18.18%), *Enterococcus gallinarum, S*

Streptococcus salivarius, and *Kocuria rhizopila*. *Pseudomonas aeruginosa* (31.81%) was the most common agent among all causative bacteria. The less-frequent gram-negative bacteria were *Escherichia coli, Klebsiella sp., Salmonella sp, Acinetobacter sp, Pseudomonas stutzeri,* and *Cupriavidus pauculus.*

Table 1. Characteristics of research subjects.

Variables	n = 180
Age (months), median (range)	73 (17-226)
Gender	
Male	110 (61.10%)
Female	70 (38.90%)
Underlying disease	
ALL	74 (41.11%)
AML	18 (10%)
Retinoblastoma	14 (7.78%)
Suspected neoplasm	6 (3.33%)
Osteosarcoma	13 (7.22%)
Ewing sarcoma	9 (5%)
Aplastic anemia	9 (5%)
Non-Hodgkin lymphoma	6 (3.33%)
Wilms' tumor	5 (2.78%)
HIV	5 (2.78%)
Hypoplastic anemia	4 (2.22%)
SLE	4 (2.22%)
Thalassemia	3 (1.67%)
Hepatoblastoma	3 (1.67%)
Others	7 (3.89%)

Table 2. Pathogens isolated from blood cultures.

General	Species	n	%
Gram-positive bacteria		11	25
	Coagulase-positive Staphylococcus	6	13.63
	Coagulase-negative Staphylococcus	2	4.54
	Enterococcus gallinarum	1	2.27
	Streptococcus salivarius	1	2.27
	Kocuria rhizopila	1	2.27
Gram-negative bacteria		33	75
	Pseudomonas aeruginosa	14	31.81
	Escherichia coli	6	13.63
	Klebsiella sp.	4	9.09
	Salmonella sp.	4	9.09
	Acinetobacter sp,	2	4.54
	Pseudomonas stutzeri	2	4.54
	Cupriavidus pauculus	1	2.27
Total		**44**	**100**

Antibiotic susceptibility among isolated microorganisms

This study investigated the antibiotic susceptibility pattern among 44 isolated microorganisms. The susceptibility rates were 100% for Azithromycin, Amoxicillin Clavulanate, Cefoperazone Sulbactam, Meropenem, Linezolid, and Doxycycline, while Cefepime, our first-line empirical antibiotic, was susceptible in 79.31% isolates (Figure 1 and Table 3). There were also found multidrug-resistant (MDR) bacteria (21 isolates, 47.73%), including 6 isolates of Extended-Spectrum Beta-Lactamase (ESBL) Gram-negative bacteria, and Methicillin-Resistant *Staphylococcus epidermidis* (MRSE), Methicillin-Resistant *Staphylococcus aureus* (MRSA), MDR-*Pseudomonas aeruginosa*, and Vancomycin-Resistant *Enterococci* (VRE) in 1 isolate each.

Outcomes of the patients with positive cultures

Among 44 positive blood cultures, we investigated the outcome of the patients, including length of stay and the proportion of mortality. Patients with positive blood cultures spent a median of 20 days in hospitalization, ranging from 5 to 67 days. Nine out of 44 patients with positive blood cultures died during hospital care. Table 4 shows the outcomes of the patients with positive cultures.

DISCUSSION

Neutropenic fever or febrile neutropenia is the most frequent and serious complication in the pediatric population with neutropenia which is commonly found in children with hematological malignancy or patients receiving chemotherapy. Another condition associated with neutropenia is an infection, autoimmune disorders, and congenital and adverse drug reactions.[3] Febrile neutropenia occurs when neutropenic children encounter an infectious pathogen. Children with neutropenia are in an immunocompromised state, thus susceptible to infectious microorganisms. In addition, the host barriers, such as the mucosal layer of the gastrointestinal tract, may be impaired, leading the host to be susceptible to the invasion of infectious pathogens.[16]

The most prevalent cause of febrile neutropenia in children is bacteria. However, viral infections are also common. Febrile neutropenia can also be caused by opportunistic illnesses such as fungal infections. Non-infectious reasons

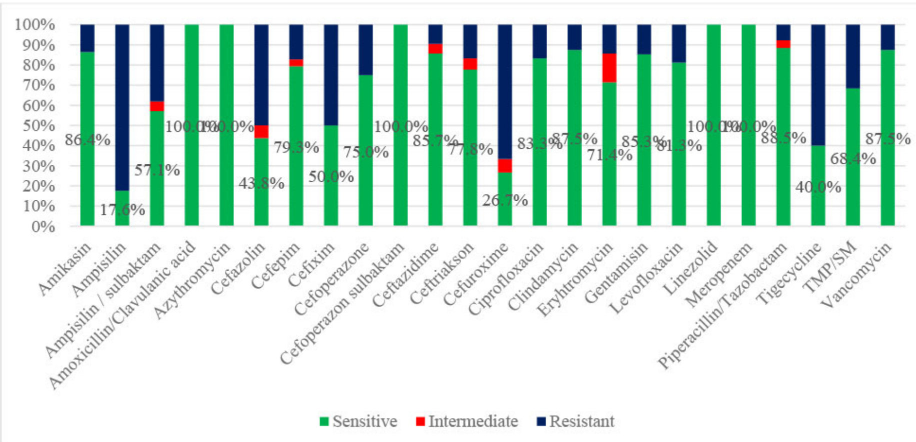

Figure 1. Antibiotic susceptibility pattern in all isolates.

should be considered in a number of cases, particularly in children with febrile neutropenia who are not responding to antimicrobial treatment. Non-infectious etiology includes drug fever caused by chemotherapy and broad-spectrum antibiotics, tumor lysis (particularly early in cancer treatment), haemophagocytic lymphohistiocytosis (HLH), or blood transfusion reaction.[17]

The microbial spectrum in children with febrile neutropenia, which was reported in previous studies in the last decades, varies greatly in each region. Our study was conducted in Indonesia, and Southeast Asia, involving 89 patients with a total of 183 episodes of febrile neutropenia.

We found that the underlying diseases of our samples were predominantly caused by acute lymphocytic leukemia (38.3%), followed by acute myeloid leukemia (9.8%). It is similar to previous studies in which the majority of the samples had hematological malignancies, such as studies by Ahangarzadeh et al. (60.4%), Stergiotis et al. (79%), and Gupta et al. (86%).[18-20]

In a recent study, gram-negative and gram-positive bacteria were found in 92% and 8% of the isolated bacteria from patients' blood cultures, respectively.[21] We also found a higher proportion of gram-negative bacteria (75%) than gram-positive bacteria (25%), and the most common gram-negative bacteria was *Pseudomonas aeruginosa* (31.9%), followed by *E. coli* (12.7%), and *Klebsiella sp.* (10.6%). Among gram-positive organisms, *Staphylococcus sp.* (17.0%) was the most frequently isolated bacteria. Our finding is similar to a study conducted by Reddy et al. in India, which reported that gram-negative bloodstream infections (92%) were more prevalent than gram-positive infections and the most frequent isolate was Klebsiella sp (48%).[20] Earlier study in India by Bothra et al. also reported that 78.2% of the isolated bacteria were gram-negative, with *Escherichia coli* (29%) being the most dominant among them.[22]

In contrast, studies conducted in the American and European regions mostly reported that the most common isolated bacteria in children with febrile neutropenia were gram-positive. Gupta et al. found that 61% of the isolated microorganisms were gram-positive, with coagulase-negative *Staphylococci* having the highest prevalence and *Pseudomonas spp*. being the most prevalent gram-negative bacterium.[20] The majority of pathogens were gram-positive (54%) in Alali et al. study, with the viridans group Streptococci having the highest prevalence, followed by coagulase-negative *Staphylococci* and methicillin-susceptible *Staphylococcus aureus*.[23] Another study in the Netherlands, conducted by Miedema et al., had a similar result in which gram-positive bacteria were found more prevalent than gram-negative bacteria, 73% and 26%, respectively. Coagulase-negative *Staphylococci* (39%) and *Streptococcus sp* (23%) were the most frequent gram-positive bacteria.[24] In the study of Stergiotis et al., which was conducted in Switzerland, 64% of cases were gram-positive organisms with mostly coagulase-negative staphylococci (32%), and 36% were gram-negative organisms with *E. coli* (17%), *Klebsiella spp* (5%), and *Pseudomonas aeruginosa* (5%) being the most common pathogen identified.[19]

Differences in bacterial spectrum in several regions can be associated with epidemiological differences in societies and medical centers. Even though studies in the American and European regions reported that the prevalence of gram-positive bacteria was higher than gram-negative bacteria, our results showed the opposite, similar to previous studies conducted in Asian and developing countries, in which gram-negative microorganisms were more prevalent than gram-positive microorganisms. The possible reasons for this are the empirical antibiotics commonly used in other hospitals in our provinces are more susceptible to gram positives bacteria, such as penicillin and the first generation of cephalosporin. There could also be a long duration of the length of stay in another hospital before being referred to our center because gram-negative bacteria infections are commonly associated with health care facilities.[25]

In our center, Cefepime is the first-line empirical antibiotic, and our results showed that the susceptibility rate was only 77.42%, while other options of broad-spectrum antibiotics, such as azithromycin, amoxicillin-clavulanate, cefoperazone-sulbactam, linezolid, and meropenem was still 100%. Those broad-spectrum antibiotics have the ability to cover gram-negative infection and thus could be considered as an alternative option for empiric antibiotic therapy in our center. Our study had a comparable result with a study by Aslan et al., which reported that the susceptibility rate for Cefepime was 84.4%, while the gram-negative organism's susceptibility to cefoperazone/sulbactam and meropenem was 93.3% and 86.6%, respectively.[11] Another study by Ahangarzadeh et al. reported the gram-negative organism's susceptibility to gentamicin, ampicillin, ceftriaxone, ceftazidime, imipenem, amikacin, and ciprofloxacin, was 66.7%, 61.5%, 37.9%, 16%, 85.2%, 61.5%, and 93.3%, respectively.[18]

Gram-negative bacteremia, especially Pseudomonas aeruginosa, which was the most prevalent microorganism in our study, has the potential to become a devastating condition; thus, antibiotic monotherapy with an antipseudomonal beta-lactam or carbapenem is recommended for initial empirical antibiotic therapy in FN by European and American guidelines.[26,27] These recommendations are consistent with our results in which the susceptibility rate for meropenem is still 100%. However, a study by Castagnola et al. observed that the distribution of resistant strains was ≥10% for antibiotic monotherapy, which was recommended as an initial empirical antibiotic therapy, such as meropenem, ceftazidime, and piperacillin-tazobactam. In addition, a combination of antipseudomonal beta-lactam and aminoglycoside was recommended in this study.[28] Related to this recommendation, our results also showed that aminoglycoside antibiotics, such as amikacin and gentamicin, still had a reasonable susceptibility rate exceeding 80%.

Table 3. Antibiotic susceptibility pattern according to gram classification.

	All isolates n/total (%)	Gram-positive bacteria n/total (%)	Gram-negative bacteria n/total (%)
Amikacin	19/22 (86,36%)		19/22 (86,36%)
Ampicilin	3/17 (17,65%)	2/2 (100%)	1/15 (6,67%)
Ampicilin/sulbactam	12/21 (57,14%)	6/6 (100%)	6/15 (40%)
Amoxicillin	1/3 (33,33%)	1/3 (33,33%)	
Amoxicillin/Clavulanic acid	4/4 (100%)	4/4 (100%)	
Azithromycin	6/6 (100%)	6/6 (100%)	
Cefadroxil	0/2	0/2	
Cefalotine	3/5 (60%)	3/5 (60%)	
Cefazoline	7/16 (43,75%)	5/6 (83,33%)	2/10 (20%)
Cefepime	23/29 79,31%)	3/5 (60%)	20/24 (83,33%)
Cefixime	3/6 (50%)		3/6 (50%)
Cefoperazone	9/12 (75%)	1/1 (100%)	8/11 (72,73%)
Cefoperazone sulbactam	18/18 (100%)		18/18 (100%)
Ceftazidime	18/21 (85,71%)		18/21 (85,71%)
Cefoxitin	0/1	0/1	
Ceftriaxone	14/18 (77,78%)	5/7 (71,43%)	9/11 (81,82%)
Cefuroxime	4/15 (26,67%)	4/6 (66,67%)	0/9
Ciprofloxacin	15/18 (83,33%)	2/4 (50%)	13/14 (92,86%)
Clindamycin	7/8 (87,5%)	7/8 (87,5%)	
Doxycycline	2/2 (100%)	2/2 (100%)	
Erythromycin	5/7 (71,43%)	5/7 (71,43%)	
Flucloxacillin	2/3 (66,67%)	2/3 (66,67%)	
Gentamicin	29/34 (85,29%)	7/8 (87,5%)	22/26 (84,61%)
Levofloxacin	13/16 (81,25%)	3/5 (60%)	10/11 (90,91%)
Linezolid	7/7 (100%)	7/7 (100%)	
Meropenem	21/21 (100%)		21/21 (100%)
Moxifloxacin	2/3 (66,67%)	2/3 (66,67%)	
Nafcillin	1/2 (50%)	1/2 (50%)	
Nitrofurantoin	1/1 (100%)	1 (100%)	
Oxacillin	2/4 (50%)	2 (50%)	
Piperacillin/Tazobactam	23/26 (88,46%)	3 (100%)	20/23 (86,96%)
Tetracycline	3/6 (50%)	3 (50%)	
Tigecycline	2/5 (40%)	1 (100%)	1/4 (25%)
TMP/SM	13/19 (68,42%)	7 (87,5%)	6/11 (54,54%)
Vancomycin	7/8 (87,5%)	7 (87,5%)	

Table 4. Outcomes of the patients with positive cultures.

Outcomes	N = 44
Length of stay (days), median (range)	20 (5-67)
Mortality, n (%)	9 (19.1%)

On the other side, issues in antimicrobial resistance are still rapidly emerging in managing pediatric infections. In response, the World Health Organisation (WHO) developed a classification system for antibiotics in March 2017.[29] Antibiotics were classified in the Access, Watch, Reserve (AWaRe) system to help with the advancement of mechanisms for antibiotic supervision at the local, national, and global levels, in conjunction to minimize antimicrobial resistance. Antibiotics are divided into classes to stress the significance of using them correctly. This allocation is designed to help governments better support antibiotic monitoring and stewardship programs.[30]

Antibiotics are classified into different groups to emphasize the importance of their appropriate use. The Access group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. The Watch group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/ or antibiotics that are at relatively high risk of selection of bacterial resistance. Then, the Reserve group includes antibiotics and antibiotic classes that should be reserved for the treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as "last resort" options.[29,30]

In this study, antibiotics in the Access group identified with a 100% susceptibility rate were amoxicillin-clavulanate, while antibiotics in the Watch group consist of Cefepime as the first-line empirical antibiotics with a susceptibility rate of 77.42% and several other drugs with a 100% susceptibility rate such as azithromycin, cefoperazone-sulbactam, and meropenem. Another antibiotic with a 100% susceptibility rate that is classified in the Reserve group was linezolid.30 The recent publication also reported that the most often prescribed antibiotics for the pediatric population in Southeast Asia belong to the Watch group in the AWaRe criteria.[29]

Multidrug-resistant (MDR) bacteria are well-recognized to be one of the most important current public health problems. The Infectious Diseases Society of America (IDSA) recognizes antimicrobial resistance as "one of the greatest threats to human health worldwide". Several issues underlie the critical danger that is posed by the rise of MDR bacteria. First and most importantly, outcomes in patients infected with MDR bacteria tend to be worse as compared to patients infected with more susceptible organisms. In this way, rising rates of antibacterial resistance have an impact on all aspects of modern medicine and threaten to decrease the yield of many accomplishments such as cancer care, transplantation, and surgical procedures. Second, tremendous added costs are associated with these infections.[31]

Multidrug-resistant organisms (MDROs), including Methicillin-Resistant *Staphylococcus aureus* (MRSA), Vancomycin-Resistant *Enterococci* (VRE), and certain gram-negative *Bacilli* (GNB), have important infection control implications. For epidemiologic purposes, MDROs are defined as microorganisms, predominantly bacteria, that are resistant to one or more classes of antimicrobial agents. Although the names of certain MDROs describe resistance to only one agent (e.g., MRSA, VRE), these pathogens are frequently resistant to most available antimicrobial agents. In addition to MRSA and VRE, certain GNB, including those producing extended-spectrum beta-lactamases (ESBLs) and others that are resistant to multiple classes of antimicrobial agents, are of particular concern.[31]

This study found a high incidence of multidrug-resistant (MDR) bacteria (21 isolates, 47.73%), including 6 isolates of Extended-Spectrum Beta-Lactamase (ESBL) Gram-negative bacteria and Methicillin-Resistant *Staphylococcus epidermidis* (MRSE), Methicillin-Resistant *Staphylococcus aureus* (MRSA), MDR-*Pseudomonas aeruginosa*, and Vancomycin-Resistant *Enterococci* (VRE) in 1 isolate each. Typically, MDR bacteria are associated with nosocomial infections. However, some MDR bacteria have become quite prevalent causes of community-acquired infections. This is an important development as the community spread of MDR bacteria leads to a large increase in the population at risk and subsequently an increase in the number of infections caused by MDR bacteria. In addition, when the incidence of a certain resistance pattern in bacteria causing community-acquired infections exceeds a specific threshold, broader spectrum antibacterial and/or combination antibacterial therapy are indicated for the empiric treatment of community-acquired infections.[31]

There were some limitations in our studies, including the absence of determining whether the infection was acquired from a community or hospital. Some blood sample was obtained in the first 48 hours of admission, and the other was above 48 hours of hospital admission, which made up for the possibility of hospital-acquired infection. We were also aware that the antibiotic susceptibility was based only from in vitro data. Therefore, it is important to distinguish them by separating the data from which the timing of the blood sample was obtained in the next studies. We also suggest for collect the patients' clinical outcomes after being given susceptible antibiotic administration by doing a cohort study.

The sample size in our study was relatively small to indicate antibiotic susceptibility. A minimum of 30 isolates for each antibiotic should be obtained. Therefore, we suggest a larger sample size in future studies. Finally, our data was based on single-center experience. Thus the results are legitimately associated with the local epidemiological condition. Epidemiological variations, the prevalence of resistant strains in the region, and the type of antibiotic treatments can all be attributed to variances in the bacterial spectrum and antibiotic resistance pattern of isolates identified between contemporary research and older studies. The execution of local epidemiological surveys has a crucial role in the management of children with febrile neutropenia, according to our findings. The limitation of this study is to evaluate whether an infection was categorized as a nosocomial infection or not. The incidence of infection must be divided into two groups: those who emerged prior to hospitalization and those who appeared after 48 hours of hospitalization.

CONCLUSION

This study found that gram-negative bacteria were the most frequent cause of infection among febrile neutropenic patients. Although the research evidence is still weak due to the small sample size, Cefoperazone Sulbactam can be a better option to replace Cefepime as an empirical antibiotic due to its significantly higher susceptibility. We suggest distinguishing the community or hospital source of infection, obtaining the cohort data of clinical outcomes after antibiotic administration, and a bigger sample size in future studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL CONSIDERATION

Our study has been certified ethically feasible, with a license number 1534/UN14.2.2.VII.14/LT/2021, which has been published by the Research Ethics Committee Faculty of Medicine, Universitas Udayana/ Sanglah General Hospital.

FUNDING

This research did not receive any financial support.

AUTHOR CONTRIBUTION

All authors contribute to the study from the conceptual framework, data acquisition, and data analysis until reporting the study results through publication.

ACKNOWLEDGMENTS

We are thankful for dr. I Wayan Gustawan, M.Sc, Sp.A (K) and Dr. dr. Made Gde Dwi Lingga Utama, Sp.A (K) as an observer and advisor in the infectious disease field. Also, the authors are grateful to Dr. dr. Ketut Ariawati, Sp.A (K), dr. Anak Agung Ngurah Ketut Putra Widnyana, Sp.A (K), and dr. Kadek Ayu Yani Lastariana, M.Biomed, Sp.A, as an observer and also an adviser in the hematology and oncology field. And last but not least, the authors are also grateful to dr. Ni Nengah Dwi Fatmawati, Sp.MK (K), Ph.D. as an observer and adviser in the microbiology field.

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