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# Microbiological profile and antibiotic susceptibility pattern in children with malignancy and febrile neutropenia

**Dimarzsiana Dara Sjahruddin**
Department of Pediatrics, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia

**Dominicus Husada**
Department of Pediatrics, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia
Corresponding author Email: dominicushusada@aol.com

**I Dewa Gede Ugrasena**
Department of Pediatrics, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Hospital, Surabaya, Indonesia

***Abstract*---**Neutropenia that occurs in hematologic malignancies or solid tumors may increase the risk of infection and lead to morbidity and mortality. This study aims to investigate the microbiological profile and antibiotic susceptibility pattern in children with malignancy and febrile neutropenia (FN). A cross-sectional study was conducted from January 2017 to June 2021 using medical records from the pediatric inpatient hematology-oncology ward of Dr. Soetomo General Hospital. The inclusion criteria are children with malignancy aged ≤ 18 years, experiencing a febrile episode of neutropenia, and were examined for blood culture at the onset of FN. A total of 291 children were eligible patients. Out of 291, 65 of them had a bacterial infection from blood cultures. Out of 65, almost 57% were dominated by Gram-negative bacteria (GNB). Gram-positive bacteria (GPB) that are often recognized are *Staphylococcus hominis*, *Staphylococcus epidermidis*, and *Staphylococcus aureus*. Meanwhile, the GNB are *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* ESBL+. The majority of GNB is almost 100% resistant to ampicillin meanwhile, GPB also reported resistance to β-lactamase. We found no correlation between microorganism infection and malignancy. GNB and GPB are partially resistant to commonly used antibiotics, especially β-lactamases and ampicillin. Alternative therapies are needed to resolve this matter.


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***Keywords*---**antibiotic resistance, neutropenia, hematologic malignancy, solid tumor.

## Introduction

Febrile neutropenia (FN) is the most common complication in pediatric patients with malignancy receiving chemotherapy. This situation contributes significantly to the increased risk of infection and mortality (Doganis et al., 2013; White & Ybarra, 2017). The overall mortality in FN has increased significantly over the past 10 years. The incidence of bacterial infections in children who suffer from malignancy and FN is quite high, 44.8% and the mortality rate reaches 80% without the use of antimicrobials (Krenn et al., 2011). The mortality risk is greater if it is accompanied by comorbid factors for example sepsis, pneumonia, meningitis, and mycoses (Lekshminarayanan et al., 2018). The increased risk of infection occurs due to the immunosuppressed state caused by the underlying malignancy and the side effects of chemotherapy. Common reported risk factors for infection are younger age, absolute neutrophil count (ANC) levels <500 cell/$mm^3$, intravascular catheter, elevated body temperature, and immunosuppressive antineoplastic regimens (Al-Mulla et al., 2014).

Children with malignancy and FN will be given broad-spectrum antimicrobial therapy as empirical therapy before the results of bacterial culture and bacterial susceptibility testing are obtained (Muliyani et al., 2014). The choice of empiric antibiotic therapy for patients with FN at high risk of infection is based on several factors including individual patient characteristics, local infrastructure to support different treatment models, drug availability and cost, microorganism pattern, local susceptibility testing, and the epidemiology of the specific pathogen (Lehrnbecher et al., 2017). The overall goal of empiric therapy is to provide adequate coverage for virulent organisms and minimize unnecessary antibiotic exposure. Empirical antibiotic regimens should be reviewed regularly taking into account individual institutional bacterial resistance patterns and changing bacteremia epidemiology (Alali et al., 2020).

Neutropenic fever is defined as a fever with an oral temperature of 38.50°C or an axillary temperature of 38.50°C over a 2 hour on measurement with ANC levels less than 500 cells/$mm^3$ or ANC levels <1000 cells/$mm^3$ and is predicted to decline to <500 cells/$mm^3$ within 48 hours (Kebudi & Kizilocak, 2018). Neutropenic fever that occurs in hematological malignancies or solid tumors, may increase the risk of infection consisting of bacterial, fungal, and viral infections, and resulted in increased morbidity and mortality (Das et al., 2018). The most common entrances for infection in solid tumors are through the skin and the use of a catheter, where the types of microorganisms that are often found are gram-positive bacteria (GPB). While the entrance of infection in hematologic malignancies occurs more through the respiratory tract and digestive infections (Delebarre et al., 2019). GPB infections, especially Viridans group streptococci (VGS) are known to be more common in patients with hematological malignancies than in patients with solid tumors (Reilly & Lange, 2007). Children with episodes of neutropenia and neuroblastoma had a higher rate of VGS infection than other solid tumors (8.1% vs 2%) despite not receiving high-dose cytarabine (HDARAC) therapy but often resulted in severe mucositis due to intensive chemotherapy (Alali et al., 2020). Considering that bacterial data on pediatric patients with malignancy who experience infection is limited in Indonesia and until now there has not been much data related to the microbiological profile and antibiotic resistance in patients with malignancy and FN. Therefore, we aim to investigate the microbiological profile and antibiotic susceptibility pattern in children with malignancy and FN.

## Method

This is a cross-sectional study. We used secondary data from medical records from the pediatric inpatient hematology-oncology ward ranging from January 1st, 2017 to June 30th, 2021. We also used bacterial culture data obtained from the Department of Microbiology, Dr. Soetomo General Hospital. The samples of this study used a total sampling of pediatric patients with malignancy accompanied by FN and had identified bacterial cultures that met the inclusion and exclusion criteria. The inclusion criteria were the following 1) Children with malignancy aged 18 years. 2) admitted to the pediatric ward 3) had an episode of febrile neutropenia, 4) the patient had positive blood cultures taken at the onset of febrile neutropenia. Incomplete blood culture results and medical records were excluded from this study. We collected the clinical characteristics of patients including sex, age, length of stay (LOS), ANC levels, the severity of neutropenia, type of malignancy, blood culture, antibiotic susceptibility, bacterial identification, microorganism species, and mortality. Ethical clearance was obtained and approved by Clinical Research Unit, Dr. Soetomo General Hospital with a letter of exemption number 0376/LOE/301.4.2/III/2021.

Statistical analysis was performed using IBM Statistical SPSS Version 25. All data were tested for normality using the Kolmogorov-Smirnov test. If the variable is not normally distributed, it will be displayed in the median interquartile range (IQR). We identified a comparison of bacterial patterns and antibiotic susceptibility in patients with hematologic malignancies and solid tumors who had FN descriptively in tabular form. The difference test conducted between the independent variables and the dependent variable on the type of malignancy experienced by children with blood cultures identified by bacteria will be tested using the Mann Whitney U test, Pearson Chi-square test, and Binary Logistic Regression. The variable was declared statistically significant if the p-value < 0.05.

## Discussion

A total of 291 pediatric patients were collected. Two hundred twenty-six of them (77.66%) had sterile blood culture results. Therefore, only 65 of them were eligible participants who tested positive of bacterial infection from blood cultures (22.33%). The mean age of children on this study were 74.91 months (6 years) with a median age of the children in this study was 65 months (5 years), ranging from 14 months to 15 years 2 months. Approximately 81.5% of pediatric patients are less than 10 years old. Most of the children with FN were in the hematologic malignancy group, which was 87.6%, and only 12.4% in the solid tumor group. Characteristics of all patients are reported in Table 1. Table 2 shows the clinical characteristics of patients with blood cultures identified by bacteria based on the type of malignancy. Some variables did not have a significant result on the type of malignancy ($p>0.05$). Only the ANC level gave a significant difference in the type of malignancy experienced by children with neutropenia ($p=0.039$).

In two hundred-ninety-one children who had blood cultures, 77.66% obtained sterile results and 22.33% of children were identified as germs. This result is supported by Alali et al. (2020) who stated that 21.4% of patients with fever and neutropenia had germs in the blood culture results. Because its epidemiology is more common in men, related to the role of sex hormones in leukemogenesis, the male sex is anticipated to have a larger prevalence than women in the hematologic malignancy group, but there is still no convincing evidence. One study reported an association between glutathione S-transferase (GST) and certain cytochrome P-450 alleles that exert a protective effect on women. Certain Human Leukocyte Antigen – DR isotype (HLA-DR) (HLA-DRB4*01) and the C282Y mutation in the homeostatic iron regulator (HFE) gene are associated with an increased risk of developing acute lymphoblastic leukemia (ALL) in males (Pizzo & Poplack, 2015).

Table 1
The characteristic children with malignancy and febrile neutropenia

| Variables | Value (%) n=65 |
|---|---|
| Sex | |
| Male | 37 (56.9) |
| Female | 28 (43.1) |
| Age (months), Median [IQR] | 65 [45 – 100.50] |
| Age (years) | |
| <10 | 53 (81.5) |
| ≥10 | 12 (18.5) |
| LOS (days), Median [IQR] | 13 [8 – 23] |
| ANC level (cell/mm$^3$), Median [IQR] | 140 [45 - 375] |
| Severity of neutropenia (cell/mm$^3$) | |
| <100 | 25 (38.4) |
| ≥ 100 | 40 (61.5) |
| Type of malignancy | |
| Solid tumor | 8 (12.4) |
| Hematologic malignancy | 57 (87.6) |
| Bacterial identification | |
| Positive Gram | 28(43.1) |
| Negative Gram | 37(56.9) |
| Mortality | |
| Survived | 42 (64.6) |
| Non-survived | 23 (35.4) |

The data are not normally distributed; Data is displayed in n (percentage); IQR= Interquartile Range

LOS in this study had a median of 13 days. Previous study showed a shorter median of LOS, which is 5 days. Infections including sepsis, pneumonia, viral upper respiratory tract infections, meningitis, gastroenteritis, mycosis, and skin and subcutaneous infections all affect LOS (Lekshminarayanan et al., 2018). Based on the severity of neutropenia, 61.5% of patients had an ANC levels above 100 cells/mm3 while 34% had an ANC <100 cells/mm3. This is in contrast to research by Kara et al. (2019) where more patients had ANC <100 cells/mm3 (68%), while the remaining 32% had ANC levels of 100-500 cells/mm3. The majority of patients with FN in this study had hematologic malignancy. Several studies also showed similar results for hematologic malignancy covering 64.9% and 61.3% (Alali et al., 2020; Kara Ali et al., 2020).

The bacteria found varied both in the gram-negative bacteria (GNB) and gram-positive bacteria (GPB) groups. Of the 28 isolates, the most common GPB species found were *Staphylococcus hominis* 7 (25%), *Staphylococcus epidermidis* 6 (21.4%), *Staphylococcus aureus* 5 (17.8%), and *Bacillus subtrilis* 2 (7%). In the hematologic malignancy group, the most common GPB was *Staphylococcus hominis* 7 out of 24 isolates (29%), while in the solid tumor group it *was Staphylococcus aureus* 2 of 4 isolates (50%) (Figure 1 A&C). The GNB were dominated by the *Pseudomonas aeruginosa* in both groups, in hematologic malignancy 10 out of 33 isolates (30.3%) and solid tumors 2 out of 4 (50%). In the hematologic malignancy group, *Klebsiella pneumonia ESBL* 4 isolates, *Escherichia coli* 4 isolate, *Escherichia coli ESBL* 3 isolates, *Enterobacter cloacae* 3 isolates, *Klebsiella pneumonia* 2 isolates and others 1 each isolate (Figure 1 B&D). The pattern of antibiotic resistance GPB in hematologic malignancy to several antibiotics is shown in Table 3. *Staphylococcus aureus (MRSA)* showed resistance to almost all of the antibiotics tested, while *Staphylococcus hominis* showed 100% resistance to the antibiotic's ampicillin, penicillin-G, oxacillin, and cefoxitin. The GNB showed resistance to ampicillin antibiotic and 100% sensitivity to meropenem antibiotic (Table 4). Patterns of resistance in GBP and GNB in solid tumors are presented in Tables 5 & 6. GNB also showed 100% sensitivity to the antibiotics Chloramphenicol, erythromycin, and clindamycin, but many GNB showed resistance to ampicillin, ampicillin-sulbactam, and chloramphenicol.

Table 2
Characteristics of children with bacteria-identified blood culture results based on the type of malignancy

| Variables | Type of malignancy | | p-value |
|---|---|---|---|
| | Solid tumor n=8 | Hematologic malignancy n=57 | |
| Sex | | | 0.673[a] |
| Male | 4 (50) | 33 (57.9) | |
| Female | 4 (50) | 24 (42.1) | |
| Age (months), Median [IQR] | 49 [21 – 112] | 69 [46.50 – 105.50] | 0.108[b] |
| Age (years) | | | 0.151[a] |
| <10 | 8 (100) | 45 (84.9) | |
| ≥10 | 0 (0) | 12 (21.1) | |
| LOS (days), Median [IQR] | 11.50 [3 -118] | 15 [8 - 24] | 0.424[b] |

| | | | |
|---|---|---|---|
| ANC level (cell/mm³), Median [IQR] | 300 [145 – 492.50] | 120 [40 – 360] | 0.039[b*] |
| Severity of neutropenia (cell/mm³) | | | 0.107[a] |
| <100 | 1 (12.5) | 24 (42.1) | |
| ≥ 100 | 7 (87.5) | 33 (57.9) | |
| Mortality | | | 0.894[a] |
| Survived | 5 (62.5) | 37 (64.9) | |
| Non-survived | 3 (37.5) | 20 (35.1) | |
| Bacterial culture | | | 0.674[c] |
| Gram positive bacteria | 4 (50) | 24 (42.1) | |
| Gram negative bacteria | 4 (50 | 33 (57.9) | |

[a]Chi-square test; [b]Mann-Whitney U test; [c] Binary Logistic Regression; *a p-value below 0.05 was significant

**Bacterial types of bloodstream infections based on malignancy in pediatric patients with febrile neutropenia**

Blood culture examination showed sterile results of 77.6%. This may be due to non-bacteremia fever or inflammation caused by the malignancy itself. A 10-year longitudinal study of infected patients with FN reported a positive blood culture of 13.5%. The most frequently suspected sites of infection were blood 10.8% and lung 9.2%, and most 72.5% were considered to have no identifiable source of infection (Al-Tawfiq et al., 2019). This result is supported by several studies in the same unit in 2015, that the positive culture results found were (30.6%) (Faradilla, 2015). In this study, the results of microbiological culture (GBP or GNB) were not associated with the type of malignancy (hematologic malignancy or solid tumor). Research conducted by Obeng- Nkrumah et al. (2015) showed similar results that there was no difference in the proportion of infections by gram-positive or gram-negative bacteria in patients with hematologic malignancies or other malignancies (Obeng-Nkrumah et al., 2015).

Positive blood culture results or bacteria identified were found in 22.4% of isolates, of which 56% were dominated by GNB. Research in India and Paris showed similar results where GNB predominated (Bhattacharyya et al., 2014; Delebarre et al., 2019). However, in a different study in Turkey (2012), GPB was found to be more dominant than GNB (Aslan et al., 2012). This discrepancy may be thought to be due to the high use of central venous catheters or implant port catheters in malignancy patients who are required for a fixed line of chemotherapy drugs in developed countries, where in developing countries they are rarely used. The highest GNB in this study were *Pseudomonas aeruginosa* and *Escherichia coli*. This can occur because the gateway to infection in children with hematologic malignancy is more often through the mouth or lower respiratory tract. Meanwhile, in the solid tumor group, the same proportions were found between the two types of bacteria. The presumed gateway of infection is more often associated with the skin or catheter for patients with solid tumors (Delebarre et al., 2019). The most common GPB species is *Staphylococcus epidermidis*. However, *Staphylococcus hominis* was only found in 7.7% of patients. The most common GNB were *Pseudomonas aeruginosa* and *Escherichia coli*. According to Garrido et al. (2019), the most common GPB were coagulase negative *staphylococci* including *Staphylococcus epidermidis, Staphylococcus hominis,* and *Staphylococcus haemolyticus* followed by *Staphylococcus aureus*, and the most common GNB were *Klebsiella pneumonia, Pseudomonas aeruginosa,* and *Escherichia coli* (Garrido et al., 2019).

**Gram Positive Bacterial Resistance Pattern**

*Staphylococcus aureus* in this study was sensitive to gentamicin and oxacillin but resistant to ampicillin and penicillin-G. The mechanism of resistance of gram-positive bacteria to β-lactamase antibiotics occurs through the production of β-lactamase enzymes or reduced affinity for binding targets, namely penicillin-binding protein (PBP). β-lactam antibiotics have a target, namely PBP, and catalyze the final stage of cell wall formation which results in cell death. The β-lactamase enzyme can inactivate the action of antibiotics, resulting in resistance. Methicillin resistance occurs due to the addition of PBP, namely PBP2/2a through foreign deoxyribonucleic acid (DNA) elements so that there is a change in the target of antibiotic binding to cells and its affinity is reduced (Jubeh et al., 2020; Karaman et al., 2020). Penicillin and ampicillin are antibiotics that are usually chosen in the treatment of β-hemolytic streptococcal infections. Tests for this group of bacteria do not need to be routinely tested for penicillin and other β-lactam antibiotics, because resistant isolates are rare. Therefore, if there are resistant isolates, they must be re-identified and retested. If it is proven to be resistant, special reporting must be carried out immediately (CLSI, 2022; Pierce & Mathers, 2022).

*Staphylococcus hominis* and *Staphylococcus epidermidis*. They were not sensitive to erythromycin. This is in line with research conducted by Al-Mulla et al. (2014), that Other species that are resistant to erythromycin are *Streptococcus pneumoniae, Kytococcus Sedentarius,* and *Staphylococcus aureus (MRSA)* while species that are resistant to clindamycin are *Streptococcus pneumoniae, Staphylococcus hominis, Staphylococcus epidermidis, Bacillus circulans, Kytococcus Sedentarius,* and *Staphylococcus aureus (MRSA).* The antibiotic clindamycin was found to be sensitive to *Staphylococcus aureus* both MSSA and MRSA. GPB resistance to macrolide antibiotics such as erythromycin and clindamycin occurs due to 23S methylation of rRNA, efflux system, and mutations in 23S rRNA and L4 protein (Jubeh et al., 2020). *Staphylococcus aureus, Bacillus subtrilis, Streptococcus group C/E, Bacillus circulans, Streptococcus agalactiae, Staphylococcus auricularis,* and *Staphylococus gallinarum* were found to be sensitive to cefoxitin while *Staphylococcus hominis* and *Staphylococcus epidermidis* were resistant to cefoxitin. *Streptococcus agalactiae* was also found to be sensitive to cefotaxime. GPB resistance to cephalosporins occurs due to the production of additional Penicillin-binding proteins (PBP) including PBP2a with lower affinity for β-lactam antibiotics (Jubeh et al., 2020).

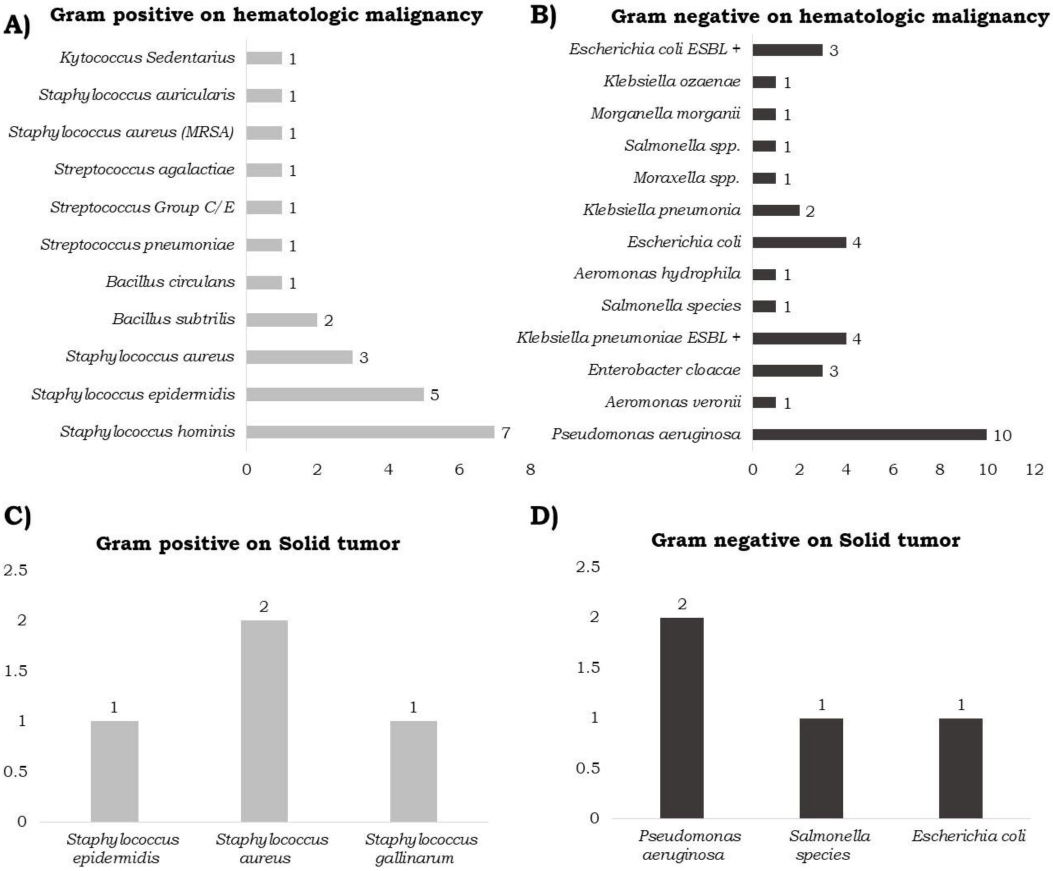


Figure 1. Frequency distribution of GPB and GNB from blood specimens based on the type of malignancy in children with febrile neutropenia. A) Microorganism species of GPB on children with hematologic malignancy; B) Microorganism species of GNB on children with hematologic malignancy; C) Microorganism species of GPB on children with solid tumor; D) Microorganism species of GNB on children with solid tumor.

Table 3
The resistance pattern of gram-positive bacteria in hematologic malignancy to several antibiotics

| Microorganism species | Isolate (n) | Gentamicin R/N | Ampicillin R/N | Penicillin-G R/N | Oxacillin R/N | Cefoxitin R/N | Sulfa trimethopr R/N | Chloramphenicol R/N | Erythromycin R/N | Clindamycin R/N |
|---|---|---|---|---|---|---|---|---|---|---|
| *Streptococcus pneumoniae* | 1 | 1/1 | - | 1/1 | - | - | 1/1 | 0/1 | 1/1 | 1/1 |
| *Staphylococcus hominis* | 7 | 0/6 | 7/7 | 6/6 | 5/5 | 7/7 | 1/2 | 0/4 | 3/5 | 4/7 |
| *Staphylococcus epidermidis* | 5 | 0/4 | 5/5 | 5/5 | 3/5 | 5/5 | 4/5 | 1/4 | 1/5 | 2/5 |
| *Staphylococcus aureus* | 3 | 0/3 | 3/3 | 3/3 | 0/3 | 0/3 | 0/3 | 2/3 | 0/3 | 0/3 |
| *Bacillus spp* | 3 | 0/2 | - | 2/3 | 0/2 | 0/3 | 0/3 | 0/3 | 0/3 | 1/3 |
| *Streptococcus Group C/E* | 1 | 1/1 | - | - | - | 0/1 | 0/1 | - | 0/1 | 0/1 |
| *Streptococcus agalactiae* | 1 | - | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| *Staphylococcus aureus (MRSA)* | 1 | 1/1 | 1/1 | 1/1 | 1/1 | - | 1/1 | 1/1 | 1/1 | 1/1 |
| *Staphylococcus auricularis* | 1 | 0/1 | - | - | 0/1 | 0/1 | - | 0/1 | 0/1 | 0/1 |
| *Kytococcus Sedentarius* | 1 | 0/1 | - | 1/1 | 1/1 | - | 1/1 | 0/1 | 1/1 | 1/1 |

R/N: Resistance to certain antibiotics/Total number of specimens tested for certain antibiotics sensitivity
[white box] >90% sensitivity [grey box] 60-90% [tan box] sensitivity <60%.

Table 4

The resistance pattern of gram-negative bacteria in hematologic malignancy to several antibiotics

| Microorganism species | Isolate (n) | Ampicillin R/N | Ampi-Sx R/N | Amoxi-cillin R/N | Piperacillin R/N | Aztreonam R/N | Cefazolin R/N | Cefotaxime R/N | Chloramph-enicol R/N | Merope-nem R/N |
|---|---|---|---|---|---|---|---|---|---|---|
| *Pseudomonas aeruginosa* | 10 | 10/10 | 10/10 | 10/10 | 0/10 | 3/10 | 10/10 | 10/10 | 10/10 | 0/10 |
| *Aeromonas veronii* | 1 | 1/1 | - | 1/1 | 0/1 | 0/1 | 1/1 | 0/1 | 0/1 | 0/1 |
| *Enterobacter cloacae* | 3 | 3/3 | 3/3 | 3/3 | 2/3 | 3/3 | 3/3 | 3/3 | 2/3 | 0/3 |
| *Klebsiella pneumoniae ESBL* | 4 | 3/3 | 3/4 | 3/4 | ¼ | 4/4 | 3/3 | 4/4 | 1/4 | 0/4 |
| *Salmonella spp* | 2 | 1/2 | 0/2 | 0/2 | 0/2 | 0/2 | 2/2 | 1/2 | 0/2 | 0/2 |
| *Aeromonas hydrophila* | 1 | 1/1 | - | 1/1 | 0/1 | 0/1 | 1/1 | 0/1 | 0/1 | 0/1 |
| *Escherichia coli* | 4 | 4/4 | 2/3 | 0/3 | 1/4 | 0/4 | 1/4 | 0/4 | 1/4 | 0/3 |
| *Klebsiella pneumonia* | 2 | 2/2 | 1/2 | 0/2 | 0/2 | 0/1 | 0/2 | 0/2 | 0/1 | 0/2 |
| *Moraxella spp.* | 1 | - | 0/1 | 0/1 | 0/1 | 0/1 | - | 1/1 | 1/1 | 0/1 |
| *Morganella morganii* | 1 | 1/1 | 1/1 | 1/1 | 0/1 | 0/1 | 1/1 | 0/1 | 1/1 | 0/1 |
| *Klebsiella ozaenae* | 1 | 1/1 | 1/1 | 1/1 | 0/1 | 0/1 | 1/1 | 0/1 | 0/1 | 0/1 |
| *Escherichia coli ESBL* | 3 | 3/3 | 3/3 | 2/3 | 1/3 | 2/2 | 3/3 | 3/3 | 2/3 | 0/2 |

R/N: Resistance to certain antibiotics/Total number of specimens tested for certain antibiotics sensitivity

[white] >90% sensitivity [grey] 60-90% [tan] sensitivity <60%

Table 5
The resistance pattern of gram-positive bacteria in solid tumor to several antibiotics

| Microorganism species | Isolate (n) | Gentamicin R/N | Ampicillin R/N | Cefoxitin R/N | Sulfa Trimethoprin R/N | Tetracycline R/N | Chloram-phenicol R/N | Erythromycin R/N | Clinda-mycin R/N | Vanco-mycin R/N |
|---|---|---|---|---|---|---|---|---|---|---|
| *Staphylococcus epidermidis* | 1 | 0/1 | - | 0/1 | 1/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 |
| *Staphylococcus aureus* | 2 | - | 2/2 | 0/2 | 0/2 | 2/2 | 0/2 | 0/2 | 0/2 | 0/2 |
| *Staphylococcus gallinarum* | 1 | - | - | 0/1 | 0/1 | - | 0/1 | 0/1 | 0/1 | 1/1 |

R/N: Resistance to certain antibiotics/Total number of specimens tested for certain antibiotics sensitivity
>90% sensitivity 60-90% sensitivity <60%

Gram Negative Bacteria Resistance Pattern

All GNB in this study showed resistance to ampicillin. Resistance to aztreonam was found in ESBL bacteria and *Enterobacter cloacae*. The β-lactamase enzyme produced by GNB causes resistance to penicillin class antibiotics. In ESBL bacteria, mutations in the genes encoding TEM-1, TEM-2, and SHV-1 also cause hydrolysis and resistance to aztreonam (Paterson, 2006). *Pseudomonas aeruginosa* resistance to β-lactam antibiotics is induced by β-lactamase activity which destroys the amide bond in the β-lactam ring and causes inactivation and ineffectiveness of antibiotics. There are four classes of β-lactamases found in *Pseudomonas aeruginosa*, consisting of classes A, C, and D which activate β-lactamses through the catalytic activity of serine residues and class B or metallo β-lactamases (MBLs) which require zinc to act. The third-generation cephalosporin ceftazidime and the fourth-generation cephalosporin cefepime are the cephalosporins commonly used in the treatment of *Pseudomonas aeruginosa* infection (Pachori et al., 2019).

Chloramphenicol in this study was found to be sensitive to *Klebsiella pneumonia* and *Escherichia coli*. This is different from the research conducted by Obeng‑Nkrumah et al. (2015) where both bacteria were resistant to chloramphenicol. *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in this study were sensitive to the antibiotic meropenem. These results are supported by Al-Mulla et al (2014) who showed that *Klebsiella pneumoniae* was 100% sensitive to meropenem, imipenem, and 82% to ciprofloxacin. *Pseudomonas aeruginosa* is 100% sensitive to ciprofloxacin, meropenem, and imipenem. Escherichia coli was 100% sensitive to imipenem and meropenem, but only 78% sensitive to ciprofloxacin. Imipenem and meropenem are carbapenems commonly used to treat Pseudomonas aeruginosa infections (Pachori et al., 2019). The retrospective collection of research samples centered on one hospital and the small number of isolates tested for each type of bacteria was this study's limitation. Some literature recommends at least 30 isolates in each antimicrobial trial (CLSI, 2014; Moehring et al., 2015; Truong et al., 2021).

## Conclusion

The microorganism pattern found in children with malignancy and FN is dominated by GNB, mostly *Pseudomonas aeruginosa*. The pattern of antimicrobial resistance has changed and most of the GNB and GPB bacteria have become resistant to ampicillin and some β-lactamase antibiotics. There is no significant difference between types of bacteria identified in blood cultures for both hematologic malignancy and solid tumors groups with FN. The need for evaluating the use of the antimicrobial ampicillin-sulbactam as the first line of treatment, especially in children with malignancy suspected of having a bacterial infection. In addition, a prospective follow-up study with a larger number of samples and antimicrobials was tested to detect all isolates to evaluate antimicrobial resistance patterns and adapt them to the most commonly used antimicrobials in health care centers.

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