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Original Article

Rationality of Empirical Antibiotic Usage among Digestive Surgery Inpatients at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia: Gyssens Criteria Analysis

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Abstract

Background: Many empirical antibiotics are prescribed unnecessarily, contributing to the rise in the incidence of antibiotic resistance. Preventing infection of surgical sites is one of the most frequent purposes of empirical antibiotic usage. Therefore, this study aimed to analyze the rationality of empirical antibiotic usage among digestive surgery inpatients based on the Gyssens criteria and clinical features outcomes.

Methods: A descriptive method was used with a cross-sectional design. Data was collected from medical records of patients underwent digestive surgery and had received empirical antibiotic therapy post-surgery from July to September 2021 at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Subsequently, the data was analyzed using the Gyssens method to qualitatively assess the rationality of antibiotic use based on specific criteria, classified from rational (category 0) to various levels of irrational use (categories I–VI). Clinical outcomes were evaluated by assessing leukocyte count, clinical symptoms of fever, and the appearance of surgical site infection before and after administration of empirical antibiotics.

Results: In total, 70 empirical antibiotic prescriptions were obtained from 42 patients, with only 40% of patients using rational antibiotics, whereas 60% of antibiotics were used inappropriately (category I–VI). Clinical evaluation showed no fever, edema, or erythema and reduced leukocytosis and exudate/pus post-therapy.

Conclusions: Inappropriate empirical antibiotic prescription for digestive surgery inpatients is high. Nonetheless, clinical outcomes showed improvements in infection-related parameters. These results emphasize the importance of stricter adherence to antibiotic stewardship and regular evaluation of empirical antibiotic practices to optimize usage and patient outcomes.

Keywords: Antibiotic usage, empirical antibiotics, Gyssens criteria, rational antibiotic use

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Introduction

Antibiotics are known to play a crucial role in the management of infectious disorders, contributing significantly to improved outcomes in contemporary surgical intervention.[1,2] Antibiotic is the most commonly prescribed medication compared to other drug classes.[3] Approximately 50% of these prescriptions are actually unnecessary,[3] giving rise to a new problem in the world of medicine, namely antibiotic resistance. Bacteria may develop resistance when exposed to antibiotic, increasing their likelihood of surviving and proliferating. Infections with resistance can counteract the mechanism of antibiotics, making the diseases is challenging to treat. In this context, available evidence has shown more than 2 million cases of antibiotic-resistant bacterial infections per year, with a mortality rate of 23,000 people in the United States and 25,000 people in Europe.[4] Despite the majority of pathogens being manageable, the number of infections caused by antibiotic-resistant bacteria is steadily rising[5] for various reasons. The key factor in the rising prevalence is the unnecessary use of antibiotic, both from the prescriptions of doctors and general use.[4,6] A study conducted by Antimicrobial Resistance in Indonesia (AMRIN) found that only 21% of antibiotics administered in two hospitals adhered to rational prescriptions. The results also show improper utilization of antibiotic including concerns about indications, dosage, and adherence to treatment programs.[6]

Surgery may become more challenging in case of antimicrobial resistance. Surgical site infections (SSIs) occur in the incision and surrounding area within 30 days following surgery.[7] Antibiotic-resistant bacteria increase the risk SSIs which have an impact on costs, morbidity, and death.[8] The first step in reducing overall unjustified use of antibiotic is to assess its use. Therefore, this study aimed to analyze the rationality of empirical antibiotic use among digestive surgery inpatients by the Gyssens criteria and the impact on clinical outcomes.

Methods

This was a descriptive study with a cross-sectional design using secondary data from medical records of digestive surgery inpatients at Dr. Hasan Sadikin General Hospital Bandung, Indonesia, receiving empirical antibiotic therapy from July to September 2021. Data of patients aged 18–59 years who underwent digestive surgical procedures and received one or more antibiotics during treatment were included, then patients diagnosed with digestive disorders were separated. Patients' characteristics and type of drugs including name, strength, dosage form, dose, amount, as well as route and duration of administration were gathered. In addition, data on leukocyte count results and clinical evidence of SSI wounds before and after therapy were also taken. Empirical antibiotic prescriptions of patients were recorded to determine the rationality and outcome of therapy by observing the clinical features of the patients a day before and after being given empirical antibiotic.

The rationality of antibiotic usage was then evaluated using the Gyssens method. The Gyssens method was one of the most widely used qualitative approaches to evaluate the rationality of antibiotic use.9 This method assessed the rationality of antibiotic use qualitatively with specific criteria namely: category 0 if the use of antibiotics was definitely appropriate, meanwhile categories I–VI if inappropriate with the following category details: if inappropriate due to improper time (category I), improper dosage (category IIa), improper dosage interval (category IIb), improper route (category IIc), inappropriate due to excessive length (category IIIa), duration was too short (category IIIb), inappropriate due to other antibiotics were more effective (category IVa), less toxic (category IVb), cheaper (category IVc), narrower spectrum (category IVd), inappropriate indication (category V), and incomplete data (category VI).[9,10] Ethical approval was received from the Ethical Committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia number LB.02.01/X.6.5/417/2022.

Results

Of the total 42 patients, the majority were 45–59 years (36%) and predominantly male (52%). The surgical wound class was determined based on the type of digestive surgery and the infection survey sheet in the medical record. The two most common

Table 1 Characteristics of Digestive Surgery Patients (n=42)

Characteristics	n (%)
Age	
18–31 years	13 (31)
32–44 years	14 (33)
45–59 years	15 (36)
Sex	
Female	20 (48)
Male	22 (52)
Surgical Wound Class	
Clean	21 (50)
Clean-contaminated	19 (46)
Contaminated	1 (2)
Dirty/infected	1 (2)
Comorbidity	
With comorbidity	15 (36)
Without comorbidity	27 (64)
Length of stay	
≤7 days	16 (38)
>7 days	26 (62)

Table 2 Diagnosis of Digestive Surgery Patients

Diagnosis	n=42	%
Calculus of gallbladder without cholecystitis	7	16.7
Cholecystitis acute	1	2.4
Calculus of bile duct with cholecystitis	3	7.1
Calculus of bile duct with cholangitis	2	4.8
Cholangitis	1	2.4
Calculus of bile duct without cholangitis or cholecystitis (choledocholithiasis)	3	7.1
Rectal ampulla	3	7.1
Neoplasm of uncertain or unknown behavior of digestive organ, unspecified	1	2.4
Other unspecified intestinal obstruction	3	7.1
Unspecified injury of abdomen, lower back & pelvis	1	2.4
Injury of the liver or gallbladder	1	2.4
Other diseases of the digestive system, unspecified	1	2.4
Other specified abdominal hernia without obstruction or gangrene	1	2.4
Unilateral or unspecified inguinal hernia, with obstruction, without gangrene	2	4.8
Unilateral or unspecified inguinal hernia, without obstruction or gangrene	1	2.4
Ventral hernia without obstruction or gangrene (ventral hernia NOS)	1	2.4
Acute appendicitis	1	2.4
Acute appendicitis with generalized peritonitis	2	4.8
Acute peritonitis	1	2.4
Anal abscess	1	2.4
Anal fistula	1	2.4
Attention to ileostomy	1	2.4
Attention to other artificial openings of the digestive tract	1	2.4
Pseudocyst of pancreas	1	2.4
Internal haemorrhoids without complications	1	2.4

categories of digestive surgical wound class were clean and clean-contaminated, 50% and 46%, respectively. Most patients had no comorbidities (64%). Patients with comorbidities such as hypertension, gastritis, pneumonia, and asthma were 36%. In addition, most patients were hospitalized for more than seven days (62%) (Table 1).

Patients who underwent digestive surgery had varying diagnoses based on different digestive organs, as shown in Table 2. The most prevalent condition was gallbladder calculus without cholecystitis (16.7%) (Table 2). Patients who had trauma, obstruction, or injury showed a tendency to acquire hypoalbuminemia (data not presented).

Of the 70 empirical antibiotic prescriptions obtained from 42 medical records, many patients (57.1%) were administered a combination of antibiotic. The most

Table 3 Antibiotic Usage Distribution

Antibiotic	Total (n= 42)	
	n	%
Metronidazole	2	4.8
Metronidazole + Ceftriaxone	11	26.2
Metronidazole + Cefixime	1	2.4
Ceftriaxone	16	38.1
Ceftriaxone + Cefixime	7	16.7
Ceftriaxone + Cefixime + Metronidazole	2	4.8
Ceftriaxone + Cefixime + Ciprofloxacin	1	2.4
Ceftriaxone + Cefixime + Levofloxacin	1	2.4
Levofloxacin + Ceftriaxone	1	2.4

Table 4 Rationality of Antibiotic Use based on the Gyssens Criteria

Gyssens Criteria	Category	Total (n=70)	
		n	%
Rational use of antibiotic	0	28	40
Inappropriate timing of antibiotic	I	0	0
Inappropriate dosage of antibiotic	II	0	0
Inappropriate interval of antibiotic	IIa	3	4.3
Inappropriate route of antibiotic	IIb	0	0
Duration of administration is too long	IIIa	4	5.7
Duration of administration is too short	IIIb	5	7.1
There is a more effective alternative	IVa	14	20
There is a safer alternative	IVb	0	0
There is a cheaper alternative	IVc	0	0
There is a narrower spectrum alternative	IVd	0	0
No Indication for antibiotic use	V	16	23
Incomplete data so that the use of antibiotic cannot be assessed	VI	0	0

frequently used empirical antibiotic either single or in combination, was ceftriaxone (92.9%), followed by metronidazole (33.3%). Meanwhile, cefixime, a third-generation cephalosporin often used in combination with other antibiotic, occupied the third place in the distribution (28.6%). Empirical antibiotic prescription in this study included a low percentage of levofloxacin (4.8%) and ciprofloxacin (2.4%) as part of the prescribed combination (Table 3).

The results of evaluating the rationality of administering antibiotics to digestive surgery inpatients at Dr. Hasan Sadikin General Hospital Bandung, Indonesia using the Gyssens method showed that rational antibiotics use was 40%, thus the remaining was in the category of irrational use (60%) with the most categories being category V (23%) and category IVa (20%). Category II b, III a, and III b contributed 17% (Table 4).

After receiving empirical antibiotic, numerous cases of leukocytosis persisted, including those associated with ceftriaxone (20%), metronidazole (11.4%), cefixime (5.7%), and ciprofloxacin (1.4%) (Table 5).

The clinical characteristics of SSI before and after the use of empirical antibiotics such as fever, presence of exudate or pus, odor, edema, and erythema were observed. Of the five patients who had preoperative exudate/pus, 3 patients resolved following the administration of empirical antibiotics while 2 patients showed no improvement even after receiving empirical combinations of metronidazole-cefixime and metronidazole-ceftriaxone (Table 6). This showed that following administration of metronidazole, ceftriaxone, and cefixime antibiotics, clinical observation did not discover any fever. The results of therapy for edema and erythema were determined to be indistinguishable.

Table 5 Leukocytosis Before and After Therapy Based on Antibiotic Usage

Antibiotic*	Leukocytosis (n= 70)			
	Pre-therapy		Post-therapy	
	n	%	n	%
Levofloxacin	1	1.4	0	0
Ciprofloxacin	1	1.4	1	1.4
Metronidazole	11	15.7	8	11.4
Ceftriaxone	29	41.4	14	20
Cefixime	7	10	4	5.7
No Leukocytosis	21	30	43	61.4

Note: *Single use or combination with other antibiotics. Pre-therapy = one day before given empirical antibiotic; post-therapy= one day after given empirical antibiotic

Table 6 Clinical Features Based on Antibiotic Usage Before and After Therapy

	Pre-therapy		Post-therapy	
	n	%	n	%
Fever				
Levofloxacin	0	0	0	0
Ciprofloxacin	0	0	0	0
Metronidazole	3	4.3	0	0
Ceftriaxone	4	5.7	0	0
Cefixime	1	1.4	0	0
No fever	62	88.6	70	100
Edema, erythema				
Levofloxacin	0	0	0	0
Ciprofloxacin	0	0	0	0
Metronidazole	5	7.1	0	0
Ceftriaxone	4	5.7	0	0
Cefixime	1	1.4	0	0
No edema, erythema	60	85.7	70	100
Exudate/pus, odor				
Levofloxacin	0	0	0	0
Ciprofloxacin	0	0	0	0
Metronidazole	3	4.3	2[a]	2.9
Ceftriaxone	4	5.7	1[b]	1.4
Cefixime	1	1.4	1[c]	1.4
No exudate/pus, odor	62	88.6	66	94.3

Note: *Single use or combination with other antibiotics. Pre-therapy= one day before given empirical antibiotic; post-therapy= one day after given empirical antibiotic; adata are in the Gyssens category IIIa and IIb; b data is in the Gyssens category IVa; c data is in the Gyssens category IIIb

Discussion

Age, gender, surgical wound classification, presence of comorbidities, and length of stay were key factors distributed among patients undergoing digestive surgery. Patients between the ages of 45 and 59 constituted the largest share of the population. This age range is included in the pre-elderly group, which is a transition period to elderly age.[12] The risk of infection is heightened in the surgical area associated with increasing age.[13] Epidemiological statistics have shown that the susceptibility of the body to infection increases with the reduction of physiological immunity and endocrine system mechanisms. This is particularly true in postmenopausal women.[14] In this study, there were slightly more male patients. This ratio is different from the results of previous survey that reported marginally more female patients (51.4%).[15]

Based on the antibiotic guidelines of the Ministry of Health of the Republic of Indonesia, the classification of surgical wound is one of the key factors in deciding whether to take antibiotic or not. In this study, the clean surgical group included hernia repair, laparoscopic cholecystectomy, and open cholecystectomy, which typically do not require prophylactic usage. Conversely, it is important to weigh the advantages and disadvantages of using prophylactic antibiotic in clean-contaminated surgery classes such as colostomy, fistulotomy, exploratory laparotomy, reanastomosis, and hernia repair with mesh. Other classes of surgery, including contaminated (2.4%) and dirty/infected (2.4%) require antibiotic therapy due to the significant risk of postoperative intra-abdominal infection.[16] A study conducted at another hospital in Yogyakarta identified surgical wound classification as a strong variable influencing the likelihood of SSI.[17] However, broad-spectrum empirical antibiotic can be used to treat both aerobic and anaerobic bacteria. This may lead to a greater improvement in the clinical symptoms of patients.[16]

The medical history of patients was identified as another factor affecting the usage of antibiotic. The length of stay following surgery mostly depends on the severity of the disease, medical history, and working diagnosis. Previous report showed that prolonged hospital stays are associated with an increased likelihood of developing a nosocomial infection.[18] As showed in one patient known to have ceftriaxone resistance and 17 days length of stay, incidents of infection and prolonged use of antibiotic elevated the risk of developing resistance, showing how bacteria adapt to antibiotic exposure.[19] This will undoubtedly increase the complexity of management and extend the length of stay, thereby raising the expense of hospital care.[20] Consequently, it is crucial to oversee and guide the proper use of antibiotic in the hospital setting.

Ceftriaxone was the most commonly prescribed empirical antibiotic in this study, as also reported in earlier studies at the same hospital in 2019 where the drug was used by 35.9% of surgical inpatients.[15] The single use of ceftriaxone is suggested as a first-line treatment due to its simple, secure, and successful administration against Enterobacter β-lactamase.[19] Enterobacter is a member of the natural bacterial flora in the body that frequently transforms into an opportunistic pathogen in postoperative infections.[21] Therefore, ceftriaxone is widely prescribed in hospitals.[22] Similar results occurred with metronidazole, often used as the second empirical antibiotic following ceftriaxone. According to literature, metronidazole is effective against pathogens generally responsible for digestive infections including gram-negative anaerobic bacteria such as Bacteroides fragilis and some gram-positive bacteria namely Clostridium spp.[19,22] Empirical use of both ceftriaxone and metronidazole together was recommended by SIS in cases of intra-abdominal infection and SSI.[22] Cefixime occasionally is not appropriate in moderate-to-severe postoperative infection because it has a spectrum comparable to ceftriaxone and is administered through the oral route.[16] Although ciprofloxacin is the most potent member of the fluoroquinolone family against some gram-negative bacteria, levofloxacin is more effective against some gram-positive bacteria.[19]

The outcomes of the Gyssens category in this study showed that 40% of antibiotic use was in the rational category. Compared to previous studies at the same hospital, 46.75% of the 301 empirical antibiotic prescriptions in general surgery unit were deemed rational.[15] In contrast, a different study carried out in 2015 at a hospital in Semarang reported that only 16% of patients undergoing digestive tract surgery and given antibiotic showed rational use.[23] A study in Bandung showed that only 2.9% of antibiotic usage was rational.[24] Although these figures indicate a shift towards more rational antibiotic usage over time, however, the proportion of irrational use of antibiotic remained substantially high. This may be due to the implementation of the Minister of Health Regulation number 8 of 2015 concerning antimicrobial resistance control program in hospitals. This program was announced in 2015 despite it had been established in 2005 across 20 teaching hospitals in Indonesia.[16]

The Gyssens method analysis in category V (no indications for the use of antibiotic) showed that patients with clean and clean-contaminated surgical wound classification used empirical antibiotic despite the absence of any infection-related information in the medical record. Empirical antibiotic is prescribed whenever there are hypotheses of infection but the pathogen responsible is undiscovered.[16] Therefore, the use must be implemented under specific circumstances, particularly in the cases of clinical signs including fever, exudate or pus, erythema, or edema showing the presence of pathogens that cause infection, or when surgical wounds are contaminated, dirty, or infected.[11,16] This indication is supported by the antimicrobial resistance control program guideline. However, the guideline states that the prescription of certain antibiotic requires the clearance of an internist specialized in infection, possibly addressing implicit hints concerning specific patient conditions.[16] Unnecessary empirical antibiotic prescribing will lead to an increased risk of developing antibiotic-resistant bacteria.

Based on the result, about 20% of medications fell within the category IVa of antibiotic indicating better available substitutes. This includes ceftriaxone, has 85–95%. protein-bound antibiotic, that given to patients with hypoalbuminemia. In such cases, alternatives with reduced protein-binding characteristic should be considered.[16] As stated in previous studies, hypoalbuminemia can decrease the amount of antimicrobial protein binding, particularly in critically ill individuals with the condition. The concentration of unbound ceftriaxone may rise by 40% and interfere with the drug mechanism of action.[25] Cefotaxime is a preferred alternative to ceftriaxone for hypoalbuminemia patients since it has fewer bounded proteins but belongs to the same class and range of antibiotic as ceftriaxone.19 Furthermore, the awareness of the doctor plays a crucial role in this problem. In an intervention study conducted at Dr. Kariadi Hospital, there was a significant increase in the quality score of antibiotic usage after effective training for practitioners.[26] This study also presented the tendency of hypoalbuminemia in the diagnosis of patients having trauma, injury, and obstruction, as observed in five out of seven patients. This hint might be useful for practitioners to select cefotaxime as the first line in patients presenting cases of trauma, injury, and obstruction.

The results showed nine cases duration of antibiotic administrations contrary to the Ministry of Health's general guidelines, stating that postoperative empirical therapy should last up to 48 to 72 hours.[16] The antimicrobial resistance control program team at Dr. Hasan Sadikin General Hospital can provide empirical antibiotic for seven days based on the patient clinical state while expecting the report of the bacteria culture. In category IIIa (the duration of antibiotic administration was too long), less than 10% of empirical antibiotic were found with a duration of administration exceeding seven days. A Dutch study suggested that the incidence of overuse could be caused by uncertainty in the diagnosis of infection, as doctors were reluctant to bear the risks of not prescribing antibiotic.[27] Additionally, 55% of doctors felt pressure from patients to prescribe antibiotic, and up to 44% felt compelled to secure patient consent for discharge after surgery.[28] A previous study reported a correlation between prolonged administration and antibiotic resistance, with higher instances of antibiotic-resistant bacteria being found in nations with overwhelming drug use.[27]

Metronidazole was often administration at inappropriate intervals. These prescriptions should have been given at intervals of eight hours each.[29] However, in this study, metronidazole formulations were administered every 12 to 24 hours. This condition was attributed to the lack of medicine supply in the hospital at a particular period. Although metronidazole is the preferred empirical antibiotic option for intra-abdominal infections, the timing of delivery must be carefully evaluated since improper administration might result in therapy failure and antibiotic resistance.[16,29]

Leukocytosis in some individuals continued to one day after given empirical antibiotic, except after levofloxacin therapy. The response of the patient to treatment is influenced by both local and systemic body components resistant to infection.

Clinical indicators of fever, the presence of exudate or pus, odor, edema, and erythema were important to identified.[11] The occurrence of postoperative fever can be an indicator of infection in the operating area given that fever is a systematic body defense mechanism against infection.[11] According to a study, postoperative fever may not always suggest an infectious etiology, prompting further evaluation based on the medical history of the patient. In cases where indicators of postoperative fever are observed in patients at high risk of infection, an empirical antibiotic is prescribed until the culture results are established.[16]

Following the administration of empirical antibiotic in this trial, fever, edema and erythema were resolved. The body response to inflammation is reflected through clinical symptoms of edema, erythema, and exudate in the SSI wound. In this context, large exudates disseminated to the surrounding tissue can make the wound appear edematous. This intensifies the inflammatory state and results in erythema or vasodilation of the skin.[11] In SSI wounds, the presence of bacteria can also cause an odor. Out of five patients of surgical wound infections with signs of exudate or odor, three patients improved after receiving empirical antibiotics, while two did not shown any improvement even after receiving empirical doses of metronidazole cefixime, and ceftriaxone. These two patients were known to have hypoalbuminemia, a condition in which a shortage of albumin impairs the ability of the body to fight inflammation and repair tissues.[25] Antibiotic are obviously necessary for these circumstances, but the Gyssens analysis showed that antibiotic administered to both patients were unreasonable. In addition, one of the patients had comorbid conditions that might make the recovery from an SSI more difficult. This suggested that several variables, including the medical history and the type of surgery undertaken, might affect the efficacy of the therapy.

Based on the results, 60% of irrational antibiotic usage incidents based on the Gyssens method category included inappropriate indications, the presence of more effective alternatives, as well as improper duration and intervals of administration. The issue of taking antibiotic outside the guidelines can be attributed to factors such as the doctor comprehension of existing problems, pressure from patient requests, and drug supplies in the hospital. Therefore, improving practitioner training efficacy and promoting cooperation among antimicrobial resistance control program team members to routinely assess antibiotic use through the Gyssens method will aid in mitigating irrational antibiotic issues. Extending the laboratory process for culture orders could also facilitate more informed antibiotic choices based on the patient condition.

The treatment outcome was largely influenced by the medical characteristics, including medical history, the working diagnosis, the type of operation, and the precision of antibiotic administration. A previous study on pediatric patients at Dr. Sardjito Yogyakarta Hospital showed a significant correlation between the accuracy of the Gyssens method and the clinical outcomes of patients.[30] However, the association between therapeutic outcomes and the administration of antibiotic in digestive surgery inpatients has not yet been studied.

It is essential to acknowledge that real-time antibiotic regulations in a hospital are influenced by numerous unwritten factors, and this study has limitations in assessing the various causes of irrational usage using the Gyssens method. In addition, the clinical symptoms observed only manifested before and one day after the therapy, limiting the ability to show how the symptoms or clinical signs change over time. The overall sample size was also small because of time constraints and study criteria.

In conclusion, the rationality of empirical antibiotics usage among digestive surgery inpatients at Dr. Hasan Sadikin Hospital, Bandung, based on Gyssens criteria analysis is in the category of irrational use. Thus, in addition to evaluating the quality of empirical antibiotic use, assessing the characteristic of patient and signs of surgical site infections is essential. Both methods are crucial in estimating the effectiveness of empirical antibiotic use in improving surgical outcomes and reducing antibiotic resistance in the future. Enhancing practitioners training of and regularly evaluating antibiotic usage with the Gyssens method could result in considerable improvements in clinical outcomes and help mitigate future bacterial resistance.

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