

Evaluation of Antibiotic Usage Using the Gyssens Qualitative Method in Pediatric Inpatients with Diarrhea at a Teaching Hospital in North Jakarta

Norman Dyanto, Diana Laila Ramatillah

Universitas 17 Agustus 1945 Jakarta, Indonesia

E-mail: normandyanto@gmail.com, diana.ramatillah@uta45jakarta.ac.id

*Correspondence: normandyanto@gmail.com

KEYWORDS

diarrhea; antibiotics;
gyssens method

ABSTRACT

Diarrhea is the second leading cause of death in children worldwide. Diarrhea is widespread in developing nations, Indonesia included. Antibiotics are ineffective if not taken as prescribed and can lead to bacterial resistance. This study aims to understand the patient profile antibiotic usage, and evaluate the appropriateness of antibiotic use in pediatric inpatients with diarrhea using the Gyssens method at a Teaching Hospital in North Jakarta during the 2022 period. This research was a retrospective study that gathered data through qualitative analysis using the Gyssens algorithm to determine the appropriateness of antibiotic use in pediatric inpatients with childhood diarrhea at a Teaching Hospital in North Jakarta. The evaluation of antibiotic usage used the Gyssens flowchart, which included inclusion and exclusion criteria for assessing the appropriateness of antibiotic use. From this research, 81 patients are identified, with the majority of cases occurring in toddlers aged 0-5 years (86.4%), and the most common gender is male (58%). The most frequently prescribed antibiotic is ceftriaxone (40.6%), with the majority receiving only one antibiotic prescription (40.7%). The evaluation of antibiotics using the Gyssens method indicates that 45 patients (55.5%) are categorized as 0; 34 patients (42%) are categorized as IVa; and 2 patients (2.5%) are categorized as IIIa. No antibiotics categorized I, IIa, IIb, IIc, IIIb, IVb, IVc, or IVd. The evaluation of antibiotic usage using the Gyssens qualitative method for pediatric inpatients with diarrhea at a Teaching Hospital in North Jakarta during the 2022 period shows appropriate use.

Attribution- ShareAlike 4.0 International (CC BY-SA 4.0)



Introduction

Diarrhea is the passage of loose or watery stools, often even as clear liquid, with a frequency higher than usual (three times or more) within a day. Signs of rapid loss of fluids and electrolytes typically accompany it. The primary management for diarrhea is

the administration of rehydration fluids as a replacement for the lost body fluids until the diarrhea stops (IKATAN DOKTER ANAK INDONESIA, 2016).

According to the International Vaccine Access Center (IVAC), based on data from the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF), diarrhea is the second leading cause of death in infants worldwide. According to estimates of child mortality data for the year 2018, diarrhea ranked second only to pneumonia, causing over 1.3 million infant deaths globally in 2016 (Ayede et al., 2018)

The prevalence of diarrhea in Indonesia, as determined by diagnoses and symptoms in the Basic Health Research (Riset Kesehatan Dasar), was 7% in 2013 and increased to 8% in 2018 (Riskesdas, 2013)

The giving of antibiotics to pediatric patients with diarrhea indicates the presence of an infection, such as bloody diarrhea or cholera. Antibiotics are ineffective when not taken in the prescribed dose and can lead to bacterial antibiotic resistance (Francino, 2016). Irrational antibiotic use can result in resistance, where bacteria develop resistance to antibiotics. When using antibiotics, it is essential to consider the dosage, administration method, and treatment indication, whether for initial treatment (empirical treatment), definitive treatment (based on culture results), or for prevention (prophylaxis) (Guarino et al., 2014). The relatively high intensity of antibiotic use raises various issues and poses a global threat to health, particularly bacterial antibiotic resistance. Research results from the Antimicrobial Resistant in Indonesia (AMRIN-Study) conducted from 2000-2005 showed that, out of 2,494 individuals in the community, 43% of *Escherichia coli* were resistant to various types of antibiotics, including ampicillin (34%), cotrimoxazole (29%), and chloramphenicol (25%). The AMRIN study recommended validated methods to control antimicrobial resistance efficiently. In Indonesia, an average of 50 antibiotic prescriptions were found monthly in hospitals and health centers, with various studies indicating that 40-62% of antibiotics are used inappropriately for conditions that do not require antibiotics (Kementrian Kesehatan Republik Indonesia, 2019).

The appropriateness of antibiotic use is typically assessed using a method called Gyssens. Gyssens is a qualitative method used to evaluate the appropriateness of antibiotic use in hospitals, which is measured retrospectively through patient medical record data (Gyssens, 2005). The assessment is made by considering the adequacy of diagnosis (clinical symptoms and laboratory results), indications, dosage, safety, and cost (Kementrian Kesehatan Republik Indonesia, 2019).

Numerous studies have evaluated antibiotic usage in diarrhea patients using the Gyssens method, such as the research conducted by (Poetri Rahmadhania et al., 2019). Their study revealed that the majority of pediatric diarrhea cases were in male patients (57.6%), within the age group of children (1-12 years) accounting for 55%, and the most common comorbid conditions were ARI (Acute Respiratory Infections) and fever (60.6%). In the same study, the Gyssens method evaluation showed results including appropriate indications (31.8%), narrower spectrum (100%), duration of administration (85%), too short duration (11.8%), correct dosage (93.3%), and inappropriate intervals (100%). Based on the evaluation results, the most common issues identified in this study using the Gyssens method were inappropriate indications and too short duration of administration.

The inpatient visit data for patients diagnosed with diarrhea and the use of antibiotics at Teaching Hospital North Jakarta in the year 2022 accounted for 40%, representing an increase from the previous year, which was 30%. This calls for an

evaluation of antibiotic usage in accordance with treatment guidelines for inpatients with diarrhea during the 2022 period at Teaching Hospital North Jakarta. The research was conducted using medical records and evaluated with the Qualitative Gyssens method to determine the appropriateness of antibiotic use in pediatric patients with diarrhea.

Research Methods

This study was a retrospective data collection research that employed qualitative analysis using the Gyssens flowchart method to assess the appropriateness of antibiotic use in pediatric inpatients with diarrhea. Teaching Hospital North Jakarta. Data sources for this research consisted of information recorded in the medical records of pediatric patients diagnosed with diarrhea.

Population and Sample

The population in this study consisted of pediatric inpatient patients with diarrhea at Teaching Hospital North Jakarta during the period of January to December 2022. The sampling method used in this research was total sampling, where the sample was drawn based on the entire population.

Data Processing

The data on antibiotic usage obtained were evaluated based on the Gyssens flowchart, including antibiotic dosage and administration interval, duration of antibiotic use, antibiotic effectiveness and toxicity, cost, spectrum, and indications for antibiotic use. The literature used for evaluation included the Ministry of Health Regulation of the Republic of Indonesia regarding the Program for Controlling Antibiotic Resistance (PPRA) and General Guidelines for Antibiotic Use (PPAB) and relevant literature available at Teaching Hospital North Jakarta.

Data Analysis

In this study, the acquired data were qualitatively analyzed using the Gyssens flowchart method for the research findings on each variable. The collected data were processed using Microsoft Excel 2010. Data presentation was provided in the form of tables and narratives.

Results and Discussions

Patient Profile

Table 1 Data Analysis of Pediatric Patients with Diarrhea at Teaching Hospital North Jakarta in 2022

No	Characteristics	Total n = 81 patients	Percentage (%)
1.	Age		
	0 – 5 years	70	86.4
	6 – 11 years	11	13.6
	Total	81	100
2	Gender		
	Male	47	58
	Female	34	42
	Total	81	100

Patient Age

Age grouping in this study is categorized into toddlers and children. The research results show more cases of diarrhea in the toddler age group compared to children, with

a total of 70 toddler patients (86.4%) and 11 child patients (13.6%). Toddlers are more susceptible to diarrhea because their immune systems are weaker than children over five years old (Simatupang, 2018). Children are highly active and curious about their surroundings at this age, and toddlers are prone to diarrhea, possibly caused by their environment (Poetri Rahmadhania et al., 2018).

Diarrhea patients are distributed across all age groups, with the highest prevalence detected in toddlers (0-5 years). The results obtained in this study are consistent with data from the World Health Organization (WHO) and the United Nations International Children’s Emergency Fund (UNICEF), which rank diarrhea as the second leading cause of death in infants globally, causing over 1.3 million deaths in infants in 2016, second only to pneumonia (Ayede et al., 2018).

Patient Gender

Grouping diarrhea patient data by gender aims to determine the proportion of male and female diarrhea patients who used antibiotics during their inpatient stay at Teaching Hospital North Jakarta in the 2022 period. The data shows that out of 81 patient medical records, there were 47 male patients (58%) and 34 female patients (42%).

The research findings indicate that a higher percentage of male diarrhea patients were admitted for inpatient care compared to female patients. This aligns with research by (Laxmi & Kaushik, 2020), which suggests that diarrhea occurrence is more common in males due to lifestyle factors, sanitation levels, and physical activities that tend to be more inclined towards getting dirty, compared to females who prefer indoor activities and playing with dolls rather than engaging in activities that involve dirt.

Antibiotic Usage Profile

Table 2 Data Analysis of Pediatric Patients with Diarrhea at Teaching Hospital North Jakarta in 2022 Based on the Total of Antibiotics

No	Total of Antibiotics	Total of Patients	Percentage (%)
1	No antibiotic use	15	18,5
2	1 Antibiotic	33	40,7
3	2 Antibiotics	23	28,4
4	> 2 Antibiotics	10	12,4
	Total	81	100

Based on Table 2, the most common antibiotic usage is a single antibiotic, with 33 patients (40.7%), followed by the use of two antibiotics in 23 patients (28.4%), usage of more than two antibiotics in 10 patients (12.4%), and no antibiotic usage in 15 patients (18.5%). In the case of pediatric diarrhea patients who are not using antibiotics, it is because there is no infection present.

The findings of this research are consistent with a study by (Astuti & Arfania, 2018), where out of 147 prescriptions, the majority consists of a single antibiotic, with 132 prescriptions (18.80%), followed by two antibiotics in 13 prescriptions (8.84%), and more than two antibiotics in 2 prescriptions (1.36%). The use of two antibiotics is typically aimed at enhancing antibiotic activity in specific infections (synergistic effect) and at slowing down and reducing the risk of resistance, particularly in cases of life-threatening infections where the causative bacteria are unknown (Kementrian Kesehatan Republik Indonesia, 2019).

Table 3 Data Analysis of Pediatric Patients with Diarrhea at Teaching Hospital North Jakarta in 2022 Based on Antibiotic Classes and Types

No	Class	Antibiotic Type	Total of Prescriptions	Percentage (%)
1	Aminoglycoside	Amikacin	20	18
		Gentamicin	16	14.4
2	Carbapenem	Meropenem	2	1.8
3	Other Antibiotics	Metronidazole	2	1.8
4	Cephalosporin	Cefotaxime	21	18.9
		Ceftazidime	5	4.5
		Ceftriaxone	45	40.6
		Total	111	100

There are 7 types of antibiotics recorded, with the total of usages found in 81 medical records. According to Table IV.3, the antibiotic group most commonly used is the cephalosporin group, with ceftriaxone having 45 usages (40.6%), followed by cefotaxime with 21 usages (18.9%), amikacin with 20 usages (18%), and then gentamicin with 16 usages (14.4%). The least prescribed type of antibiotic is ceftazidime, with only 5 usages (4.5%), and meropenem and metronidazole each have 2 usages (1.8%) out of all antibiotic usages.

The high usage of ceftriaxone in this study is due to its exceptional stability against beta-lactamase hydrolysis, a key factor in antibiotic resistance. As a result, ceftriaxone exhibits lower resistance. Ceftriaxone belongs to the third-generation cephalosporin group, offering a broader spectrum, especially against gram-negative bacteria, and it is highly stable against beta-lactamase hydrolysis compared to the first and second generations. The selection of antibiotics in the hospital is based on antibiotic usage guidelines, diagnostic guidelines, as well as the hospital's formulary approved by the hospital director. Additionally, clinicians rely on antibiotic therapy guidelines that can be used for empirical treatment within the hospital setting.

Evaluation of Antibiotic Usage using the Gyssens Method

Table 4 Analysis of Data for Diarrhea Patients in Toddlers and Children at Teaching Hospital North Jakarta Based on Gyssens Categories

No	Gyssens Category	Total n = 81 Patients	Percentage (%)
1	0	45	55.5
2	III A	2	2.5
3	IV A	34	42

Based on Table 4, Gyssens Category 0, which represents appropriate antibiotic administration, is the highest with 45 patients (55.5%). Gyssens Category IIIA, indicating extended antibiotic use, has 2 patients (2.5%), and Gyssens Category IVA, representing a more effective antibiotic selection, includes 34 patients (42%). This evaluation will be further explained using Figure 1 below.

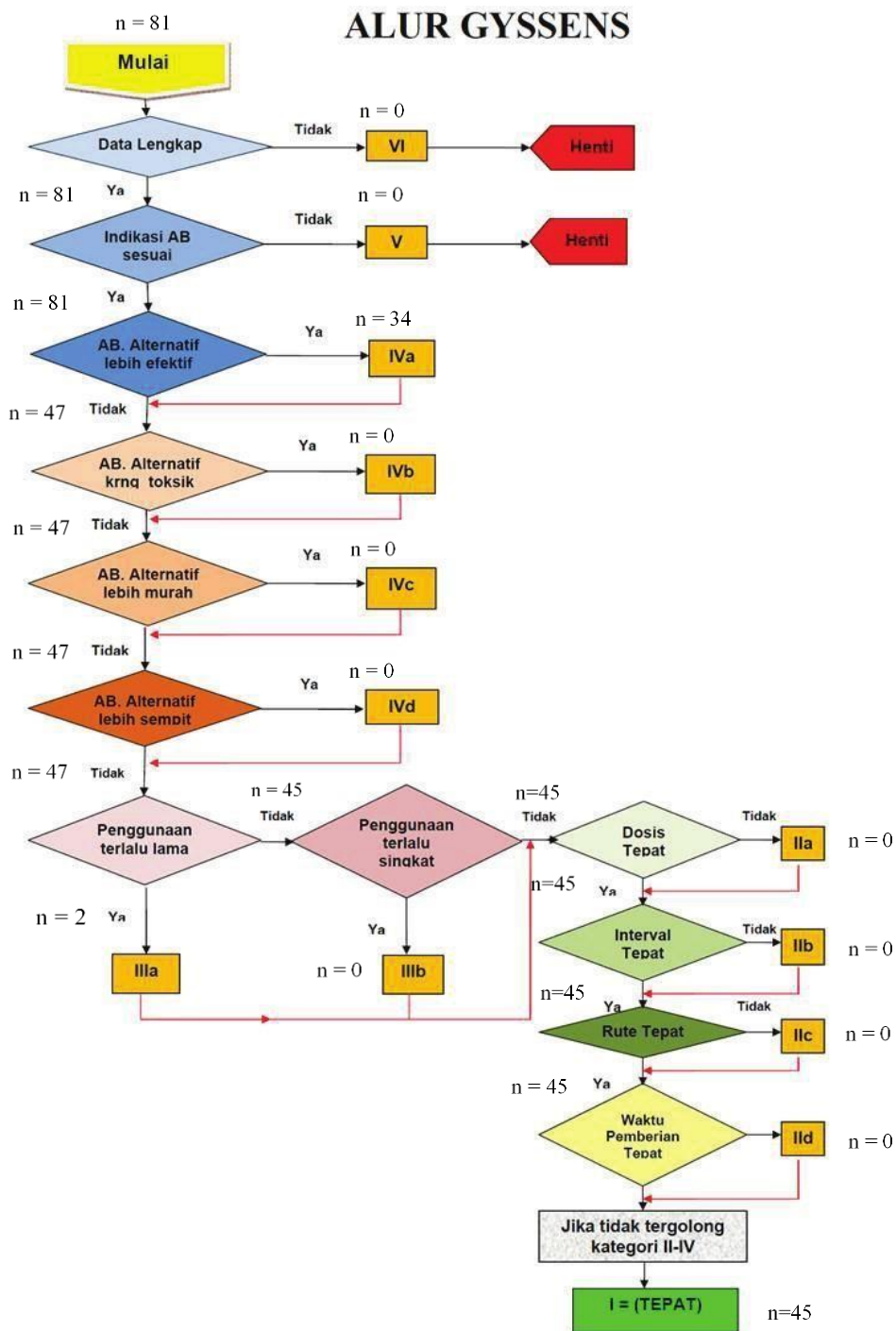


Figure 2 Determination of Antibiotic Usage Based on Gyssens Categories at North Jakarta Teaching Hospital for the Year 2022 Incomplete Data (Category VI)

Based on the evaluation results, no antibiotic usage is to be categorized as Category VI, as all patient data was complete. In this study, we found medical records for a total of 81 pediatric diarrhea patients at Teaching Hospital North Jakarta, and we verified the completeness of patient data, including patient names, medical record numbers, age, and gender.

Indications for Antibiotics are Appropriate (Category V)

Based on the evaluation results, no antibiotic usage was found in the 81 pediatric diarrhea patients who were categorized. Antibiotics without appropriate indications occurred when antibiotics were used when they were not necessary or did not match the patient's clinical condition. This included using antibiotics with Gyssens method evaluation in patients who did not show signs of bacterial infection and viral infection. Blood tests in all these patients did not indicate an increase in leukocyte count (a bacterial infection marker) or monocytes or eosinophils (parasitic infection markers) (Sutedjo, 2012). Macroscopic examination of feces revealed no mucus or blood, and microscopic examination showed no high levels of erythrocytes or leukocytes and no amoebas. These factors were the reasons why patients did not require antibiotic therapy.

Other Antibiotic Options Are More Effective (Category IVa)

In the evaluation, there were 81 pediatric diarrhea patients, and 34 of them were categorized as category IVa. These 34 patients included 13 who were using ceftriaxone and 5 who were using cefotaxime. In these cases, both antibiotics are sufficient for treating diarrhea because third-generation cephalosporins are active against *E. coli* and *Klebsiella* sp. Ceftriaxone and cefotaxime are effective and recommended as empirical therapies for infections caused by gram-negative bacteria (Katzung, 2018).

Furthermore, 2 patients were found to be using metronidazole and meropenem, both of which were categorized IVa. This is because they are not the first-line therapy for diarrhea according to the literature, as reviewed based on diagnosis, clinical symptoms, and blood or feces examination results. Metronidazole is an antiprotozoal drug with considerable antibacterial activity against anaerobic bacteria, including species like *Bacteroides* and *Clostridium*. Metronidazole is indicated for the therapy of anaerobic infections, vaginitis, abdominal infections, and *Clostridium difficile* infections (Katzung, 2018). However, metronidazole is not the antibiotic of choice for *Salmonella* infections. Meropenem is a broad-spectrum antibiotic, and if used for diarrhea, the risk is high, potentially leading to side effects such as nausea and vomiting, and seizures at high doses given to patients with Central Nervous System (CNS) lesions or renal insufficiency (Shane et al., 2017).

In the case of 12 other patients, these antibiotics were categorized as Category IVa, as the combination was not the first-line therapy for diarrhea or diarrhea and its accompanying conditions. Therefore, their use should be more closely monitored according to the literature, considering the diagnosis, clinical symptoms, and results of other laboratory tests.

In situations where antibiotics are not the first-line treatment, it is essential to monitor the patient's response closely. The first-line treatment may not yield good outcomes, or there may be other antibiotics that are more recommended and suitable for the patient's condition, leading to a more optimal therapeutic outcome. Bacterial cultures were not conducted on all patients in this study, so the use of antibiotics can be considered empirical. The antibiotics prescribed in this study have a broad spectrum because they are used to address infections where the exact causative bacteria are not known (Leekha et al., 2011). There were still cases of prescribed antibiotics that did not align with the diarrhea treatment guidelines despite the broad-spectrum nature of the antibiotics, as per the evaluation results using the Gyssens method, 34 patients (42%) were categorized as Category IVa.

Alternative Antibiotic Options with Toxic Effects (Category IVb)

Based on the evaluation results of 47 patients, there was no use of antibiotics that were categorized as this category.

Antibiotics categorized in the IVb category can be due to drug interactions that can increase their toxicity. The effects of such interactions can be quite diverse, ranging from mild effects like reduced drug absorption or delayed absorption to an enhancement of the toxic effects of other drugs. For instance, administering ciprofloxacin to children under 12 years of age can lead to cartilage damage.

Alternative, More Affordable Antibiotics (Category IVc)

The evaluation results of 47 patients using the Gyssens method in this study indicate that no antibiotic usage is categorized into category IVc. Antibiotics available in Indonesia come in the form of generic drugs, brand-name drugs, or patented drugs. The prices of antibiotics vary significantly. The cost of antibiotics with the same active ingredients can differ by up to 100 times when compared to their generic counterparts. This price difference is even more pronounced for parenteral formulations, which can be 1000 times more expensive than oral formulations with the same content. The evaluation of antibiotics falling into category IVc was based on the drug price list from Teaching Hospital North Jakarta.

Alternative Antibiotics with a Narrower Spectrum (Category IVd)

The evaluation results of 47 patients using the Gyssens method in this study indicate that no antibiotic usage is categorized as category IVd. The selection of alternative antibiotics with a narrower spectrum should be based on the results of bacterial cultures or the local bacterial patterns. Bacterial cultures were not conducted for all cases in this study, so the specific bacteria causing diarrhea in the patients were unknown. There is no data available regarding the most common causes of diarrhea at Teaching Hospital North Jakarta. As per the evaluation, no antibiotic prescriptions were categorized as category IVd.

Antibiotic Duration (Categories IIIa and IIIb)

The duration of antibiotic use has a specific time limit to prevent bacterial resistance due to improper antibiotic use. Based on the evaluation of 47 patients, 2 patients (2.5%) were categorized as prolonged antibiotic use (Category IIIa) by using ceftriaxone for 10 days in cases 6 and 10. According to the Hospital Therapy Guidelines for the year 2019, the recommended duration of ceftriaxone use is 3-5 days. If patients do not show improvement, ceftriaxone should be replaced with another antibiotic more suitable for the patient's clinical condition. As per the Ministry of Health guidelines, the recommended duration for empirical antibiotic use is 2-3 days, and further evaluation is based on the patient's clinical condition, microbiological examination, or other supporting data. Bacterial cultures were not performed for all cases in this study, so the evaluation was solely based on developing the patient's clinical condition.

Patients receiving empirical antibiotics for 2-3 days are aimed at inhibiting the growth of bacteria suspected to be the cause of the infection. If the use of empirical antibiotics leads to an improvement in the patient's clinical condition, then the use of antibiotics can continue until the patient recovers. On the contrary, if a patient does not show improvement within 2-3 days after administering empirical antibiotics, it is advisable to switch to another antibiotic that is more suitable for the patient's clinical condition. According to the evaluation results of antibiotic usage in this study, no antibiotics were found to be categorized as Category IIIb based on the development of the patient's clinical condition.

Incorrect Antibiotic Dosage (Category IIa)

Based on the evaluation results of antibiotic usage in this study, no antibiotics were found to be categorized as Category IIa. The determination of dosage suitability is established based on the therapeutic range of the required antibiotic, which includes the Minimum Effective Concentration (MEC) and the Minimum Toxic Concentration (MTC) (Avenia, N., Sanguinetti, A., Ciocchi, R., Docimo, G., Ragusa, 2014). Antibiotic prescription is considered incorrect in terms of dosage when the dosage used is either too high or too low compared to the recommended dose. An excessively high dosage can lead to toxic effects on the body, while an excessively low dosage can affect the duration of drug action, ultimately influencing the therapeutic effects produced. The dosage of a drug administered to a patient should be adjusted based on the patient's age, body weight, and clinical condition (Cipolle et al., 2004).

Incorrect Antibiotic Administration Interval (Category IIb)

Based on the evaluation results of 45 patients using the Gyssens method, no antibiotics were found to be categorized as Category IIb in this study. The accuracy of antibiotic administration intervals is analyzed by comparing them to literature recommendations. Antibiotics administered in inpatient settings should be given at consistent intervals to maintain a constant drug concentration in the bloodstream. Irregular intervals can lead to inconsistent drug levels, resulting in suboptimal drug levels for killing the microorganisms responsible for diarrhea and preventing the development of resistance. Short antibiotic administration intervals can increase drug levels in the body, potentially leading to toxicity. On the other hand, long intervals can cause a decrease in drug levels in the body or decrease levels below the minimal effective concentration, making microorganisms more likely to develop resistance as the drug levels are insufficient to kill them. The determination of intervals can be based on the drug's half-life and its mechanism of action.

Incorrect Antibiotic Administration Route (Category IIc)

Based on the evaluation results of 45 patients, no antibiotic usage was found to be categorized as Category IIc. The route of drug administration is one of the crucial factors for achieving optimal therapy and should be tailored to the patient's clinical condition and needs. Proper administration route selection involves choosing the appropriate dosage form that aligns with the diagnosis, patient condition, and drug characteristics. The administration route should be the safest and most beneficial for the patient. For instance, if a patient is vomiting, it would be more appropriate to administer the drug intravenously.

Incorrect Timing of Administration (Category I)

The evaluation of 45 patients using the Gyssens method in this study revealed that no antibiotics were categorized as Category I.

Antibiotic usage is considered timely when the administration of antibiotics aligns with the first day until the completion of the antibiotic therapy. According to (Yuniftiadi, 2010), the timing of antibiotic administration is highly critical as it affects the drug's availability in the systemic circulation, subsequently influencing the therapeutic effects produced. This importance arises from the fact that, on the first day following a complete blood examination, all patients received antibiotic therapy. Delayed antibiotic use increases the risk of sepsis. As indicated by (Dolin et al., 2019), using broad-spectrum antibiotics for empirical therapy can reduce the occurrence of sepsis caused by bacteria.

Appropriate Antibiotic Usage (Category 0)

Based on the evaluation using the Gyssens method, a total of 45 patients (55.5%) were categorized as Category 0. Antibiotics are categorized as Category 0 because they

have successfully passed the Gyssens method evaluation criteria from Category I to VI. Antibiotics that have passed Category I to VI are considered to meet the criteria for appropriate antibiotic usage, including the right indication, the right drug, the right dosage, the right route of administration, and the right administration interval.

This assessment is based on the standards for antibiotic usage set by the Ministry of Health of the Republic of Indonesia in 2011, the Guidelines for Prophylactic and Therapeutic Antibiotic Usage in Teaching Hospital North Jakarta, as well as several supportive theories that meet the standards for antibiotic therapy usage. Research on antibiotic usage in pediatric inpatient diarrhea patients at Teaching Hospital North Jakarta based on the Gyssens method has not been conducted previously. The observations in this study are expected to serve as information for healthcare professionals and can be used as an intervention tool for the pharmacy department at Teaching Hospital North Jakarta regarding the quality of antibiotic usage in pediatric diarrhea patients. Some usages require special attention, so it is hoped that inappropriate antibiotic usage in pediatric diarrhea patients can be reduced, thus achieving the therapeutic treatment goals.

Conclusion

The sociodemographic analysis of pediatric inpatients with diarrhea at Teaching Hospital North Jakarta in 2022 revealed that the majority of cases involved toddlers (86.4%), with males comprising the majority (58%) in terms of gender.

Antibiotic usage in these patients encompassed Amikacin, Gentamicin, Cefotaxime, Ceftriaxone, Ceftazidime, Meropenem, and Metronidazole, with the Cephalosporin group, particularly Ceftriaxone, being the most frequently prescribed (41.4%). It is notable that a significant portion of antibiotic prescriptions consisted of single-agent use (40.7%) compared to combination antibiotics.

The percentage results of antibiotic usage accuracy in pediatric inpatients with diarrhea at Teaching Hospital North Jakarta in 2022, using the Gyssens method and based on the guidelines in place, revealed that Category 0 was applicable to 45 patients (55.5%). However, there were still instances of less accurate antibiotic usage, with Category IVa encompassing 34 patients (42%) and Category IIIa involving 2 patients (2.5%).

References

- Astuti, D., & Arfania, M. (2018). Analisis Penggunaan Antibiotika Dengan Metoda ATC/DDD Di Rumah Sakit Swasta Kab Karawang. *Pharma Xplore: Jurnal Sains Dan Ilmu Farmasi*, 3(2).
- Avenia, N., Sanguinetti, A., Ciocchi, R., Docimo, G., Ragusa, M. (2014). Management of Acute Gastroenteritis. *American Journal of Health System Pharmacy*, 36(1), 1–9.
- Ayede, A. I., Kirolos, A., Fowobaje, K. R., Williams, L. J., Bakare, A. A., Oyewole, O. B., Olorunfemi, O. B., Kuna, O., Iwuala, N. T., & Oguntoye, A. (2018). A prospective validation study in South-West Nigeria on caregiver report of childhood pneumonia and antibiotic treatment using Demographic and Health Survey (DHS) and Multiple Indicator Cluster Survey (MICS) questions. *Journal of global health*, 8(2).
- Cipolle, R. J., Strand, L. M., & Morley, P. C. (2004). Pharmaceutical care practice: the clinician's guide. (*No Title*).
- Dolin, H. H., Papadimos, T. J., Chen, X., & Pan, Z. K. (2019). Characterization of pathogenic sepsis etiologies and patient profiles: a novel approach to triage and treatment. *Microbiology insights*, 12, 1178636118825081.
- Francino, M. P. (2016). Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. *Frontiers in microbiology*, 6, 1543.
- Guarino, A., Ashkenazi, S., Gendrel, D., Vecchio, A. Lo, Shamir, R., & Szajewska, H. (2014). European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. *Journal of pediatric gastroenterology and nutrition*, 59(1), 132–152.
- Gyssens, I. C. (2005). Audits for monitoring the quality of antimicrobial prescriptions. In *Antibiotic Policies* (bll 197–226). Springer.
- IKATAN DOKTER ANAK INDONESIA, I. D. A. I. (2016). *Rekomendasi penatalaksanaan kejang demam*. Badan penerbit Ikatan Dokter Anak Indonesia.
- Katzung, B. G. (2018). Rational prescribing & prescription writing. *Basic & clinical pharmacology*, 1146.
- Kementrian Kesehatan Republik Indonesia. (2019). *Laporan Riskesdas 2018 Nasional* (bl 674).
- Laxmi, V., & Kaushik, G. (2020). Toxicity of hexavalent chromium in environment, health threats, and its bioremediation and detoxification from tannery wastewater for environmental safety. *Bioremediation of industrial waste for environmental safety: volume I: industrial waste and its management*, 223–243.
- Leekha, S., Terrell, C. L., & Edson, R. S. (2011). General principles of antimicrobial therapy. *Mayo clinic proceedings*, 86(2), 156–167.
- Riskesdas, R. I. (2013). Riset Kesehatan Dasar. *Jakarta: Kemenkes RI*.
- Shane, A. L., Mody, R. K., Crump, J. A., Tarr, P. I., Steiner, T. S., Kotloff, K., Langley, J. M., Wanke, C., Warren, C. A., & Cheng, A. C. (2017). 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clinical Infectious Diseases*, 65(12), e45–e80.
- Simatupang, G. (2018). *Ini Penyebab Program Keluarga Berencana Gagal*. Kompas.
- Sutedjo, A. . (2012). *Buku Saku Mengenal Penyakit Melalui Hasil Pemeriksaan Laboratorium*. Amara Books, Yogyakarta.

Norman Dyanto, Diana Laila Ramatillah

Yuniftiadi, F. (2010). *Kajian Rasionalitas Penggunaan Antibiotik di Intensive Care Unit RSUP Dr. Kariadi Semarang Periode Juli–Desember 2009*. Faculty of Medicine.