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Profile of multidrug-resistant bacteria causing urinary tract infections in inpatients and outpatients in Jakarta and Tangerang

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ABSTRACT

BACKGROUND

Urinary tract infections (UTIs) caused by bacteria occupy the second highest rank of common infectious diseases in the world. Empirical use of antibiotics may give rise to multidrug-resistant (MDR) bacteria because of irrational prescription. Choice of antibiotics to treat UTIs is limited because of MDR bacteria. Thus, this study was conducted to investigate the bacterial antibiotic susceptibility patterns in inpatients and outpatients in Jakarta and Tangerang.

METHODS

Bacterial isolates were obtained from midstream urine specimens from 43 inpatients and 43 outpatients with UTIs in Jakarta and Tangerang. Bacteria were isolated on blood and MacConkey agar media using colony count method. Isolate identification and their susceptibility patterns were performed using VITEK2 compact system according to manufacturers' instructions. Data were analyzed using Chi-square test.

RESULTS

A total of 89 bacterial isolates consisting of 15 bacterial species were successfully isolated from 86 specimens. Gram-negative bacteria were the most common etiology of UTIs in inpatients and outpatients. MDR bacteria were found in 52 of the 89 isolates. ESBL-producing *E. coli* was the most common MDR bacteria. ESBL-producing *E. coli* and other MDR bacteria showed good susceptibility to ertapenem, meropenem, amikacin, and tigecycline. There were no significant differences regarding the MDR bacterial count in inpatients and outpatients (p=0.521).

CONCLUSION

E. coli was found to be the most common MDR bacteria causing UTIs in inpatients and outpatients in Jakarta and Tangerang. Higher resistance to many antibiotics was found in MDR bacterial isolates in inpatients compared to outpatients. MDR bacteria in outpatient UTIs were highly resistant to commonly used antibiotics.

Keywords: MDR bacteria, urinary tract infection, susceptibility pattern

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INTRODUCTION

Urinary tract infection (UTI) is the most common urogenital disease in the world and the second most common infection, [1] with around 150 million people suffering from UTI.[2] The prevalence and incidence of UTIs are still high in the Indonesian population, with the ages of 40-60 years and above 65 years having a prevalence of 3.2% and 20%, respectively.[3] The high prevalence and incidence of UTIs are not only a health problem, but also cause economic problems.[4]

Management of UTIs can be applied in the inpatient and outpatient setting depending on the severity of the patient's UTI. The management of UTIs in both settings requires the use of antibiotics which may often be inappropriate when used empirically, consequently causing antimicrobial resistance and the emergence of multidrug-resistant (MDR) bacteria. Thus, the presence of MDR in UTI-causing bacteria has made the treatment of UTIs to be harder and might cause further complications.[5]

Several studies around the world have reported the antibiotic susceptibility profile of bacteria in UTIs. Every country must have their own guidelines on UTI treatment, including for MDR bacteria. Therefore, data regarding UTIs caused by MDR bacteria and their susceptibility in inpatient and outpatient settings are needed to treat them accordingly and prevent further antimicrobial resistance and complications caused by untreated UTIs.[6]

Most UTI patients in the outpatient setting are treated empirically.[7,8] In most resource-limited health facilities, community acquired urinary tract infections are the predominant type of UTI and are inappropriately treated with antibiotics due to a lack of laboratory services, as well as sufficiently trained medical personnel.[9] Inadvertently, this leads to the emergence and spread of multidrug-resistant (MDR) bacterial strains in the community.[10] Unfortunately, limited data on UTIs in communities, coupled with a lack of antibiotic stewardship and an absence of laboratory services, result in irrational uses of antibiotics, especially the widely available cheap ones, which are often of variable quality.[11,12] Thus, a study should be conducted among outpatients and inpatients attending healthcare facilities in Indonesia to further prevent a rise in the incidence of antimicrobial resistance and MDR bacteria in UTIs.

METHODS

Research design

This study was a cross-sectional study conducted in the Clinical Microbiology Laboratory, Faculty of Medicine, University of Indonesia, from September 2020 until July 2022.

Research subjects

The study consecutively enrolled outpatients with UTIs in community health centers in South Tangerang and inpatients with UTIs in hospitals in Jakarta. The sample size was determined using the hypothesis test formula for 2 independent samples. Using $\alpha = 0.05$, $\beta=0.1$ and effect size = 0.6, the final calculation yielded a total sample of 86 individuals, consisting of 43 inpatients and 43 outpatients. Inclusion criteria for this study were adults aged 18-90 years who had symptoms of uncomplicated UTI. Exclusion criteria for this study were children or pregnant women and patients who consumed antibiotics 3 days prior to the collection of the urinary specimens.

Data and sample collection

A questionnaire was used to collect data on age and gender. About 5–10 mL of clean-catch, mid-stream urine (MSU) samples were self-collected in a sterile urine container after appropriate instructions were provided to the participants. Samples were transported in a cool box at temperatures of between 4 and 8°C to the Clinical Microbiology Laboratory, Faculty of Medicine, University of Indonesia, for processing within 2 h of collection.

Culture and susceptibility testing

Urine specimens were inoculated on blood and MacConkey agar plates using a 0.001 mL loop. The agar plates were then incubated at 35-37ºC for 18-24 hours. Bacterial morphology was observed and counted in CFU/mL. Urinary specimens had significant bacterial growth of UTI-causing bacteria with a count of $\geq 10^5$ CFU/mL. Identification of significant bacterial growth was performed using Gram staining and VITEK2 compact system (bioMérieux). VITEK ID GN cards were used for identification of Gram-negative bacteria, while VITEK ID GP cards were used for Gram-positive bacteria. Colonies with significant growth were tested by antimicrobial susceptibility testing (AST). Inoculum suspension was adjusted to 3 mL standardized saline (0.45%-0.5% NaCl, pH 4.5-7) with suspension turbidity to 0.5 McFarland which is equivalent to 1.5 x 10^8 CFU/mL. VITEK AST-GN93 cards were used for AST of Gram-negative bacteria and VITEK AST-GP67 cards for Gram-positive bacteria. Interpretation of AST results was based on minimal inhibitory concentration (MIC) of every antibiotic in the VITEK2 test panel. The antibiotics tested on VITEK AST-GN93 cards (bioMérieux) were ampicillin, ampicillin-sulbactam, piperacillin-tazobactam, cefazolin, ceftazidime, ceftriaxone, cefepime, aztreonam, ertapenem, meropenem, amikacin, gentamicin, ciprofloxacin, tigecycline, nitrofurantoin, and trimethoprim-sulfamethoxazole (TMP-SMX). The antibiotics tested in VITEK ID/AST-GP67 (bioMérieux) were benzylpenicillin, cefoxitin screen, ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, oxacillin, cefalexin, cefazolin, ceftriaxone, gentamicin, streptomycin, ciprofloxacin, levofloxacin, moxifloxacin, erythromycin, clindamycin, quinupristin-dalfopristin, linezolid, vancomycin, tetracycline, tigecycline, nitrofurantoin, rifampicin, and TMP-SMX.

Statistical analysis

Data were further analyzed statistically and descriptively. Bacteria that are classified as MDR are bacteria that are resistant to at least one antibiotic from three different classes. Statistical analysis was conducted using IBM Statistics SPSS 24.0 to analyze the difference in MDR proportions of patients in inpatient and outpatient settings using chi square test, with p-value less than 0.05 indicating a significant difference. Lambda correlation test was also done to analyze the correlation between nitrite and leukocyte esterase in *E. coli* and *K. pneumoniae* isolates. The MDR proportions of patients in inpatient and outpatient settings were shown in percentage form. The AST results were shown in the form of graphs.

Ethical clearance

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, University of Indonesia/Cipto Mangunkusumo Hospital (HREC-FMUI/CMH), Jakarta, Indonesia, under No. KET-471/UN2.F1/ETIK/PPM.00.02/2019. All patients gave informed consent prior to the study.

RESULTS

Sample characteristics

Urine specimens were collected from 86 patients. The mean age of all the patients was 53.0±18.0 years. There was no significant difference in age between male and female patients ($p>0.05$). The characteristics of the patients are shown in Table 1. Out of 95 urine specimens, 86 specimens had significant growth with a colony count $\geq 10^5$ CFU/mL that were collected from 43 patients in inpatient and 52 patients in outpatient settings. All significant specimen growths showed a single morphology except three specimens that had two different bacterial isolates which resulted in a total of 89 bacterial isolates. From the urine dipstick test, 44 urine specimens were found to be nitrite positive while 42 urine specimens were nitrite negative. Regarding the leukocyte esterase (LE) test, 49 urine specimens were LE positive with 5 urine specimens testing leukocytes +++ that is

Table 1. Characteristics of inpatients and outpatients

Characteristics	Inpatients (n=43)	Outpatients (n=43)	p value
Age (years)	58.0 ± 17.0	47.0 ± 17.0	> 0.05
Gender			
Male	18	10	0.065
Female	25	33	
Previous history of UTIs			
Yes	5	8	0.000
No	18	31	
Unknown	20	4	
Previous antibiotic use past 3 months			
Yes	11	10	0.146
No	18	26	
Unknown	14	7	

equivalent to 500 leukocytes/μL. On lambda correlation test, both nitrite (r=0.125) and leukocyte esterase (r=0.1) had weak correlation to the presence of MDR bacteria. Among the 89 bacterial isolates, 14 bacterial isolates were Gram positive bacteria while 75 bacterial isolates were Gram negative. The distribution of bacterial Gram stain in the inpatient and outpatient settings were different. In the inpatient setting, there were 4 Gram positive bacterial isolates and 42 Gram negative bacterial isolates. On the other hand, in the outpatient setting, there were 10 Gram positive bacterial isolates and 33 Gram negative bacterial isolates. Table 2 shows the UTI patients' sample characteristics in inpatient and outpatient settings.

Profile MDR bacteria causing UTIs in inpatients and outpatients

The profile of MDR bacteria causing UTIs in inpatients and outpatients can be seen in Figure 1. There were 10 species of Gram-negative bacteria and 5 species of Gram-positive bacteria. Among all the bacterial isolates, there were 28 bacterial isolates that were found to be MDR in the inpatient (61%) and 24 bacterial isolates in the outpatient (56 %) settings. When analyzed statistically, there were no significant differences regarding the MDR bacterial count in inpatients and outpatients among Gram positive (p=1.00) and Gram-negative bacteria (p=0.521).

The most common MDR bacteria in both inpatients and outpatients were ESBL-producing *E. coli*. Regarding Gram-positive bacteria, *E. faecalis* and *E. faecium* were the most common MDR bacteria causing UTI in inpatients (Figure 2). Another ESBL-producing bacteria, *K. pneumoniae*, was also identified but only found in inpatients. Table 3 shows the profile of ESBL-producing *E. coli* and *K. pneumoniae* causing UTIs in inpatients and outpatients in Jakarta and Tangerang.

Table 2. UTI patients' sample characteristics in inpatients and outpatients settings

Isolate characteristics		Inpatients (n=43)	Outpatients (n=43)
Significant bacterial growth		43 (100%)	43 (100%)
Total number of bacterial isolates		46 (100%)	43 (100%)
Gram positive bacteria		4 (8.7%)	10 (23.2%)
Gram negative bacteria		42 (91.3%)	33 (76.7%)
Nitrite positive	Gram positive bacteria	1	2
	Gram negative bacteria	15	27
Leukocyte esterase positive	Gram positive bacteria	2	4
	Gram negative bacteria	22	21

Note : UTI : urinary tract infection

Table 3. Profile of ESBL-producing bacteria causing UTIs in inpatients and outpatients

ESBL Bacteria	Inpatients (n=15)		Outpatients (n=9)		p value
	n	%	n	%	
Escherichia coli	10	52.6	9	47.4	0.051
Klebsiella pneumoniae	5	100.0	0	0	

Note = ESBL : extended-spectrum beta-lactamase

Profile of antimicrobial susceptibility of MDR bacteria causing UTIs in inpatients and outpatients

Figure 3 shows the profile of antimicrobial susceptibility of non-ESBL-producing MDR *E. coli* in inpatients and outpatients. The non-ESBL-producing MDR *E. coli* were more susceptible than did the ESBL-producing MDR *E. coli* in both inpatients and outpatients. However, non-ESBL-producing MDR *E. coli* in inpatients were found to have reduced susceptibility to ciprofloxacin. The susceptibility of non-ESBL-producing MDR *E. coli* to ampicillin and ampicillin/sulbactam was less than 60% in both inpatients and outpatients. Susceptibility to trimethoprim-sulfamethoxazole was better in outpatients than in inpatients.

Figure 4 shows the antimicrobial susceptibility pattern of ESBL-producing MDR *E. coli* in inpatients and outpatients. ESBL-producing MDR *E. coli* have low susceptibility to many commonly used antibiotics. Susceptibility to nitrofurantoin was more than 60% in both inpatients and outpatients, but unfortunately this drug is not available in Indonesia. The susceptibility to piperacillin-tazobactam was 90% in inpatients. The susceptibility of ESBL-producing MDR *E. coli* was 100% to ertapenem, meropenem, amikacin, and tigecycline in the outpatient setting. Other antibiotics in outpatients with good susceptibility were gentamicin with a susceptibility rate of 55.6%.

Klebsiella pneumoniae was found in both inpatients and outpatients. However, MDR *K. pneumoniae* including ESBL-producing *K. pneumoniae* were only found in inpatients. Figure 5 shows the antimicrobial susceptibility pattern of ESBL-producing MDR *K. pneumoniae* in inpatients. Low susceptibility was also found to various antibiotics. Full susceptibilities were found to ertapenem, meropenem, and amikacin. Furthermore, antibiotics with good susceptibility were piperacillin-tazobactam, gentamicin, and tigecycline with susceptibility rates of 80%, 60%, and 60%, respectively. Fully resistant bacteria were also found to ampicillin, ceftriaxone, aztreonam, ciprofloxacin, and trimethoprim-sulfamethoxazole.

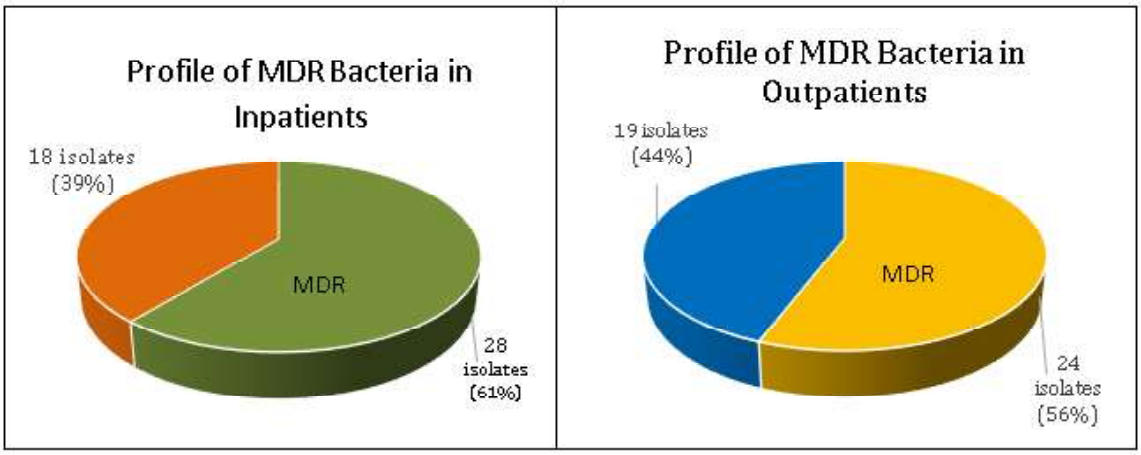

Figure 1. Profile of multiple drug resistance bacteria causing urinary tract infections in inpatients and outpatients

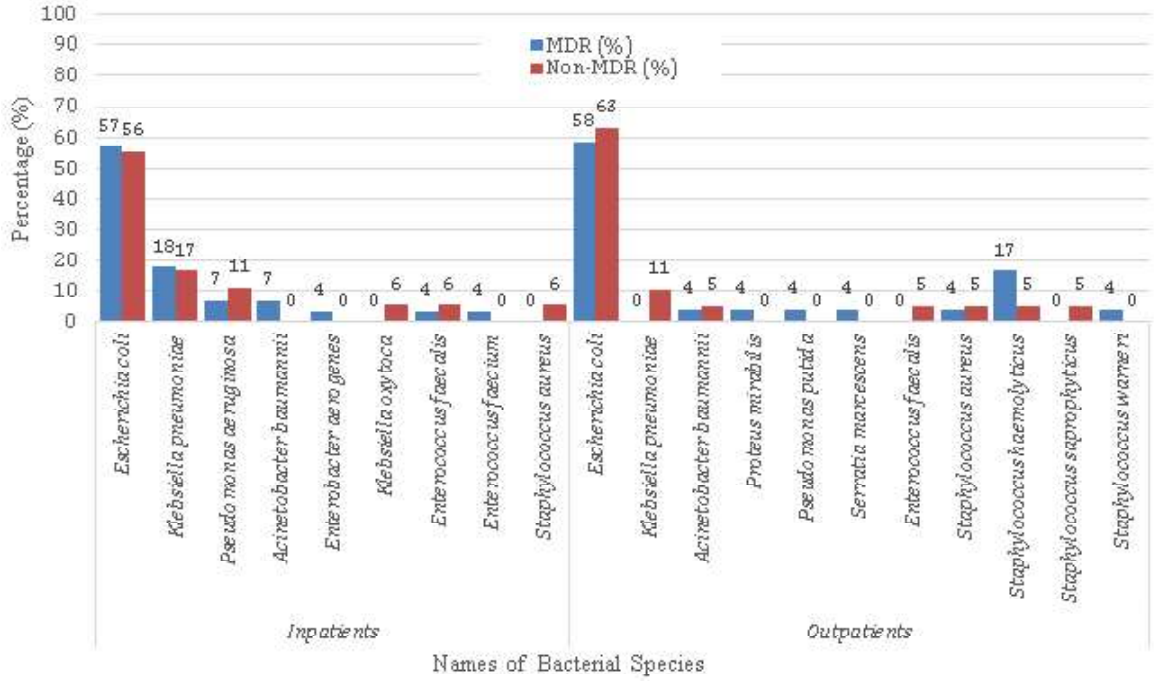

Figure 2. Profile of multiple drug resistance bacteria causing urinary tract infections in inpatients and outpatients

DISCUSSION

In this study, MDR bacteria causing UTIs were more frequently Gram-negative than Gram-positive in both inpatients and outpatients. Similar findings were obtained in many studies.[13-17] Thus, UTI caused by Gram-negative bacteria are harder to treat, because more antibiotics are no longer effective and this may increase the resistance rate. Therefore, increased awareness of MDR

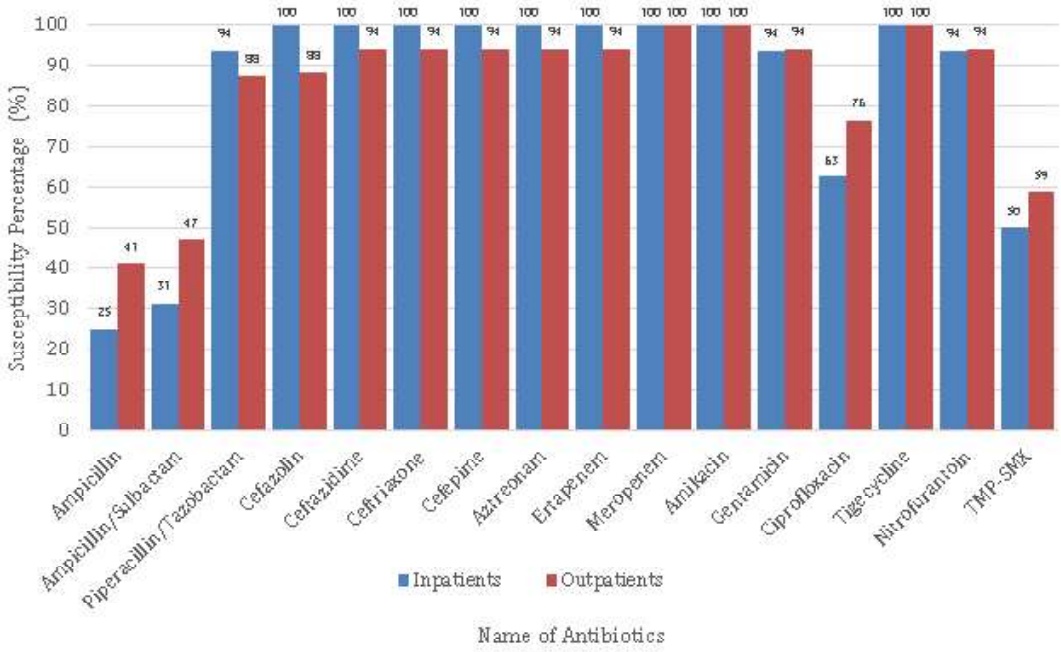

Figure 3. Susceptibility profile of non- extended-spectrum beta lactamase-producing multiple drug resistant *E. coli*. * TMP-SMX, trimethoprim-sulfamethoxazole

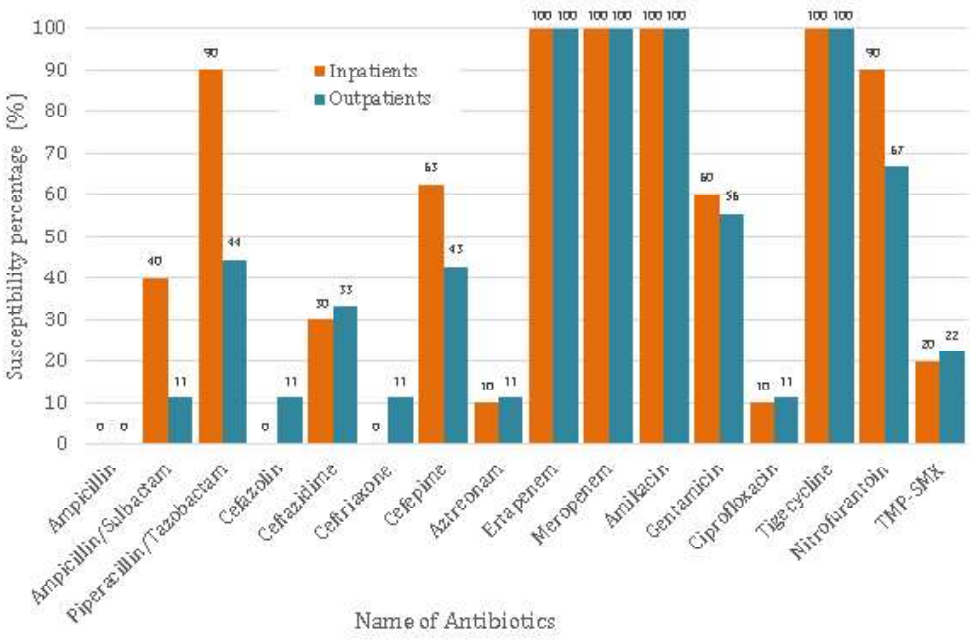

Figure 4. Susceptibility profile of extended-spectrum beta lactamase-producing multiple drug resistant *E. coli*. *TMP-SMX, trimethoprim-sulfamethoxazole

in Gram-negative bacteria is needed especially when *E. coli* or *K. pneumoniae* are identified because they may produce ESBL.

The MDR bacterial pattern was found to be different for UTI in inpatients and outpatients. Multiple drug resistance *E. coli* were mostly ESBL-producing (63.3%) and only 36.7% were non-ESBL-producing. Regarding the setting of the patient, ESBL-producing MDR *E. coli* were mostly found in inpatient (52.6%) compared to outpatient settings (47.4%). This finding is in accordance with the study in Algeria by Nabti et al. [14] that reported ESBL-producing MDR *E. coli* were mostly found in inpatient settings. In

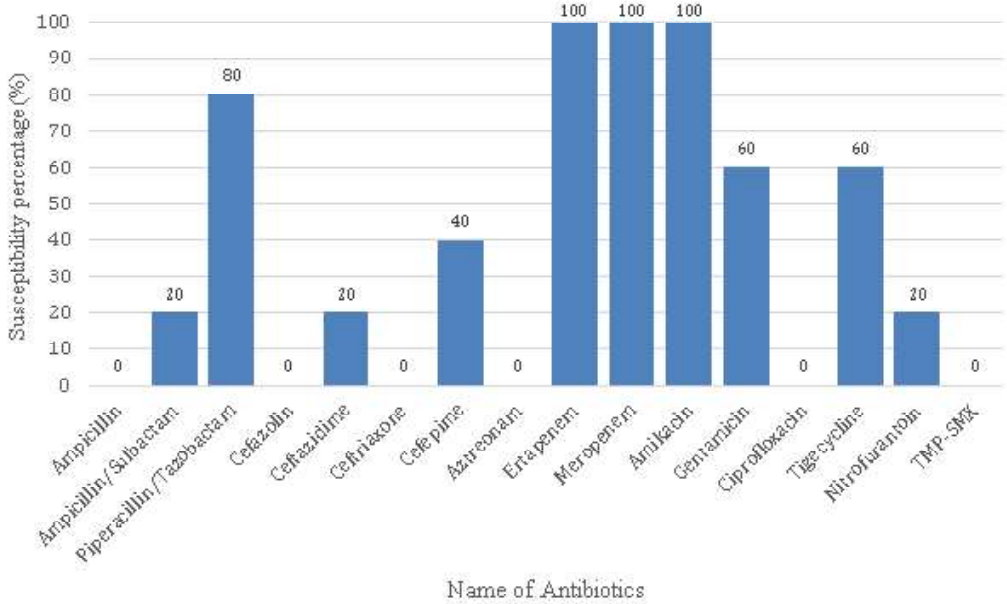

Figure 5. Susceptibility profile of extended-spectrum beta lactamase-producing multiple drug resistant *K. pneumoniae* in inpatients. *TMP-SMX, trimethoprim-sulfamethoxazole

contrast, this finding is different from a hospital study in Pakistan that reported the domination of MDR *E. coli* in UTI by non-ESBL-producing species.[15]

Extended-spectrum beta-lactamase bacteria were found more in inpatients than in outpatients (62.5% vs 37.5%). The ESBL bacteria found in this study were *E. coli* and *K. pneumoniae*. Among all ESBL producers in inpatients and outpatients, *E. coli* was found to be the most common ESBL producer (79.2%). Two studies also reported the same finding regarding *E. coli* being the most common ESBL producer in UTI patients.[15-17] Thus, the presence of ESBL-producing *E. coli* as the most common MDR bacteria in this study may be a consideration to form a new strategy to treat MDR causing UTIs.[18] Another study in Luxembourg conducted in children with UTI also found that *E. coli* was the most common MDR bacterial isolate.[19]

Another ESBL-producing MDR bacteria found in this study was *K. pneumoniae* which was only found in inpatients. This finding is supported by various studies that only found ESBL-producing *K. pneumoniae* in the inpatient setting and as a main cause of nosocomial UTI outbreaks in Sri Lanka and Japan.[15,20] A prevalence study conducted in Iran also found ESBL-producing MDR *K. pneumoniae* to be more commonly found in inpatients compared to outpatients.[21] Therefore, UTIs caused by ESBL-producing MDR *K. pneumoniae* in inpatients must be treated rationally and the practice of infection prevention and control must be done to prevent transmission to other patients.

The most common MDR Gram-positive bacteria in this study were *E. faecalis* and *E. faecium*, mainly found in inpatient settings. A study in Bangladesh also reported the same species in UTIs in inpatient settings.[22] Another study in China reporting on the resistance rate of *E. faecalis* found that more than 50% of the bacterial isolates were MDR.[23] The high rate of resistance of Gram-positive bacteria in UTI patients might be caused by the empirical use of antibiotics not mainly aimed at Gram-positive bacteria. This is due to the clinicians mostly thinking the main cause of UTI to be Gram-negative bacteria and neglecting Gram-positive bacteria. Thus, clinicians must be more aware of bacterial patterns and their susceptibility in UTI patients, especially inpatients, who have received long-term care.

In spite of the fact that MDR bacterial are more frequently found in inpatients than in outpatients, there is no significant difference regarding the number of MDR isolates in both settings. This finding is similar to a report in Mexico by Zavala-Cerna et al.[24] that reported a high rate of MDR bacteria in outpatient settings. Thus, this finding might raise concerns about the increasing numbers of MDR bacteria in outpatient settings. The increasing number of MDR bacteria in outpatient settings might be caused by the increase in ESBL-producing bacteria and the empirically prescribed antibiotics. Therefore, prescription of antibiotics for the treatment of UTI patients in outpatients must follow the local report of bacterial profile and their susceptibility to antibiotics.

The susceptibility profiles to antibiotics in this study were found to be slightly different between MDR bacteria in inpatients and outpatients. Non-ESBL-producing MDR *E. coli* in inpatients were found to have reduced susceptibility to ciprofloxacin. Susceptibility to trimethoprim-sulfamethoxazole was better in outpatients than in inpatients. This finding is similar with the study in Indonesia by Rosana et al.[25] that reported a significant difference in the efficacy of trimethoprim-sulfamethoxazole in outpatients, because it was almost twice less effective than in hospitalized patients.

Extended-spectrum beta-lactamase - producing MDR *E. coli* was found to be still susceptible to ertapenem, meropenem, amikacin, tigecycline, piperacillin-tazobactam, and nitrofurantoin. Similar susceptibility profiles were observed in ESBL-producing MDR *K. pneumoniae* which showed good susceptibility to ertapenem, meropenem, amikacin, and

piperacillin-tazobactam. The susceptibility profiles to antibiotics were similar to a study conducted in Iran that reported ESBL-producing *E. coli* and *K. pneumoniae* still showed good susceptibility to the carbapenem group of antibiotics and piperacillin-tazobactam.[26] On the other hand, non-ESBL-producing MDR *E. coli* showed good susceptibility to many antibiotics except to ampicillin and ampicillin-sulbactam. Reduced susceptibility to ciprofloxacin was also found. This finding is concerning, in that ciprofloxacin, being a fluoroquinolone antibiotic, is one of the most important antimicrobials, because it plays a role in the treatment of more severe infections, such as septicemia. The possible explanation regarding the increase of resistance to ciprofloxacin is due to its empirical use for the therapy of UTI.[27] Thus, it is recommended to limit its uses to clear therapeutic indications. Overall, this study reported similar susceptibility patterns as a study conducted in Dr. Pirngadi General Hospital, Medan, that also found that MDR bacteria were still susceptible to amikacin and meropenem.[28] Another similar finding was also reported in Iran that found that UTI patients in inpatient settings were still susceptible to imipenem and amikacin, while UTI patients in outpatient settings were still susceptible to amikacin and nitrofurantoin.[17] However, nitrofurantoin is not available in Indonesia as of the writing of this study although the present study and several other studies reported that nitrofurantoin still have good efficacy.

Based on the findings reported in this study, it is recommended that the administration of antibiotics for UTI patients with MDR bacteria rely on the bacterial species isolated and the treatment setting. If the pathogen is ESBL-producing MDR *E. coli*, amikacin, tigecycline, piperacillin-tazobactam, or a carbapenem group antibiotic may be given to UTIs in inpatients. In outpatients, nitrofurantoin may be recommended due to the good efficacy. However, as there are no nitrofurantoin available in Indonesia as of this current writing, alternative oral antibiotics such as gentamicin may be given. If the etiologic agent is non-ESBL-producing MDR *E. coli* in outpatients, oral ciprofloxacin or trimethoprim-sulfamethoxazole may be considered to be given. Rosana et al.[8] reported that another antibiotic that can also be used as one of the primary medications for uncomplicated UTIs in outpatients is fosfomycin-trometamol, that is supported by the guidelines of the Infectious Disease Society of America (IDSA), European Association of Urology (EAU), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Indonesian Society of Obstetrics and Gynecology. In inpatient settings, 3rd generation cephalosporins such as ceftriaxone or aminoglycoside antibiotics such as gentamicin may be considered for administration. On the other hand, the recommended antibiotics are different for ESBL-producing MDR *K. pneumoniae* in inpatients that only have good susceptibility to carbapenem group antibiotics such as meropenem and amikacin.

Possible study limitations include 1) the single-hospital setting, which might not represent the scenario of other hospitals and 2) missing information on referring departments for outpatients and other clinical characteristics that might be associated with culture positivity and resistance, as the study was based on available hospital records.

CONCLUSION

ESBL-producing *E. coli* and *K. pneumoniae* were the most common MDR bacteria causing UTIs in inpatients and outpatients in Jakarta and Tangerang. MDR bacteria causing UTIs in inpatients have good susceptibility to ertapenem, meropenem, amikacin, and tigecycline. Amikacin and carbapenem group antibiotics such as meropenem can be antibiotics of choice to treat MDR UTI caused by ESBL-producing *K. pneumoniae*. Gentamicin, ciprofloxacin, trimethoprim-sulfamethoxazole or fosfomycin-trometamol may be an option to treat MDR UTIs of outpatients in Jakarta and Tangerang. We recommend continuous MDR surveillance

of uropathogens aim at developing evidence-based empirical treatment guidelines.

CONFLICT OF INTEREST

The author(s) declare that they have no conflict of interests.

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AUTHOR CONTRIBUTIONS

YR and GK designed the study. LH and EAS supervised fieldwork and collected data and samples. YR and GK analyzed the results. YR and GK wrote the first draft of the report, with revisions and input from LH and EAS. All authors contributed to revisions and approved the final version.

DATA AVAILABILITY STATEMENT

All data have been included in the manuscript.

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