OPEN ACCESS

Belitung Nursing Journal

E-ISSN: 2477-4073 | P-ISSN: 2528-181X

Volume 10, Issue 2
March - April 2024

Edited by Assoc. Prof. Dr. Yupin Aungsuroch & Dr. Joko Gunawan

The Official Publication of
Belitung Raya Foundation
Department of Publication, Indonesia

Original Research

Open Access

Belitung Nursing Journal
Volume 10(2), 185-191

https://doi.org/10.33546/bnj.3139

Infection-related mortality and infection control practices in childhood acute myeloid leukemia in a limited resource setting: Experience with the Indonesian national protocol

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Abstract

Background: In resource-limited settings, addressing infections remains a substantial challenge in the management of children with Acute Myeloid Leukemia (AML). In Indonesia, infection-related mortality (IRM) is thought to be high compared to high-income countries. However, there has been no previous study of infection profile and IRM in Indonesian patients with AML.

Objective: This study aimed to describe infections and IRM in children with AML treated according to the Indonesian National AML protocol and to describe the implementation of infection control practices in resource-limited settings.

Methods: This retrospective observational study used secondary data from the medical records of pediatric patients with AML treated with the National Protocol at Dr. Sardjito Hospital, Yogyakarta, Indonesia, from April 2012 to September 2018. Essential patient characteristics, time of IRM, and cause of death were recorded, and infection control practices were observed. Data were analyzed using descriptive statistics.

Results: 113 patients with AML were treated with the National protocol, and 83 met the inclusion criteria. Infections occurred in 69 (83%) patients with a total of 123 episodes (mean 1.8/patient). Death was seen in 48 (58%) patients, with 19 (23%) IRM. The majority of infections were in the gastrointestinal tract (*n* = 51, 30.5%), sepsis (*n* = 29, 17%), and respiratory tract (*n* = 28, 17%). Infections mostly occurred during the first induction (41%). There were 90 (73%) episodes of clinically documented infection and 33 (27%) episodes of microbiologically documented infection. The positivity rate of blood cultures was only 27%. The majority of bacteria detected were gram-negative (*n* = 25, 69%), and among them were Klebsiella pneumonia (19%) and Escherichia coli (19%). Candida albicans was detected in 1 (2%) culture. Suboptimal infection prevention and control were found in the clinical practice.

Conclusion: Infections and infection-related mortality in children with AML treated using the National protocol were frequent, mainly occurring during the first induction phase. Compliance with infection prevention and control measures needs improvement. Urgent attention is required for better supportive care, including isolation rooms, antibiotics, and antifungals. The predominance of Gram-negative bacterial infections highlights the necessity for further research into effective prophylaxis. Enhanced healthcare and nursing professional vigilance and tailored antibiotic strategies are vital. Improving compliance and ensuring adequate supportive care resources are essential, emphasizing nursing's pivotal role. Further research is crucial to drive advancements in infection control strategies.

Keywords

Indonesia; acute myeloid leukemia; infection; mortality; resource limited settings; hospitals

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Article info:
Received: 28 November 2023
Revised: 25 December 2023
Accepted: 28 January 2024

E-ISSN: 2477-4073 | P-ISSN: 2528-181X

Background

Children with acute myeloid leukemia (AML) are at a particularly high risk of infection, likely due to the intensity of their therapy, which results in repeated episodes of prolonged and profound neutropenia (Sung et al., 2007). Their increased vulnerability to infections arises from disturbances in skin and mucosal defenses (such as oral and gastrointestinal barriers), microbial movement across the gastrointestinal tract, compromised cell-mediated immunity, and deficiencies in both

the quantity and functionality of phagocytes. In addressing infection control and prevention among this group, the focus is reducing risks associated with the underlying malignancy and its treatment (Dutta & Flores, 2019). The limitations of facilities and infrastructure in Indonesia, as a lower-middle-income nation (LMIC), where resources for the care of children with cancer are severely constrained, coupled with a minimal national health budget, require stakeholders to ensure that management is truly effective and efficient.

The Indonesian National AML protocol was developed in October 2011 and implemented in 2012 to provide more appropriate management of the conditions and availability of resources in Indonesia where supportive care is not yet optimal, and there are limitations in obtaining chemotherapy. Therefore, this national protocol was designed to be less toxic. This protocol uses doxorubicin, cytarabine, etoposide, plus intrathecal methotrexate, given with four cycles of administration at week 1, week 5, week 9, and week 13. Prophylaxis for bacterial and fungal infections is given between chemotherapy courses (weeks 2-4, 6-8, and 10-12). The two-year overall survival of patients with AML treated with the Indonesian National AML protocol reached 18.6%. This result was higher compared with other protocols. Supportive care and infection control were considered to be one factor in the increase in overall survival (Supriyadi et al., 2015). Despite the increase in survival, the incidence of infections and infection-related mortality remained high.

Infections contribute to mortality and prolonged hospitalization, delayed or compromised chemotherapy administration, and further affect patients' quality of life (Bochennek et al., 2016). As a benchmark, treatment-related death in connection with chemotherapy accounts for around 5% of deaths, with infection as the leading cause of death (85%) in children with AML in Nordic countries (Molgaard Hansen et al., 2010). Patients with immunocompromised conditions, such as those with cancer, face increased susceptibility to a range of infectious diseases. Extended and severe granulocytopenia after chemotherapy predisposes patients to an increased likelihood and severity of infections in individuals with hematologic malignancy. Infection prevention in patients with hematologic malignancies undergoing chemotherapy is based on correcting granulocytopenia, antimicrobial prophylaxis, and infection prevention and control measures (Ruhnke et al., 2014). Implementation of infection prevention and control strategies is essential. This includes a structured approach that addresses patients, healthcare settings, community, and healthcare professionals, including physicians and nurses (Ariza Heredia & Chemaly, 2018). Nursing plays a crucial role in infection control, both preventive and curative. Patient handling is primarily carried out by nurses, emphasizing the pivotal role of the nursing aspect in infection control.

Infection prevention and control measures for patients with hematologic malignancies include hand hygiene and the use of personal protective equipment such as gloves, gowns, and masks. Reducing the risk of fungal infections from the environment can be achieved by offering low-bacteria or sterile food, placing patients in isolation rooms with single beds, ensuring proper ventilation, and utilizing air filtration technologies (Ariza Heredia & Chemaly, 2018).

Given this background, a focused study of infections in patients treated with the Indonesian National AML protocol was conducted to gain more information about the infection pattern and infection-related mortality and to describe the current implementation of infection prevention and control. Therefore, it is hoped that the treatment of AML patients will be improved, including supportive care such as culture examinations and the availability of antibiotics, antifungals, and other necessary supportive care. The nursing aspect is particularly significant in this study, emphasizing the crucial role of nurses in infection control, both in preventive and curative aspects. Patient handling, primarily by nurses, highlights their pivotal role in infection control.

Methods

Study Design and Setting

This observational study utilizes retrospective data of pediatric AML at Dr. Sardjito Hospital, Yogyakarta, Indonesia, from April 2012 to September 2018. This design was selected due to its data availability through the Yogyakarta Pediatric Cancer Registry and its cost and time efficiency, without requiring extensive resources. Additionally, the aim was to reflect actual clinical practice and assess the occurrence of infections in the treatment of pediatric AML patients in the hospital. The study was conducted at Dr. Sardjito General Hospital, a tertiary referral and academic hospital in Yogyakarta Special Province. The hospital serves an estimated population of 5.8 million, with approximately 1.3 million children below the age of fifteen (Central Statistical Agency, 2017). Due to the absence of a national pediatric cancer registry in Indonesia during the study period, the study was limited to a single center, making comparing data with other centers impractical. Data collection was limited until 2018, as there was an update in AML treatment protocol in 2019.

Participants

Children aged between 0 and 18 years old, newly diagnosed with AML and treated with the National AML protocol, were eligible. Relapsed patients who had previously received different kinds of treatment and cases where infection-related mortality occurred in relapsed patients were excluded. Essential patient characteristics, infection timing, infection site, microbiological culture results, and infection-related mortality were noted. The study was limited to infections requiring hospitalization or occurring during hospitalization at Dr. Sardjito Hospital.

Outcomes and Definitions

Infection-related mortality (IRM) was defined as death resulting from a recent severe infection, as determined by the pediatricians or the study coordinator. Each case of children with AML was followed. Any infection during hospitalization was noted. Cases with bacterial, viral, or invasive fungal infections necessitating intravenous treatment or resulting in or prolonging a hospital stay are included as severe infections. All mortalities in cases where the primary event was death attributed to infection are included as infection-related mortality (Sung et al., 2007).

Neutropenic fever is characterized by a temperature equal to or exceeding 38 ℃ sustained for at least an hour,

accompanied by an absolute neutrophilic count of fewer than 500 cells/microliter of blood (Davis & Wilson, 2020). Clinically documented infection (CDI) was defined as the presence of fever with local or systemic inflammation whose microbiological pathogenesis cannot be examined or proven. Microbiologically Documented Infection (MDI) was defined as every case with positive detection of the infectious organism from culture sampling, even without any localized or systemic inflammation (Taj et al., 2015). The timing of infection was divided into 6 phases: before chemotherapy, during 1st induction (weeks 1-4), during 2nd induction (weeks 5-8), during 1st consolidation (weeks 9-12), during 2nd consolidation (weeks 13-16), and after week 16. The site of infection is the main site where severe infection happens to a patient. In one episode of infection, several sites can be affected. Sites are categorized into respiratory, integument, gastrointestinal (GI) tract, central nervous system (CNS), genitourinary, eye, ear-nose-throat (ENT), and sepsis (Bochennek et al., 2016). Categorical variables were presented with frequency and percentage, while continuous variables were described with the mean.

Data Collection

Nurses, residents, and oncologists conducted observations of the implementation of infection control practices. Observations were carried out from the time the patient was admitted, whether from the outpatient clinic or the emergency unit to the oncology ward during the study period. Additionally, the hospital's infection prevention and control team conducted weekly observations, monitoring adherence to hand hygiene and the use of personal protective equipment.

Data Analysis

Descriptive statistics, including frequency and percentage, were employed in this study.

Ethical Consideration

This study was approved by The Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada-Dr. Sardjito General Hospital with reference number KE/FK/0317/EC/2018.

Results

One hundred thirteen pediatric AML patients underwent treatment following the Indonesian National AML protocol. The study included 83 pediatric AML patients; 12 patients were excluded because of relapsed disease, and the rest were excluded due to incomplete data. There were 29 females and 54 males. The mean age of diagnosis was 8.8 years, with most patients diagnosed at 0-5 years old (36%). The majority of AML morphology based on FAB classification was M4. Of the 83 patients treated with the Indonesian National AML protocol, 69 patients (83%) experienced at least one infection, and 19 patients (23%) died due to infection-related mortality (IRM). Infections were further noted as episodes, ranging from 1 to 5 per patient. Among the 83 patients, there were 123 episodes of infection. The mean number of episodes was 1.8 among the 69 patients who suffered from infections. Neutropenic fever was observed in 53 patients (64%) (**Table 1**).

Table 1 Characteristics of the children with AML and infection profile (*n* = 83)

Characteristics	*f*	%
Sex		
Male	54	65
Female	29	35
Age (years)		
0 to 5	32	39
6 to 10	14	17
11 to 15	26	31
16 to 18	11	13
FAB† classification		
M1	10	12
M2	10	12
M3	3	4
M4	24	29
M5	12	14
M6	2	2
M7	8	10
Other types	14	17
Infection		
Yes	69	83
No	14	17
Survival and mortality		
Alive	35	42
Dead	48	58
IRM‡	19	40 (19/48)
Non-IRM‡	29	60 (29/48)

†FAB: French-American-British; ‡IRM: Infection-related mortality

The majority of infections (41%) occurred during the first induction phase (weeks 1-4), gradually decreasing throughout the subsequent phases (**Figure 1**). The trend of infection-related mortality (IRM) also showed a similar pattern, with the majority of IRM (58%) occurring during the first induction phase (weeks 1-4). No cases of IRM were found during the first and second consolidation phases (**Figure 2**).

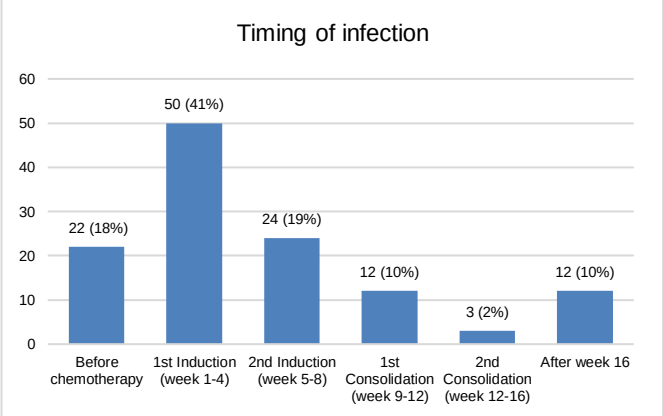


Figure 1 Timing of infection (*n* = 123)

The most common site of infection was the gastrointestinal tract (*n* = 51), followed by sepsis (*n* = 29) and the respiratory system (*n* = 28). **Figure 3** further describes the sites of infection. It is important to emphasize that in one episode of infection, more than one site can be affected. A different pattern was found in infection-related mortality (IRM), where most cases were caused by sepsis or septic shock (78%), followed by pneumonia (11%) and infectious diarrhea (11%).

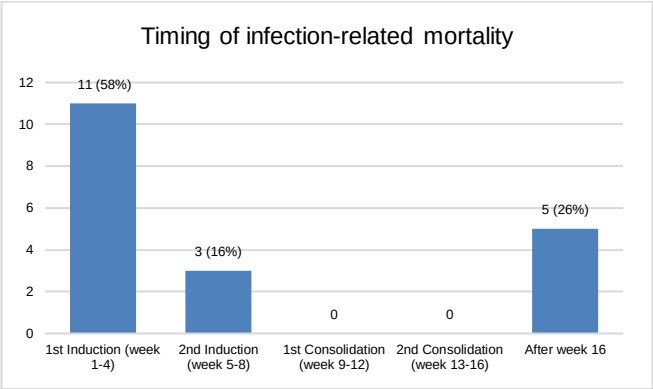
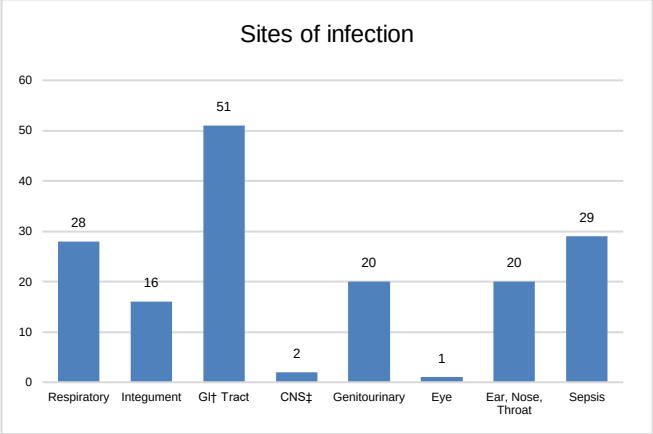


Figure 2 Timing of infection-related mortality (*n* = 19)



†GI: Gastrointestinal; ‡CNS: Central Nervous System

Figure 3 Sites of infection

Out of 123 episodes of infection, microbial culture results were traced for 79 cases (64%). These comprised 55 blood cultures, 11 urine cultures, ten fecal cultures, and three cultures from other sources (such as wound bases or secretions). Among these, 33 cultures tested positive, with 15 positive blood cultures (27%). Based on these findings, there were 33 cases of MDI (27%), while other infections were categorized as CDI (**Figure 4**).

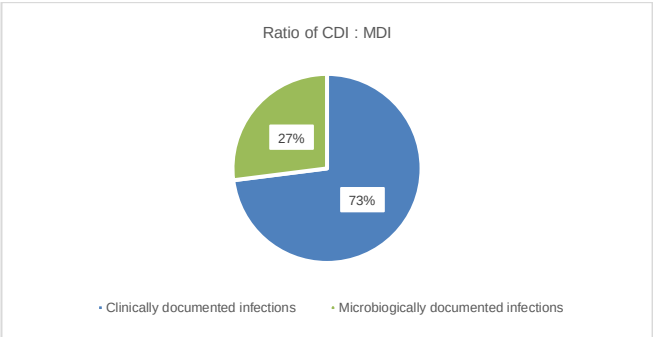


Figure 4 Ratio of clinically documented infections to microbiologically documented infections

Based on the positive cultures, there were 10 Gram-positive bacteria, 25 Gram-negative bacteria, and one result positive for fungi. Polymicrobial infections were found in some cultures. Additionally, other specific infections were noted. One patient was diagnosed with tuberculosis and treated with anti-tuberculosis drugs. Clinical candidiasis was diagnosed in 7 patients, with one positive culture result. One patient was infected with scabies, two patients with varicella, one patient with CMV, and one patient with Hepatitis A. Nineteen patients died due to infection (23%). Among them, five had positive microbial cultures (26%), while the remainder were categorized as CDI. The most frequently found organisms in IRM patients were Klebsiella pneumonia, detected in 3 cultures, followed by Escherichia coli and Enterobacter cloacae, both detected in 1 culture (**Table 2**).

Table 2 Causative organisms

Gram Positive	Gram Negative	Fungi
1. Streptococcus viridans (*n* = 2) 2. Streptococcus pneumoniae (*n* = 1) 3. Staphylococcus epidermidis (*n* = 2) 4. Staphylococcus haemolyticus (*n* = 2) 5. Staphylococcus coagulase-negative (*n* = 1) 6. MRSA Staphylococcus aureus (*n* = 1) 7. Kocuria rosea (*n* = 1)	1. Klebsiella pneumonia (*n* = 7) 2. Escherichia coli (*n* = 7) 3. Pseudomonas aeruginosa (*n* = 3) 4. Enterobacter cloacae (*n* = 3) 5. Enterobacter aerogenes (*n* = 2) 6. Acinetobacter baumannii (*n* = 2) 7. Burkholderia cepacia (*n* = 1)	1. Candida albicans (*n* = 1)

Discussion

Infection Profile and Infection-Related Mortality

Infection has remained a significant issue among Indonesian patients undergoing treatment with the National AML protocol over the past decade. Within this cohort, 83% of patients experienced infections necessitating hospitalization or occurring during chemotherapy. The majority of infections and IRMs happened during the initial induction phase of chemotherapy. A study from India also indicated a higher incidence of infection during the induction phase, which decreased by 50% during consolidation (Kalaskar et al., 2017). The IRM rate in our study was still considered very high (40%). A study from Turkey reported a 14% rate of IRM in pediatric AML without the use of preventive antibiotics and antifungals (Zengin et al., 2017). Some studies from developed countries showed a significantly lower rate, ranging from 1.5% to 11% (Bochennek et al., 2016; Klein et al., 2020; Sung et al., 2007). Despite differences in infection profile and IRM rate, the timing of infection appeared primarily similar during the induction phase.

The most common site of infection in our study was the gastrointestinal tract, a finding consistent with research from Gujarat, India, where 48% of infections were clinically detected in the gastrointestinal tract, including the oral cavity (Parikh et al., 2018). Other studies have shown a predominance of bloodstream infections (Bochennek et al., 2016; Sung et al., 2007; Zengin et al., 2017). In our study, IRM is mainly attributed to sepsis or septic shock. A study from Germany also identified septic infection as the primary cause of IRM, followed by respiratory infections (Creutzig et al., 2003).

The blood culture positivity rate in our study was 27%, which was lower than a similar study from India, where 65% of blood cultures showed positivity (Kalaskar et al., 2017). The negative result of blood cultures could be attributed to prior administration of antibiotics, sampling error, or infections caused by fastidious bacteria, including anaerobic bacteria.

The proportion of MDI in our study was 27%, lower than the study in India, which reviewed 50 patients with AML undergoing induction chemotherapy and reported a 30% MDI rate (Parikh et al., 2018). A multicenter study primarily from Germany reported infectious complications in children treated with AML-BFM 2004, showing a 32.4% MDI rate (Bochennek et al., 2016). A study in Missouri even reported a 44.8% rate of culture-positive infections (Ali et al., 2017).

Gram-negative bacteria were the primary organisms observed in this study, with Klebsiella pneumonia and Escherichia coli being the dominant species. This finding aligns with a global study indicating that Gram-negative bacteria predominantly cause infections in patients with AML. In contrast, other studies, primarily conducted in developed countries, displayed a different pattern with Gram-positive bacteria predominating (Ali et al., 2017; Bochennek et al., 2016).

Implementation of Infection Control Practices in a Resource-Limited Setting

Hand hygiene techniques for healthcare workers, patients, and visitors at Dr. Sardjito Hospital adhere to the guidelines of the World Health Organization from 2009. According to these guidelines, handwashing with soap and running water is recommended if hands are dirty or exposed to bodily fluids. Alternatively, alcohol-based hand rubs should be used if hands are not dirty (Indonesia Ministry of Health, 2017). Hand hygiene is practiced at five key moments: before patient contact, before performing an invasive procedure, after exposure to the patient's bodily fluids, after contact with a patient, and after contact with the patient's surroundings. However, adherence to these guidelines is ineffective, as some healthcare workers, including doctors, nurses, and even patient families, do not consistently comply with handwashing protocols. This is despite the availability of hand sanitizers at the entrance and within patient care areas.

The use of masks, when indicated, is generally followed by both healthcare workers and patient families. However, despite receiving education on the importance of wearing masks when necessary, some patient families do not adhere to this practice in patient care areas. Protective gowns are utilized as required, depending on the patient's condition. Dietary guidelines for cancer patients include washing vegetables and fruits before consumption and thoroughly cooking meat, eggs, or seafood to minimize bacterial contamination (Dykewicz et al., 2000). Standard diets are provided for patients with hematologic malignancies at the hospital. However, children with weakened physical conditions and reduced appetites may not be interested in the hospital's menu. As a result, parents of these patients may bring food from outside the hospital, which may not meet hygiene standards in preparation and presentation. Currently, the hospital has modified the menu for pediatric cancer patients, providing attractive serving containers to encourage them to consume the hospital-provided meals.

The next infection prevention and control step involves administering prophylactic antibiotics and antifungal medications. Prophylactic antibiotic administration can reduce the risk of death in patients with hematologic malignancies and solid tumors who experience severe and prolonged neutropenia (Chong et al., 2017; Ruhnke et al., 2014). Antifungal prophylaxis can also decrease the incidence of Candida and Aspergillus spp infections during induction chemotherapy (Tomblyn et al., 2009). However, current challenges include limited accessibility to certain antibiotics, such as those covering Pseudomonas aeruginosa and antifungals.

Isolation rooms equipped with HEPA filters, positive air pressure, effective sealing, and regular infection control measures can significantly reduce the occurrence of fungal infections, febrile neutropenia-related events, and mortality rates (Stoll et al., 2013). Nevertheless, not all patients can be accommodated in isolation rooms due to limited capacity, with only three available isolation protection rooms in our study setting. The existing isolation protection rooms have neutral air pressure and are not equipped with positive air pressure or HEPA filters. Due to the limited isolation space, not all immunocompromised patients are placed in isolation rooms but in regular patient care rooms with isolated patients in one room.

The standard design for patient care rooms for immunocompromised patients includes single rooms, a distance of ≥ 1-1.8 meters between patient beds, and the availability of alcohol-based hand rubs in each room (Indonesia Ministry of Health, 2017). However, the available room size does not meet the standards, as each patient bed has a clean floor area of less than 12 square meters.

A systematic review study identified consistent gaps in nurses' and patients' knowledge and adherence to IPC in pediatric settings, which could result in suboptimal practice. The inconsistent implementation of hand hygiene and transmission-based precautions highlights clinicians' and consumers' roles in the potential risks of infection transmission (Kilpatrick et al., 2021). Improving compliance with IPC interventions is crucial to reducing the risk of infection in pediatric malignancies. Research has shown significant improvements in hand hygiene resources, prompts, and behavior when consistently supervised and recorded through the WHO Hand Hygiene Self-Assessment Framework (World Health Organization). Vigilant monitoring and effective infection control measures are essential for maintaining a high standard of care in pediatric oncology units.

This study indicates that the incidence of infection in AML patients is indeed very high. Therefore, interventions related to the prevention and management of infections need to be promptly evaluated and followed up, involving healthcare professionals such as nurses, physicians, and the patient's family. Low-cost interventions such as hand hygiene compliance, clinical surveillance, training, and education have positively improved IPC in lower- and middle-income countries (Faizan et al., 2020). Additionally, the use of protective gowns, masks, and gloves as appropriate, supporting dietary principles, placing patients in positively pressurized isolation rooms with HEPA filtration, administering proper antibiotics and antifungal medications, maintaining a distance of ≥ 1-1.8 meters between patient beds, and ensuring that each patient bed has a clean floor area between 12-16 square meters is also necessary. It is hoped that stakeholders will promptly consider these findings to implement concrete policies related to infection control for pediatric AML and pediatric cancer patients.

Implications of the Study for Nursing Practice

This study has several implications for nursing practice: 1) Nurses need to be especially vigilant during the initial induction phase of chemotherapy, as this is when the majority of infections and infection-related mortalities occur. Close monitoring for signs of infection, prompt assessment, and timely intervention are crucial during this period. 2) Given the predominant occurrence of gastrointestinal tract infections, nurses should pay particular attention to maintaining gastrointestinal hygiene, monitoring for signs of infection in this area, and ensuring appropriate management. 3) Nurses are pivotal in educating patients and families about infection prevention measures, including hand hygiene, proper mask use, and dietary guidelines. Regular training sessions and educational materials should be provided to reinforce these practices. 4) Collaboration among healthcare professionals, including nurses, oncologists, and infection prevention teams, is essential to implement comprehensive infection prevention and control strategies effectively. 5) Nurses can advocate for the allocation of resources to enhance infection control practices, such as the availability of isolation rooms with appropriate ventilation and equipment, adequate supplies of prophylactic antibiotics and antifungal medications, and training programs for healthcare staff.

Limitations and Recommendations for Future Research

This study has several limitations: 1) A single-center study restricts the generalizability of findings. Future research should aim for multicenter studies to provide a broader perspective and facilitate comparison with other settings. 2) Exclusion of patients due to incomplete data highlights the challenge of data collection in retrospective studies. Future research should prioritize comprehensive data collection to ensure robust analysis and interpretation. 3) The study's restriction to data collected until 2018 may not capture recent advancements or changes in treatment protocols. Future studies should include a more extended study period to provide a more comprehensive understanding of trends. 4) While this study provides valuable insights into the epidemiology of infections in pediatric AML patients, future research should focus on interventional studies to evaluate the effectiveness of specific infection prevention and control measures. 5) Future research should consider incorporating patient-centered outcomes, such as quality of life and treatment satisfaction, to provide a holistic understanding of the impact of infection prevention and control strategies on pediatric AML patients and their families. By addressing these limitations and focusing on the recommendations for future research, nursing practice can be further informed and enhanced to optimize the care of pediatric AML patients, ultimately improving outcomes and reducing the burden of infections.

Conclusion

In summary, the rate of infections and IRM in this study was considerably high, highlighting the urgent need for enhanced healthcare and nursing practice in infection prevention and control. Infections and IRM mainly occur during the first induction and require particular attention for infection prevention and control, emphasizing the critical role of healthcare and nursing vigilance and proactive monitoring during this phase. The predominance of Gram-negative bacterial infections in this study warrants consideration for antibiotic prophylaxis, calling for nursing advocacy for tailored antibiotic strategies. There is a need for improvement in compliance with infection prevention and control interventions, highlighting the importance of nursing education and training in reinforcing these measures among healthcare staff and patients. Supportive care is urgently needed, particularly in providing isolation rooms, antibiotics, and antifungals, necessitating nursing advocacy for adequate resource allocation. Further research into infection prevention and appropriate infection control seems essential to enhance the prognosis for children with acute myeloid leukemia in settings with limited resources, highlighting the pivotal role of healthcare and nursing research and collaboration in driving advancements in infection control strategies.

Declaration of Conflicting Interest

The authors have declared there is no conflict of interest in this study.

Funding

The authors declared that this study did not receive any funding.

Acknowledgment

The authors would like to express gratitude to the Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada - Dr. Sardjito General Hospital for approving this research.

Authors' Contributions

Conceptualization and design (ES), Administration (IP, SS), Data collection and assembly (IP, IA, SS), Data analysis and interpretation (ES, BA, GJL), Manuscript writing (ES, ZW, IA, GJL), Final approval of manuscript (All authors). All authors were accountable for this study according to ICMJE authorship criteria.

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Data Availability

The datasets generated during and analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author upon reasonable request.

Declaration of Use of AI in Scientific Writing

The authors have declared that no generative AI and AI-assisted technologies are used in writing.

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Cite this article as: Supriyadi, E., Purwanto, I., Widiastuti, Z., Armytasari, I., Sandi, S., Ardianto, B., & Kaspers, G. J. L. (2024). Infection-related mortality and infection control practices in childhood acute myeloid leukemia in a limited resource setting: Experience with the Indonesian national protocol. *Belitung Nursing Journal, 10*(2), 185-191. https://doi.org/10.33546/bnj.3139