



The Study of Drug-Related Problems in Pediatric Inpatients Utilizing Antibiotics in Universitas Sumatera Utara Hospital Medan, Indonesia

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Abstract

BACKGROUND: Drug-related problems (DRPs) and errors occur frequently in general health and pediatric care due to several reasons.

AIM: This study aims to determine the DRPs incidence in pediatric inpatients utilizing antibiotics in Universitas Sumatera Utara Hospital, Medan, Indonesia.

MATERIALS AND METHODS: It was carried out in May–July 2019 using a retrospective cross-sectional method and the data obtained from June to December 2018.

RESULTS: In the aforementioned hospital, the medical records of patients were 575 among which 135 (23.47%) met the inclusion criteria and the males, 84 (62.22%) were higher than females. Furthermore, majority of them, 55 (40.74%) were 5–11 years old, and 86 (63.70%) had a maximum stay length of ≥ 5 days. There were 73 DRPs events in 37 patients, namely, 46 (63.01%) low doses, 22 (30.14%) overdoses, 2 (2.74%) side effects of drugs, and 3 (4.11%) drug interactions. The most experienced antibiotic DRPs were in cefotaxime 14 (19.17%) and the most diagnosed was in appendicitis 14 (10.37%) utilization.

CONCLUSION: There were antibiotic DRPs in pediatric inpatients in Universitas Sumatera Utara Hospital, Medan.

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Introduction

Drug-related problems (DRPs) are a collection of problems associated with drugs utilization, which occur in many health services. This is experienced by patients residing outside the place of treatment and those admitted in the hospital [1]. The various reasons for DRPs include incorrect selection of drug regimen, excessive amount of drug regimens, unwanted side effects of the drug, and drug duplication which have the same effect as therapeutic interaction arising between one drug and another [2], [3].

In addition, errors in pediatric care are very common because of several reasons. First, the number of drugs off the label administered to pediatrics. Second, mistake in calculating the dose of the drugs. Third, pharmacokinetics of several drugs depends on age and weight. Besides, information related to drug dosage, patient age, and bodyweight is not available in support action decision-making therapy [3]. A study at one of the pediatric hospitals in Canada quotes that many patients are treated with antibiotics in cases of runny and stuffy nose, as well as cough. Most of these

cases are not due to bacteria, however, some are caused by viral infection [4].

Other results showed that from 2742 drugs prescribed in India, antibiotics contributed 26.8% of the medication errors recorded in a government hospital. From the results, hospitals need to compile related policies for better antibiotics prescription [5]. An American study stated that group antibiotics aminoglycosides utilization is very potential in causing hearing disorder side effects [6]. Globally, antibiotics are the most frequently used drugs today, and they have also become a mainstay in therapy provision at health-care facilities. A report from various countries mentioned that the budget needed for antibiotics is 40% higher than the overall medicine budget [7], [8]. Hence, this study aims to determine DRPs incidence in pediatric inpatients of utilizing antibiotics in Universitas Sumatera Utara Hospital, Medan.

Ethics approval

This research has been approved by the Health Research Ethics Committee of Universitas

Sumatera Utara, with reference number 255/KEPK FK USU RSUP HAM/2019.

Materials and Methods

The research was conducted in May–July 2019 using a retrospective cross-sectional method and the data obtained from June to December 2018. From Universitas Sumatera Utara Hospital, 135 medical records of antibiotic utilization in pediatric inpatients were employed as a sample. Identified DRPs included indications of needing drugs, drugs without proper indication, improper drug selection, fewer doses, more doses, adverse drug reaction, drug interactions, and failure to receive medication by Cipolle.

Results and Discussion

Gender, age, length of stay, and disease diagnosed

Among the 135 pediatric inpatients, 84 (62.22%) were male and 51 (37.78%) were female, as shown in Table 1. The proportion in this study indicated that the males were higher in number than the females. The patients were divided into four groups based on different ages, where the highest number, 55 (40.74%) was in the group of 5–11 years. Furthermore, 36 (26.67%) belonged to the group of 12–17 years, 33 (24.44%) were 1–4 years, and 11 (8.15%) were <1 year, as shown in Table 1. Most of the pediatric inpatients belonged to the group of 5–11 years. The average hospitalization duration of Universitas Sumatera Utara Hospital was ≥ 5 days, while the shortest was <5 days. Appendicitis has been the most frequently found disease among the patients. The research by Damanik *et al.* (2016) stated that from this study was obtained 22 male child patients (62.9%) and 13 female child patients (37.1%) that are suffered from appendicitis, with average age of 11.89 years. Based on the epidemiological data, appendicitis incidence occurred around 1% of children under the age of 15, with incidence peak on 10–12 years old. The risk of perforated appendix lumen occurrence is higher in the children compared to the adults [9], [10].

Type of drug-related problems incidence in pediatric inpatients in the Universitas Sumatera Utara Hospital

DRPs incidence in pediatric inpatients at Universitas Sumatera Utara Hospital was classified based on the classification compiled by Cipolle. In the

Table 1: The characteristics of pediatric inpatients in Universitas Sumatera Utara Hospital

Patient characteristics	No. of patients	Percentage
Gender		
Male	84	62.22
Female	51	37.78
Age		
<1 year	11	8.15
1–4 years old	33	24.44
5–11 years old	55	40.74
12–17 years old	36	26.67
Length of stay		
<5 days	49	36.29
≥ 5 days	86	63.70

315 medical records, 73 incidents occurred, where the underdose was the most common with 46 incidents (63.01%), along with 22 (30.14%) overdoses, 3 (4.11%) drug interactions, and 2 (2.74%) side effects of drugs, as shown in Table 2.

Table 2: Type of DRPs incidence in pediatric inpatients in the Universitas Sumatera Utara Hospital

DRPs	Number of DRPs	Percentage
Indications without drugs	0	0
Drugs without proper indication	0	0
Improper drug selection	0	0
Low dose	46	63.01
Overdose	22	30.14
The side effect of drugs	2	2.74
Drug interactions	3	4.11
Failure to receive the medication	0	0
Total	73	100

DRPs: Drug-related problems

There was a high incidence of underdose and overdoses detected during the treatment. Inadequacy can result from the lack of specific policies for the pediatric age group regarding the prescription of antibiotics. In some cases, the high dosages prescribed, are reasons of concern because they are not supported by current guideline [11]. Among the inadequacies found in this study, the highest prevalence was overdose (63.01%). Tonello *et al.* observed underdose in the following antibiotics: Ampicillin, gentamicin, and penicillin [12]. The use of piperacillin + tazobactam among infants presented higher frequency of underdose in the study by Giroto and Silva [13]. The administration of doses lower to recommend may lead to therapeutic flaw and contribute with the onset of bacterial resistance, once there is a reduction in the efficient plasmatic concentration of the antibiotic [14]. Pereria and Bezerra also found this result but with higher frequency (53.9%) [15]. The overdose of antibiotics in children may lead to toxicity and increasing mortality rates [16]. Besides, the lack of adequate medications in pediatrics leads to the need for fractioning the dose, to adapt it to the pediatric age group, which can compromise the safe use of the drug. According to Giroto and Silva, the inadequate use of antibiotics can increase the costs with hospitalization due to the longer period of hospitalization, to the non-resolution of the clinical situation or to intercurrent adverse events, such as intoxication and hypersensitivity reaction [13].

Antibiotics associated with DRP events

The following is a table of antibiotics associated with drug-related problems events occurring

in a pediatric inpatient ward during the study. Antibiotics used in the Universitas Sumatera Utara Hospital were based on the national formulary. A list of the biggest antibiotics used is shown in Table 3.

Table 3: List of antibiotics associated with DRP events

Antibiotics	I	II	III	IV	V	VI	VII	VIII	Number of DRPs	Percentage
Cefazoline				4	1				5	6.84
Cefotaxime				11	2	1			14	19.17
Cephadoxyl				3	1	1			5	6.84
Ceftriaxone				8	4				12	16.43
Metronidazole				4	3				7	9.58
Cefixime					4				4	5.47
Amikacin				1					1	1.36
Gentamicin				6	3				9	12.32
Rifampicin				3			1		4	5.47
Ampicillin					3				3	4.10
Clindamycin				1					1	1.36
Amoxicillin				3					3	4.10
Pyrazinamide				1	1		1		3	4.10
Isoniazid							1		1	1.36
Erythromycin				1					1	1.36
Meropenem									0	0
Without antibiotics									0	0

I: Indication without drugs, II: Drug without proper indication, III: Improper drug selection, IV: Low dose, V: Overdose, VI: The side effect of drugs, VII: Drug interaction, VIII: Failure to receive the medication

Based on the analysis, the gender domination was male, 84 (62.22%) (Table 1), which tends to be a common gender distribution shown in majority of the previous studies and some also showed a similar result [17]. Furthermore, males were more prone to infections than females because the females have a stronger humoral and cellular immunological response to infection or antigenic stimulation [18].

Most of the pediatrics, 55 (40.74%) belonged to the age distribution of 5–11 years (Table 1). This indicates the condition of 5–11 years toward individual susceptibility to numerous infective diseases. The age distribution tends to be natural because, during this period, the children's immune power is less and highly susceptible to infections [18].

The average hospitalization duration of Universitas Sumatera Utara Hospital was ≥ 5 days, as shown in Table 1. One reason for longer stay length (≥ 5 days) is that the patients under Government Health Scheme were supposed to be admitted for a minimum of 7 days to avail its benefits and delaying of the disease diagnosis. This potentially leads to unnecessary antibiotic exposure to children. A similar study conducted by Ufer *et al.* in 2005 indicated the mean treatment duration was directly proportional to the hospital stay [19]. Antibiotic resistance means that the microorganisms are able to survive and resist the exposure to antimicrobial drugs. The resistant genes can be genetically transferred from one microorganism to the other [20]. Although a few antibiotics are known, antibiotic resistance is a potential issue that needs to be critically ascertained. The resistance to antibiotics is a protective mechanism which the microorganisms possess to survive [21]. Antimicrobial resistance is not new, but the number of resistant organisms, the geographic locations affected by drug resistance, and the breadth of resistance in single organisms are unprecedented and mounting [22]. Antibiotic resistance patterns have also changed in recent decades, probably due to the selective pressure imposed by frequently

used antibiotics. This has led to the resistance of pathogens toward antibiotics, antibiotic resistance is the global issue and one of the effective measures to promote correct use of antibiotics and delay of antibiotic resistance is the antimicrobial stewardship program. Therefore, balancing the need for antibiotic use, management of infections, and prevention of antibiotic overuse will be the major challenge [23], [24].

Appendicitis has been the most frequently found disease among the patients and the most common abdominal emergency, which also accounts for more than 40,000 hospital admissions in England yearly [25]. It is the most common between the ages of 10 and 20 years, but no age is exempted [26]. The diagnostic sequence of colicky central abdominal pain followed by vomiting with the pain's migration to the right iliac fossa was first described by Murphy but this tends to be only present in 50% of patients [27].

DRPs are problems that frequently occur in general health care because of several reasons which include incorrect drug regimen selection, excessive amount of drug regimens, unwanted side effects of the drug, and drug duplication which have the same effect as therapeutic interaction arising between one drug and another [28]. Furthermore, errors in pediatric care are very common because of several reasons. First, the number of drugs off the label administered to pediatrics. Second, mistake in calculating the dose of the drugs. Third, pharmacokinetics of several drugs depends on age and weight. Besides, information related to drug dosage, patient age, and body weight is not available in support action decision-making therapy [29]. The DRP incidence in pediatric inpatients at Universitas Sumatera Utara Hospital was classified based on the classification compiled by Cipolle. Dosage criteria were less in this study, which is the utilization of doses below the value or dosage limits commonly used. The criteria for less dosage are the drug dose that is $< 80\%$ of the dose standard, determined based on "Specialite Drug Information" by the Indonesian Pharmacist Association, "Drug Doses" by Frank Shann, and "Handbook of Pediatric Dose" by the Association of Indonesian Pediatric Physician. The FDA set the lower limit for drug equivalence to be 80%. Since DRPs incidence strongly correlated with the number of medications received by patients, and this situation also potentially increased DRPs risk that prevent the therapeutic goal [30], [31], [32]. The 73 events of DRPs that occurred in 37 patients were 46 (63.01%) low dose, 22 (30.14%) overdose, 2 (2.74%) adverse drug reactions, and 3 (4.11%) drug interactions. From the results, it can be seen that majority of the DRPs was related to dose, namely, underdose and overdose followed by drug interaction and side effect of drugs. A similar study conducted by Zazuli *et al.* in 2017 reported that majority of the DRPs was related to dose selection ($n = 226$; 49.34%) [33].

Antibiotics associated with DRPs have a total number of 73 events, among which the third-generation

cephalosporin antibiotics have the greatest DRP incidence compared to other groups. The third-generation cephalosporins show more stability to beta-lactamases than the first or second generations, especially those produced by *Klebsiella*, *Haemophilus influenzae*, and *Escherichia coli*. As an empiric therapy, the third-generation cephalosporins are used for central nervous system infections including meningitis as they potentially cross the blood–brain barrier, then genitourinary tract infections, bone and joint infections, community-acquired pneumonia, and skin and soft-tissue infections. For specific therapy, they are active against Gram-negative meningitis, Lyme disease, *Pseudomonas* pneumonia, Gram-negative sepsis, *Streptococcal endocarditis*, melioidosis, penicillinase-producing *Neisseria gonorrhoeae*, chancroid, and Gram-negative osteomyelitis [33], [34]. Importantly, the third-generation cephalosporins are usually not active against *Chlamydia trachomatis* [34]. Above all, cefotaxime 14 (19.17%) contributed the most DRP events in this study.

Conclusion

The majority of the DRPs were related to dose, namely, 46 (63.01%) low dose and 22 (30.14%) overdose incidents followed by 3 (4.11%) drug interactions and 2 (2.74%) side effects of drugs. More active role of clinical pharmacist in the pediatric ward is recommended to improve interdisciplinary patient-centered care among the health-care team. Furthermore, an institutional-based surveillance system is needed to increase the appropriateness of antibiotic usage.

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