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Fluoroquinolone should be reconsidered as empirical therapy for adult inpatient urinary tract infections in tertiary hospital: a perspective descriptive study from the microbiological and cost-effectiveness aspects

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ABSTRACT

Background: Urinary Tract Infections (UTI) has become difficult to treat because of its increasing resistance characteristics to antimicrobial agents, especially to fluoroquinolone. The objective of this study was to describe the effectiveness of fluoroquinolone as empirical therapy for adult inpatient UTI.
Methods: This descriptive cross-sectional study was performed at Prof. Dr. I.G.N.G. Ngoerah Hospital, a tertiary Hospital in Denpasar, Bali, from January 2020 until March 2020. All urine specimens were examined using bioMérieux VITEK® 2 System.
Result: A total of 155 urine samples met the inclusion and exclusion criteria. We found *Escherichia coli* (39.4%) as the most common microbes followed by *Klebsiella pneumoniae* (12.3%). Most of the isolates are multi drug resistant organisms (MDRO) (52.9%) and 57% (49) of the Enterobacteriaceae isolates are extended spectrum beta lactamases (ESBLs). The average duration of the empirical antibiotic therapy was 3.7 days for all fluoroquinolone. Ciprofloxacin (53.5%) is the most common empirical therapy, followed by levofloxacin (16.8%). Antimicrobial sensitivity tests showed that bacteria remained highly sensitive to amikacin (96%) and meropenem (94%). The sensitivity test for ciprofloxacin and levofloxacin was only 26% and 4% respectively. The suitability antibiotic results of fluoroquinolone as empirical therapy were only 20% from 110 isolates. The cost ineffectiveness of fluoroquinolone as empirical therapy is Rp.8,402,400 for 3 months.
Conclusion: We concluded that both fluoroquinolone (ciprofloxacin and levofloxacin) have a very low sensitivity rate and are not cost-effective, therefore the use of those antimicrobial agents as empirical therapy should be reconsidered.

Keywords: fluoroquinolone, empirical therapy, urinary tract infection.
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INTRODUCTION

Urinary tract infection (UTI) is an infection that often occurs in hospitals.[1] UTI is also included in the most infections that occur besides acute respiratory infections (ARI). Epidemiologically, women are more frequently affected by UTI than men.[2,3] This is related to the differentiation from anatomy of the urinary tract between women and men.[4] UTI also has several risk factors that can increase or exacerbate the incidence of UTI, such as genital hygiene, sexual activity, history of recurrent UTI, and other comorbid factors. UTI can be divided into uncomplicated UTI and complicated UTI. Complicated UTIs are theoretically more difficult to treat than non-complicated UTIs but the longer it takes, the more difficult it is to treat UTIs due to the increasing number of UTI cases due to bacteria that are resistant to various types of antibiotics.[2,5]

Gram-negative bacteria are the most common cause of UTI. Among these Gram-negative bacteria, *Escherichia coli* (*E. coli*) is the bacteria with the highest number of causes of UTI.[1] UTI occurs when bacteria enter the urinary tract from the urethra and rise to the bladder which causes cystitis or if it rises to a higher place, namely the kidneys, pyelonephritis can occur which is even more difficult to treat. Then, if the infection is not treated properly, the bacteria can spread from the kidneys to the blood, hereinafter referred to as bacteremia.[6]

Basically, various types of antibiotics can be used to treat UTIs. Several antibiotics that are commonly used as a treatment option for UTIs are trimethoprim-sulfamethoxazole or fluoroquinolone groups such as ciprofloxacin and levofloxacin.[7] In tertiary hospitals which are type A referral hospitals, ciprofloxacin and levofloxacin are the most commonly used antibiotics as antibiotic therapy in UTI cases.[8] However, most Gram-negative bacteria, especially *E. coli* as the most common cause of UTIs, have started to develop high levels of resistance to these fluoroquinolone class antibiotics.[9]

Fluoroquinolone class antibiotics such as ciprofloxacin and levofloxacin, if not used properly, can cause harm. The first is the loss from a microbiological aspect, namely when the antibiotics given do not match the results of the antimicrobial

sensitivity test. Second, the loss in terms of cost effectiveness. Because the empirical antibiotics used turned out to have a very low percentage of sensitivity in cases of adult UTIs due to *E. coli*, the use of these empirical antibiotics was an expenditure that was not cost-effective.

This study aims to find descriptive data regarding the effectiveness of fluoroquinolone antibiotics (ciprofloxacin and levofloxacin) against UTI cases caused by *E. coli* in tertiary hospitals, both from a microbiological and cost-effectiveness standpoint.

METHODS

This study uses a cross-sectional descriptive as a research design. This research was conducted at the Clinical Microbiology Laboratory, Prof. dr. I.G.N.G. Ngoerah hospital, Denpasar, Bali which is a tertiary hospital in Bali. Research data was taken from January 2020 to March 2020 or for 3 months.

The data taken comes from electronic patient medical record data (SIMARS). The data collected were mainly data on patient characteristics (age, gender, empirical therapy used) as well as sample characteristics. Data on the results of identification and sensitivity tests or culture results, were taken from secondary data in the clinical microbiology laboratory. All urine specimens were examined using an automatic identification and sensitivity test machine (bioMérieux VITEK® 2 System.. The inclusion criteria for this study were all urine specimens with the results of the identification test being *E. coli* from patients at Prof. Dr. I.G.N.G. Ngoerah Hospital, both polyclinic patients, inpatients, and patients from the Emergency Room. In addition, all samples must come from patients who are not currently using antibiotic therapy or the patient has used the last antibiotic more than 72 hours before the sample was taken. The exclusion criteria were all specimens that came from outside the Prof. Dr. I.G.N.G. Ngoerah Hospital and all specimens that did not meet the basic principles of microbiological sampling.

Samples for urine culture examination were taken and accommodated using sterile pot containers with screw caps and placed in plastic bags to minimize leakage and contamination. All samples were taken using aseptic techniques and with good and correct microbiological specimen collection principles, namely clean catch urine or midstream urine, suprapubic urine aspiration, and urine from a catheter. Samples that have been taken will be immediately taken to the clinical microbiology laboratory in less than 2 hours, but if the samples taken cannot be sent immediately, then the samples will be stored first in the refrigerator at 4°C. All samples that do not meet the above criteria will be immediately excluded.[10]

All samples that have met the inclusion and exclusion criteria will be continued for microscopic examination, namely Gram staining before later implanting them in agar media and carrying out identification and sensitivity tests using an automatic identification and sensitivity testing machine, namely the bioMérieux VITEK® 2 System.[10,11] Furthermore, all samples with positive *E. coli* urine culture results will be included in the research data which will then be processed using the SPSS version 25 program. Analysis of the cost burden of using fluoroquinolone class of antibiotic therapy was carried out descriptively using cost data from the pharmacy installation at Prof. dr. I.G.N.G. Ngoerah Hospital. The price for ciprofloxacin 200 mg IV is IDR 12,414.00 per vial and the price for levofloxacin 500 mg IV is IDR 23,204.00 per vial.

RESULTS

A total of 155 urine samples met the inclusion and exclusion criteria within a period of three months (1 January 2020 to 31 March 2020). We found *Escherichia coli* with 61 isolates (39.4%) as the most microbes, followed by *Klebsiella pneumoniae* with 19 isolates (12.3%). Apart from that, several other bacteria were also found to cause UTIs as shown in the table below.

Most of the isolates were multi drug resistant organisms (MDRO) as many as 82 isolates (53%) and 57% (49) of the Enterobacteriaceae isolates were extended spectrum beta lactamases (ESBLs), as shown in Figure 1 and Figure 2.

Table 1. Microorganisms from urine culture results.

Microorganism	Frequency	
	Absolute	Percentage
Escherichia coli	61	41%
Klebsiella pneumoniae	19	13%
Other Gram-negative bacteria	18	12%
Acinetobacter baumannii	16	11%
Gram-positive bacteria	10	7%
Candida sp.	8	5%
Enterobacter cloacae	7	5%
Proteus mirabilis	6	4%
Pseudomonas aeruginosa	4	3%

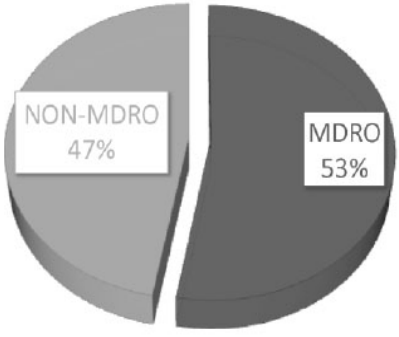

Figure 1. Percentage comparison of the number of MDRO and Non-MDRO bacteria.

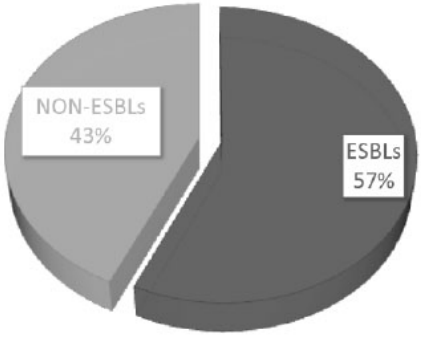

Figure 2. Percentage comparison of the number of ESBL and non-ESBL bacteria.

Ciprofloxacin (54%) was the most frequently used empiric therapy, followed by cefoperazone (18%) and levofloxacin (17%), as shown in Table 2.

Antimicrobial sensitivity tests showed the best sensitivity to amikacin (96%) and meropenem (94%). The sensitivity rates for ciprofloxacin and levofloxacin were only 26% and 4%, respectively, as shown in Figure 3. The results of the compatibility of empirical antibiotics with the culture results of all types of antibiotics were only 40%, while the results of the suitability of fluoroquinolone antibiotics (ciprofloxacin and levofloxacin) as therapy empirically only 20% of the total 110 isolates (table 3).

Based on the data above, quantitative calculations were carried out to calculate the estimated costs incurred due to the discrepancy between empirical antibiotic therapy and the results of the antibiotic sensitivity test. In table 4, it can be seen that the cost-effectiveness of fluoroquinolones as empiric therapy is IDR 8,402,400 for 3 months.

Table 2. Empirical antibiotic.

Empirical Antibiotic	Frequency	
	Absolute	Percentage
Ciprofloxacin	83	54%
Cefoperazone	28	18%
Levofloxacin	26	17%
Ceftriaxone	13	8%
Cefixime	5	3%

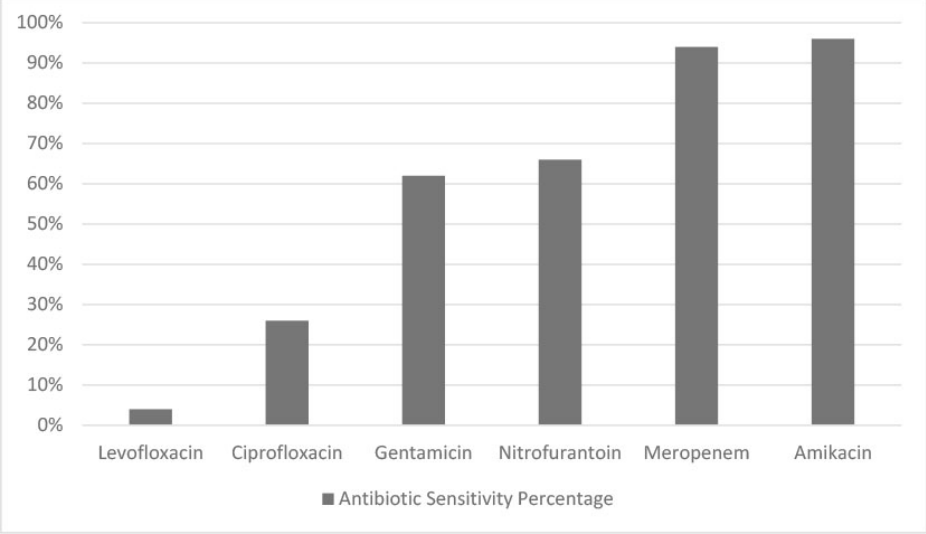

Figure 3. Percentage of antibiotic sensitivity to *E. coli.*

Table 3. Appropriateness of the use of fluoroquinolones as empirical therapy.

Empirical Antibiotic	Appropriate Use of Empirical Therapy and Sensitivity Test Results	
	Appropriate	Not Appropriate
Ciprofloxacin	22	61
Levofloxacin	0	26
TOTAL	22	87

Table 4. Cost calculation of ineffective fluoroquinolones.

Antibiotic	Price (IDR)	Duration (days)	Frequency	Total Cost (IDR)
Ciprofloxacin 200mg IV (BID)	12.414	3	58	4.320.072
Ciprofloxacin 200mg IV (BID)	12.414	6	3	446.904
Levofloxacin 500mg IV (q24h)	23.304	6	26	3.635.424
TOTAL				8.402.400

DISCUSSION

Urinary tract infections are most often caused by *E. coli* bacteria. The results of this study also found that the most common bacteria from all samples was *E. coli* (41%). This is also in accordance with the literature which says that E. coli is the most common bacterium that causes UTI in adults.[5,12,13] In addition, of all *Entereobacteriaceae* collected from research, as many as 57% were ESBLs bacteria. This shows that most of the bacteria that cause UTI from tertiary hospitals are bacteria that are resistant to most antibiotics. These findings are in accordance with epidemiology in several places which say there is an increase in resistance in bacteria that cause adult UTIs.[12,14,15]

Empirical therapy is therapy given to patients based on literature data, national/international guidelines, and local antibiogram pattern data. Ciprofloxacin is an antibiotic that is often prescribed as empiric therapy in UTI cases.[8,16,17] This is in accordance with empirical antibiotic therapy data obtained in this study, namely ciprofloxacin was the most frequently prescribed antibiotic (54%), followed by another fluroquinolone, namely levofloxacin (17%). Levofloxacin is also often used as a therapy for adult UTIs, especially in cases of complicated UTI and pyelonephritis.[8,18] The tertiary hospital where this study data was taken uses fluoroquinolones, especially ciprofloxacin as empirical UTI therapy in adults.

This study also tried to look at the suitability of the use of other empiric antibiotic therapy, and only found a concordance of 40% between the administration of all empirical therapy and the results of the sensitivity test. In addition, based on the data collected in this study, the suitability of using fluoroquinolones as empiric therapy, when compared with the results of antibiotic

sensitivity tests, is very low at 20%. The low concordance rate between empiric therapy and the results of antibiotic sensitivity tests indicates that the use of fluoroquinolones (ciprofloxacin and levofloxacin) should be reconsidered.[7,19]

After doing descriptive calculations, the amount of money spent on inappropriate fluoroquinolone therapy was quite large, namely IDR 8,402,400.00 for three months. Research conducted by Alanazi et al. suggested that the antibiotics with the best level of effectiveness were nitrofurantoin and amoxicillin/clavulanic acid.[20] As for antibiotics with the best level of cost effectiveness is nitrofurantoin.[18,20]

This study also aims to obtain data on the antibiotics with the best sensitivity levels, namely amikacin (96%) and meropenem (94%). Several studies say that the effectiveness of amikacin in cases of UTI is very good, even for cases of UTI caused by ESBL bacteria such as *E. coli*.[21,22] Based on the data presented above, the use of fluoroquinolones as empiric therapy for UTI in adults needs to be considered because it is not effective both from a microbiological and cost perspective.

CONCLUSION

E. coli is the most common cause of UTI in adults with the most empirical therapy being fluoroquinolones, namely ciprofloxacin and levofloxacin. The suitability of giving empiric antibiotic therapy with sensitivity test results is quite low, so giving fluoroquinolone as empiric therapy needs to be reconsidered. Amikacin and Meropenem are the two types of antibiotics that have the best level of sensitivity so that in the future it may be considered for their use as empiric therapy, but it is also necessary to consider the patient's renal function and the restrictions on the use of these two types of antibiotics.

CONFLICT OF INTEREST

The authors declare that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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ETHICAL STATEMENT

Authors have secured informed consent for using medical records and data regarding this manuscript.

AUTHOR CONTRIBUTION

IKAIA involved in concepting the study. IKAIA and MS conducted the study. IKAIA analyses the data. IKAI and MS concepting, designing and supervising the manuscript. All authors prepare the manuscript and agree for this final version of manuscript to be submitted to this journal.

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