Pharmacy Education (2023) 23(2) 184 - 189
https://doi.org/10.46542/pe.2023.232.184189

IAI SPECIAL EDITION

RESEARCH ARTICLE

Impact of appropriate empirical antibiotics therapy on the clinical outcome of patients with urinary tract infections (UTIs)

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Keywords
Appropriate use
Empirical antibiotic
Outcome therapy
Urinary tract infection

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Abstract

Background: Urinary tract infections (UTIs) have a high prevalence in Indonesia. UTI treatment is commonly done through empirical antibiotics usage; therefore the appropriate use of empirical antibiotics needs to be assessed. **Objectives**: This study was conducted to determine the impact of the appropriate use of empirical antibiotics on the outcome therapy of hospitalised UTI patients. **Methods:** This study was cross-sectional with retrospective data collected from patients' medical records. The population were all hospitalised patients who had received empirical antibiotic therapy for UTIs. Subjects were collected with purposive sampling. The appropriate application of empirical antibiotics, including the right type, dosage, route, duration, and frequency, was evaluated according to several guidelines. The collected data was then analysed descriptively. **Results:** The results showed that among 196 patients included in this study, antibiotics were appropriately used according to the type, route, dose, frequency, and duration in as many as 45.9% of patients, and 41.8% of them had improvements in therapy outcomes. On the other hand, 54.1% of patients were not using antibiotics according to the guidelines, and 48.0% of them still had improvements in therapy outcomes. Based on the Chi-squared test, the *p*-value was > 0.05 (0.64), and so the conclusion was made that there is no significant relationship between the accuracy of empirical antibiotic application with the outcomes of therapy. **Conclusion:** Thus, the application of empirical antibiotics following the guidelines does not always have an impact on improving treatment outcomes for UTI patients in the Universitas Gadjah Mada (UGM) Academic Hospital inpatient ward.

Introduction

A urinary tract infection (UTI) is a condition where bacteria proliferate above a certain level in the urinary tract. Annually, there are 90-100 UTI patients per 100,000 people (Wiwin, 2017). This infection may attack children and adults. The dominant identified UTI risk factor is antibiotic application and catheter utilisation (Tenney *et al.*, 2018). More than 95% of UTI-causative bacteria are *Enterobacteriaceae*, such as *Escherichia coli* and *Enterococcus faecalis* (Clarkson *et al.*, 2010).

The primary therapy for UTI treatment is through antibiotics. Inappropriate antibiotic use may affect patient therapy outcomes (Wulandari *et al.*, 2016). This may also trigger antibiotic resistance, thus an evaluation of empirical antibiotic use for UTI treatment is necessary (Gharbi *et al.*, 2019). The evaluation of antibiotic use for UTIs at one of Yogyakarta's hospitals in 2017 showed that 29.7% of cases involved irrational antibiotic use which was caused by an inappropriate drug choice (1.03%), dosage inaccuracy (13.85%), inaccuracy in the duration of antibiotic provision

(16.92%), and inaccuracy in the assessment of patient condition (6.15%) (Adriani, 2017).

This study was conducted at Universitas Gadjah Mada (UGM) Academic Hospital, which started the antibiotics resistance controlling programme (ARCP) in May 2018. This study was conducted to support ACRP at UGM Academic Hospital because there was still insufficient information regarding the appropriate use of antibiotics at the start of ACRP implementation. This study also explores the impact of empirical antibiotics towards the different groups. Furthermore, UTIs are also included in the top 10 most common diseases in the hospital.

This study aimed to understand the impact of empirical antibiotics' appropriate use on the therapy outcomes for urinary tract patients in the inpatient ward of UGM Academic Hospital. Appropriate use of empirical antibiotics is expected to improve patients' therapy outcomes.

Methods

Design

This study was a cross-sectional study using retrospective data collected from medical records of UTI patients in the inpatient ward of the UGM Academic Hospital. The study population was composed of UTI patients receiving empirical antibiotics in the inpatient ward of the UGM Academic Hospital from July 2018 – July 2019 (implementation of ACRP in the UGM Academic Hospital was established). Data collection was conducted from August to December 2020. Samples were collected by purposive sampling. Samples were excluded if there were incomplete medical records, including the absence of age, antibiotic usage (type, dosage, route, frequency, and duration), and vital signs before and after receiving empirical antibiotics for UTI treatment. Ethics approval for this study was obtained from the Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada – Dr. Sardjito General Hospital with approval number KE/FK/0455/EC/2019.

Assessment

The instruments used in this study were patients' data collection sheets. Guidelines for pediatric patients included the 2018 UGM Academic Hospital Antibiotics' Guidelines, Drug Information Handbook (DIH) 17th edition, and 2011 Pediatric UTI Disease Management Guidelines by IDAI (Indonesian Pediatrics Society). Guidelines for adult patients included the 2015 Clinical Practice Guidelines by Internal Disease and Nephrology Medical Group Staff UGM Academic Hospital and UTI antibiotics management guidelines in the 2018 Pharmacotherapy Self-Assessment Program book.

Data were analyzed descriptively, including patients' characteristics (demography and disease characteristics), the appropriate use of empirical antibiotics (type, route, dosage, frequency, and duration), and empirical antibiotics' therapy outcomes (vital signs: blood pressure, pulse, body temperature, respiration rate). The empirical antibiotics in this study were defined as the initial antibiotic regimen started within 24 hours of admission.

Meanwhile, data regarding the relationship between the appropriate use of empirical antibiotics and outcomes were analysed using the Statistic Package for Social Science version 20.0 software (IBM, Armonk, NY). Variables were analysed using the chi-squared test.

Results

The number of samples collected was 196 from a total population of 385 patients. Demographic characteristics showed that there were more female UTI patients (68.4%) than male patients (31.6%). UTI cases mostly occurred at the age of > 6-12 years old (17.9%), then followed by the age of > 2-6 years old (16.8%). Patients aged > 12-18 years old had the lowest number (5.1%) of UTI cases. From the social history report, only 6.1% of all patients were active smokers, and none were alcoholics. UTI diagnosis was divided into two groups: primary (34.2%) and secondary (65.8%). Demographic characteristics and empirical antibiotics usage among UTI patients can be seen in Table I.

The analysis of appropriate empirical antibiotics usage showed that 45.9% of patients received appropriate empirical antibiotics in terms of type, route, dosage, frequency, or duration. Patients that received the appropriate type of antibiotic were then analysed for their empirical antibiotics route, dosage, frequency, and duration concurrently.

Evaluation of the appropriate use of empirical antibiotics was classified into two types according to patient's age: paediatric (0-18 years old) and adult (> 18 years old). The results showed that out of 196 patients, 89.8% patients received the appropriate antibiotics regimen and route of administration, while 75.5% of patients received the appropriate dosage, 54.6% had appropriate usage frequency, and 88.3% had an appropriate treatment duration (Table II).

Table I: Demographic characteristics for UTI patients and empirical antibiotic usage patterns

Patients' characteristics		Number (n)	Percentage (%)
Gender	Male	62	31.6
	Female	134	68.4
Age	> 30 days- two years	18	9.2
	> two - six- years	33	16.8
	> six - 12 years	35	17.9
	> 12 - 18 years	10	5.1
	> 18 - 25 years	15	7.7
	> 25 - 35 years	11	5.6
	> 35 - 45 years	13	6.6
	> 45 - 55 years	12	6.1
	> 55 - 65 years	22	11.2
	> 65 years	27	13.8
Lifestyle	Smoking	12	6.1
	Non-smoking	184	93.9
Empirical antibiotics usage pattern		**Number (n)**	**Percentage (%)**
Single therapy	Ceftriaxone	64	32.7
	Levofloxacin	25	12.8
	Ampicillin	16	8.2
	Cefoperazone-sulbactam	13	6.6
	Cefixime	9	4.6
	Cefotaxime	8	4.1
	Ciprofloxacin	4	2.0
	Cefuroxine	3	1.5
	Cotrimoxazol	1	0.5
	Cefoperazone	1	0.5
Combination therapy	Ampicillin + Gentamicin	6	3.1
	Ampicillin + Azythromicin	1	0.5
	Ampicillin-sulbactam + Gentamicin	1	0.5
	Ceftriaxone + Amikacin	1	0.5
	Ceftriaxone + Metronidazole	1	0.5

Table II: Appropriate use of empirical antibiotics among UTI patients in the medical ward of the UGM Academic Hospital

Appropriate use of empirical antibiotics		Appropriate		Not appropriate	
		n	%	n	%
Type of antibiotic		176	89.8	20	10.2
Route of administration		176	89.8	20	10.2
Dosage		148	75.5	48	24.5
Usage frequency		107	54.6	89	45.4
Treatment duration		173	88.3	23	11.7
Appropriate use of empirical antibiotics toward different age groups		**Appropriate**		**Not appropriate**	
		n	**%**	**n**	**%**
Type of antibiotics	Adult (N = 100)	81	81.0	19	19.0
	Paediatrics (N = 96)	95	99.0	1	1.0
Route of administration	Adult (N = 100)	81	81.0	19	19.0
	Paediatrics (N = 96)	95	99.0	1	1.0
Dosage	Adult (N = 100)	75	75.0	25	25.0
	Paediatrics (N = 96)	73	76.0	23	24.0
Usage frequency	Adult (N = 100)	35	35.0	65	65.0
	Paediatrics (N = 96)	72	75.0	24	25.0
Treatment duration	Adult (N = 100)	89	89.0	11	11.0
	Paediatrics (N = 96)	84	87.5	12	12.5

The type of antibiotics that were considered inappropriate were those which were not listed in the guidelines. These were a combination of Ciprofloxacin and Metronidazole in paediatrics, and Cefoperazone, Cefuroxime, and Cefotaxime in adult patients. All of the appropriate types of antibiotics were given with a suitable route of administration. The most frequent inappropriate antibiotic usage in dose, frequency, and duration in paediatrics was the combination of Ampicillin and Gentamicin, while in adults was Ceftriaxone. There were antibiotics that were used for an inappropriate duration because they were only used for less than two days.

The relationship between the appropriate use of empirical antibiotics and therapy outcomes shows a p-value of 0.64. Hence, this value is > 0.05, showing no significant relationship between the appropriate use of empirical antibiotics and therapy outcomes (Table III).

Table III: The relationship between the appropriate use of empirical antibiotics and therapy outcomes

Appropriate use of empirical antibiotics	Therapy outcomes				Total patients	*p*-value
	Improved		Not improved			
	n	%	n	%		
Appropriate	82	41.8	8	4.1	90	0.64
Not appropriate	94	48.0	12	6.1	106	

Discussion

The results showed that UTIs commonly affected females, with a total of 134 female patients (68.4%), compared to male patients. This result is in line with the research of Nawakasari and Nugraheni (2019), which demonstrated that the incidence of UTIs in women is 65.27% higher than in men. This is because the urethra in women is shorter, so bacteria can easily enter the urinary tract and cause infection (Hanna-Wakim *et al*., 2015). According to age groups, UTIs most often occur in the age of > 6-12 years old (17.9%). The age of 6-12 years is the age of school children. According to Pamungkas (2012), factors linked to getting UTIs in school-age children are low personal hygiene, lack of cleanliness of school toilets, the habit of holding back urination, and not circumcising male children.

The appropriate usage of empirical antibiotics was assessed in stages, starting from type suitability, then route, duration, frequency, and duration. The analysis uses literature that isn't from the UGM Academic Hospital due to limited data in the guidelines. Conformity is only seen in the first use of antibiotics without looking at alternative antibiotics. The results of the study showed that there were 95 patients (48.5%) who used empirical antibiotics according to the guidelines.

The study result showed no significant relationship between the appropriate use of empirical antibiotics and patient therapy outcomes in the UGM Academic Hospital. Therefore, the appropriate use of empirical antibiotics according to the guidelines does not always have an impact on patients' therapy outcomes in the inpatient ward of the UGM Academic Hospital.

Several guidelines were used for analysis due to limitations of the UGM Academic Hospital Antibiotic Usage Guidelines. If there was no detailed information in the UGM Academic Hospital Antibiotic Usage Guidelines, then other literature was used.

Most paediatric patients received the appropriate type, route, dosage, frequency, and duration of empirical antibiotics, yet the therapy outcomes were not improving, which was most likely caused by comorbidities. Examples of patient comorbidities include appendicitis, acute gastroenteritis (AGE), febrile seizure, asthma, and typhoid fever.

Paediatric patients who were receiving ciprofloxacin and metronidazole with diagnoses of acute watery diarrhoea and UTIs were inappropriately using antibiotics according to guidelines. This type of antibiotic is not suitable because metronidazole should not be used for diarrhoea without a clear cause. These antibiotics are only useful if the diarrhoea is bloody because it is highly likely to be infected with Shigellosis (ICHRC, 2016).

In adult patients, 81 were receiving empirical antibiotic therapy in accordance with the 2015 UGM Academic Hospital Clinical Practice Guidelines and 2018 PSAP, while 19 others were not receiving suitable therapy because the therapies were not listed as treatment options. In adult patients, the most commonly used antibiotic is ceftriaxone because it can selectively inhibit bacterial cell wall synthesis by binding to the transpeptidase part, namely penicillin-binding proteins (PBPs) which catalyse peptidoglycan polymers to form the building blocks of bacterial cell walls. Inhibiting the formation of PBPs will result in damage and destruction of the cell wall, which leads to the lysis of bacterial cells

(Wardhana *et al*., 2018). Cefoperazon-sulbactam, cefoperazone, cefuroxime, and cefotaxime are not included in the guidelines because they have not been tested for sensitivity to UTI-causing bacteria. Based on research conducted at the UGM Academic Hospital, *Klebsiella pneumoniae* and *Escherichia coli* bacteria are not sensitive or resistant to cefuroxime.

There was one case of an adult patient who received an appropriate empirical antibiotic but was not getting better. The patient received ceftriaxone as the empirical antibiotic, with the primary diagnosis of type 2 diabetes mellitus, comorbidities diagnosed with anaemia, protein metabolism disorder, hyponatremia, hypokalaemia, and pneumonia. The patient was diagnosed with a UTI when undergoing treatment in the hospital and died after being hospitalised for eight days. The patient's unrecovered condition might have been caused by the comorbidities which aggravated their overall condition.

According to the guidelines, out of the 106 patients who received inappropriate antibiotics, 48.0% achieved better therapy outcomes. This might have been caused by the sensitivity of the applied antibiotics. Therefore, although it was inappropriate according to the guidelines, these antibiotics were effective in treating UTI-causing bacteria.

The determination of antibiotic application did not follow the guidelines for several children but remains to be used by referring to other sources such as Drug Doses 17th edition by Frank Shann and Urotext Basics by R.A.S Hemat. Hence, the therapy outcomes remained to be better. In this case, ciprofloxacin was given every 12 hours instead of eight hours, as suggested in the guidelines. According to Shann (2017), giving ciprofloxacin every 12 hours is acceptable. Ciprofloxacin is a concentration-dependent killing antibiotic, so its effectiveness depends on the duration of delivery. Another example is a patient who received an inappropriate dosage of gentamicin which was given once per day at a concentration of 5-7 mg/kgBB (Shann, 2017). According to Hemat (2001), giving gentamicin once per day is equally efficient as the standard dosage and is safer, especially for patients with a kidney function disorder. Several patients receiving higher dosages of gentamicin also showed improvements.

Paediatric patients receiving an inappropriate dosage of cefixime, either too low or too high, still might have improved therapy outcomes. Cefixime is one of the third-generation cephalosporin antibiotics, which are considered time-dependent killing antibiotics. Therefore, its effectiveness depends more on the duration of drug delivery in retaining its minimum resistance level (Kemenkes, 2011). According to the guidelines, an inappropriate usage frequency of time-dependent killing antibiotics might prolong the duration of inpatient care (Levison and Levison, 2009). Patients who receive ampicillin less frequently require extended amounts of time to improve their outcomes compared to patients who receive the antibiotic at an appropriate frequency.

Examples of antibiotics given to adult patients but not listed in the guidelines are cefoperazone-sulbactam and cefoperazone. According to the National Agency of Drug and Food Control of the Republic of Indonesia (BPOM RI) in the National Drug Information Centre, these antibiotics are also suggested to be able to treat UTIs. A dosage of 400 mg of cefexime is suggested to be inappropriate, but dosages of 100-200 mg are still adequate to overcome UTIs, as suggested in the National Formulary (Kemenkes, 2019).

Further research needs to be conducted and it must critically focus on the use of empirical antibiotics, particularly for more extended amounts of time (more than 24 hours in order to determine the overall differences).

Conclusion

It can be concluded from this study that the appropriate use of antibiotics according to the guidelines does not guarantee the improvement of therapy outcomes which can be due to several factors, such as the antibiotic or the patient's condition.

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