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The profile of bacteria isolated from urine culture of adults with urinary tract infection in Yogyakarta 2007-2022

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ABSTRACT

Local data regarding antimicrobial susceptibility patterns of bacteria from urine culture is limited in Indonesia, particularly in Yogyakarta. This study was conducted to provide epidemiology data of bacteria and their resistance profile, including the profile of bacteria that producing extended-spectrum beta-lactamase (ESBL) and carbapenemase in the urine of patients with urinary tract infection (UTI) in Yogyakarta. A descriptive retrospective study was conducted by assessing laboratory records of urine culture from adult patients at the Microbiology Laboratory, Department of Microbiology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta between 2007 and 2022. Of the 842 urine cultures, 464 (55.11%) isolates were recovered. Among these isolates, 50 (10.78%) were fungi, 67 (14.44%) were Gram-positive bacteria, and 347 (74.78%) were Gram-negative bacteria. *Enterococcus* sp. (41 (61.19%)) was the most bacteria found in the Gram-positive bacteria group, while *Escherichia coli* (38.90%) were the most bacteria found in the Gram-negative bacteria group. This study also identified Gram-negative bacteria producing ESBL enzymes (58.70%) and carbapenemases (27.94%). Gram-negative bacteria are the most common bacteria found in urine cultures of adult UTI patients in Yogyakarta, and the resistance profile of these bacteria is concerning.

ABSTRAK

Data lokal terkait pola kepekaan kuman terhadap antimikroba pada urin relatif jarang dijumpai di Indonesia, khususnya di Yogyakarta. Penelitian ini bertujuan untuk menyediakan data epidemiologi terkait bakteri dan profil kepekaannya, termasuk profil bakteri penghasil *extended-spectrum beta-lactamase* (ESBL) dan *carbapenemase* pada urin pasien dewasa dengan infeksi saluran kemih (ISK) di Yogyakarta. Penelitian retrospektif deskriptif dilakukan dengan menilai catatan laboratorium kultur urin dari pasien dewasa di Laboratorium Mikrobiologi, Fakultas Kedokteran, Kesehatan Masyarakat, dan Keperawatan UGM, Yogyakarta antara tahun 2007 hingga 2022. Dari 842 kultur urin, 464 (55,11%) isolat ditemukan. Diantara isolat tersebut, 50 (10.78%) adalah jamur, 67 (14,44%) bakteri Gram positif, dan 347 (74,78%) bakteri Gram negatif. *Enterococcus* sp. (41 (61,19%) merupakan bakteri terbanyak yang ditemukan pada kelompok bakteri Gram positif, sedangkan, sedangkan *Escherichia coli* (38,90%) merupakan bakteri terbanyak yang ditemukan pada kelompok bakteri Gram negatif. Penelitian ini juga mengidentifikasi bakteri Gram negatif penghasil enzim ESBL (58,70%) dan carbapenemase (27,94%). Bakteri Gram negatif adalah bakteri yang paling umum ditemukan pada kultur urin pasien ISK dewasa di Yogyakarta, dan profil resistensi bakteri ini mengkhawatirkan.

Keywords:
bacteria;
infection;
urine;
urinary tract infection;
Yogyakarta

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INTRODUCTION

Urinary tract infections (UTIs) can cause significant public health problems, particularly severe infections which can be a major economic burden on the healthcare system and deter patients from an optimal quality of life.[1] It affects 150 million people each year worldwide with high recurrence rates and rehospitalization.[1,2] UTIs are commonly treated with β-lactam antibiotics that raised a global concern for the emergence of antimicrobial resistance including extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing bacteria.[3,4] These resistance, in addition to the existing patient's comorbidities or risk factors, and the limited choice of effective antibiotics, increase the number of attributable deaths, disability-adjusted life years, and the economic burden of the infections.[1,4,5]

Careful assessment of signs, symptoms, and history of disease are important components to diagnose clinical UTI. However urine culture is crucial to identify the cause of infection and establish the diagnosis.[6] The urine culture is a part of diagnostic stewardship that can supply information on the causative agents and their susceptibility patterns.[6] Therefore, it will subsequently facilitate the most suitable antibiotic treatment, reduce cost, and improve patient outcomes.[6,7] However, urine culture is not always available in Indonesia and many limited resources countries.[8] It also required several days to produce a result.[8]

Local surveillance for UTI-causing pathogens and antimicrobial susceptibility is necessary in the absence of urine culture.[9] It will also share benefits in predicting the cause of infection as well as the empiric antibiotic treatment of UTI patients in the same area or similar characteristics of environment.[9] However, the data was scarcely available or published in limited-resources areas, particularly in Yogyakarta. This study was conducted to supply epidemiology data of bacteria and their resistance profile, including the profile of ESBL- and meropenemase-producing bacteria from the UTI patients in Yogyakarta.

MATERIAL AND METHODS

Design of study

A descriptive retrospective study was conducted by collecting data of urine culture from a register of laboratory records (secondary data) at the Microbiology Laboratory, Department of Microbiology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta during the period of 2007-2022. API (BioMerieux) was used for microorganism identification, then the susceptibility test was conducted with a disk diffusion method to evaluate their sensitivity against antibiotics on Mueller-Hinton agar. Result interpretation was performed following the Performance Standards for Antimicrobial Susceptibility Testing of Clinical and Laboratory Standards Institute (CLSI) M100.

The CLSI definition was used in this study to screen ESBL producer which can be identified from their phenotypic resistance against extended penicillin, monobactam (aztreonam), 3rd generation cephalosporins with or without resistance against 4th generation cephalosporins.[10] Carbapenemase producer was identified from their resistant trait against one or more carbapenems (i.e. meropenem, imipenem, ertapenem, or doripenem) phenotypically.[10] Meropenem is used to screen carbapenemase producers as it offers the best sensitivity and specificity features compared to other carbapenems.[11]

Data analysis

Data were collected using an anonymous data sheet to keep patient confidentiality and analyzed using STATA 17 ME. The species or genus of microbes that were recovered from the urine culture were tabulated, also their susceptibility profile against the antibiotics tested. Summary statistics was conducted for descriptive study using the command "tab" to obtain frequency distribution tables, cross-tabulation, or two-way tables. The positive results were presented in the frequency distribution table [n (%)] with the detail of calculation in the footnote of TABLE 2 and 3. A total of 842 urine cultures from adult (18 y.o. or older) patients were documented during the study period. Before the study initiation, ethical approval was obtained from the Institutional Review Board (The Medical and Health Research Ethics Committee (MHREC)) of Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta (Reference number: KE/FK/0052/EC/2023).

RESULTS

Of the 842 urine cultures, 464 (55.11%) isolates were recovered during examination. Among those isolates, we identified 50 (10.78%) fungal isolates, 67 (14.44%) Gram-positive isolates, and 347 (74.78%) Gram-negative isolates.

Gram-positive isolates recovered from the urine culture

Among Gram-positive bacteria isolates, the most frequent bacteria identified in UTIs were *Enterococcus* sp. [41 (61.19%)], followed by *Staphylococcus aureus* [12 (17.91%)], *Enterococcus faecalis* [11 (16.42%)], *Streptococcus agalactiae* [2 (2.99%)], and *S. pneumoniae* [1 (1.49%)] (TABLE 1).

ESBL-producing and Gram-negative isolates recovered from the urine culture

This research elucidated that the most common Gram-negative bacteria identified from urine patients with UTIs were *E. coli*, accounted for 38.90% of total Gram-negative isolates (TABLE 2). The other Gram-negative bacteria recovered from those cultures were *Pseudomonas* sp. [60 (17.29%)], *P. aeruginosa* [42 (12.10%)], *Klebsiella pneumoniae* [38 (10.95%)], *Enterobacter* sp. [12 (3.46%)], *Proteus mirabilis* [10 (2.88%)], *Klebsiella* sp. [8 (2.31%)], *K. aerogenes* (also known as *E. aerogenes*) [4 (1.15%)], *P. fluorescens* [4 (1.15%)], *Acinetobacter baumannii* [3 (0.86%)], *Citrobacter* sp. [3 (0.86%)], *Providencia rettgeri* [3 (0.86%)], *Proteus penneri* (2 (0.58%)), *Proteus* sp. [2 (0.58%)], *P. putida* [2 (0.58%)], *Serratia* sp. [2 (0.58%)], and less common Gram-negative bacteria [17 (4.90%)].

TABLE 1. Gram-positive bacteria isolated from urine samples of UTI patients in Yogyakarta 2007-2022

Name of bacteria/species	n (%)
Enterococcus sp.	41 (61.19)
S. aureus	12 (17.91)
E. faecalis	11 (16.42)
S. agalactiae	2 (2.99)
S. pneumoniae	1 (1.49)
Total	67 (100.00)

Bacteria with "sp." means that the isolate identification was only up to genus level

TABLE 2. Gram-negative bacteria which isolated from urine samples of UTI patients and ESBL-producing pathogens in Yogyakarta 2007-2022

Name of bacteria/ spesies	Isolates recovered from urine samples [n (%)]*	Isolates tested for ESBL [n (%)]**	Isolates with ESBL phenotypes [n(%)]***
E. coli	135 (38.9)	135(100)	57 (42.22)
Pseudomonas sp.	60 (17.29)	55 (91.67)	49 (89.09)
P. aeruginosa	42 (12.1)	41 (97.62)	35 (85.37)
K. pneumoniae	38 (10.95)	38 (100)	20 (52.63)
Enterobacter sp.	12 (3.45)	12 (100)	7 (58.33)
P. mirabilis	10 (2.88)	9 (90)	1 (11.11)
Klebsiella sp.	8 (2.30)	8 (100)	5 (62.5)
K. aerogenes	4 (1.15)	4 (100)	4 (100)
P. fluorescens	4 (1.15)	4 (100)	3 (75)
A. baumannii	3 (0.86)	3 (100)	1 (33.33)
Citrobacter sp.	3 (0.86)	3 (100)	2 (66.67)
P. rettgeri	3 (0.86)	3 (100)	1 (33.33)
P. penneri	2 (0.58)	2 (100)	1 (50)
Proteus sp.	2 (0.58)	2 (100)	1 (50)
P. putida	2 (0.58)	2 (100)	1 (50)
Serratia sp.	2 (0.58)	2 (100)	1 (50)
S. maltophilia	1 (0.29)	1 (100)	0 (0)
Escherichia sp.	1 (0.29)	1 (100)	0 (0)
E. fergusonii	1 (0.29)	1 (100)	1 (100)
E. cloacae	1 (0.29)	1 (100)	1 (100)
A. caviae	1 (0.29)	1 (100)	1 (100)
B. pseudomallei	1 (0.29)	1 (100)	1 (100)
C. youngae	1 (0.29)	1 (100)	0 (0)
Kluyvera sp.	1 (0.29)	1 (100)	0 (0)
Leclercia sp.	1 (0.29)	1 (100)	0 (0)
P. alcaligenes	1 (0.29)	1 (100)	1 (100)
P. alcalifaciens	1 (0.29)	1 (100)	0 (0)
S. marcescens	1 (0.29)	1 (100)	1 (100)
S. odorifera	1 (0.29)	N/D	N/D
S. liquefaciens	1 (0.29)	1 (100)	1 (100)
Yersinia rohdei	1 (0.29)	1 (100)	1 (100)
Edwardsiella tarda	1 (0.29)	1 (100)	1 (100)
Edwardsiella sp.	1 (0.29)	1 (100)	1 (100)
Total	347 (100)	339 (97.69)	199 (58.70)

N/D: no data; (%)* is the number of Gram-negative isolates divided by total of Gram-negative isolates recovered from the urine culture; (%)** is the number of Gram-negative isolates which were tested for ESBL phenotypes divided by total of respective Gram-negative species or isolates recovered from the urine culture; (%)***) is the number of Gram-negative isolates with ESBL phenotypes divided by total of respective Gram-negative isolates or species which were tested for ESBL phenotypes; Bacteria with "sp." means that the isolate identification was only up to genus level

TABLE 3. Gram-negative carbapenem-resistant bacteria from urine samples of UTI patients in Yogyakarta 2007-2022

Name of bacteria/ Species	Isolates tested for carbapenem-resistant phenotype [n (%)]$^{\phi}$	Isolates with carbapenem-resistant phenotype [n (%)]$^{\phi\phi}$
Pseudomonas sp.	60 (100)	27 (45)
E. coli	135 (100)	23 (17.04)
K. pneumoniae	38 (100)	10 (26.32)
P. aeruginosa	40 (95.24)	10 (25)
Enterobacter sp.	12 (100)	5 (41.67)
Klebsiella sp.	8 (100)	4 (50)
P. fluorescens	4 (100)	3 (75)
Serratia sp.	2 (100)	2 (100)
Proteus sp.	2 (100)	1 (50)
Citrobacter sp.	2 (66.67)	1 (50)
P. rettgeri	3 (100)	1 (33.33)
A. caviae	1 (100)	1 (100)
B. pseudomallei	1 (100)	1 (100)
Edwardsiella sp.	1 (100)	1 (100)
E. tarda	1 (100)	1 (100)
Leclercia sp.	1 (100)	1 (100)
S. liquefaciens	1 (100)	1 (100)
Y. rohdei	1 (100)	1 (100)
P. mirabilis	10 (100)	1 (10)
A. baumannii	3 (100)	0 (0)
C. youngae	1 (100)	0 (0)
E. cloacae	1 (100)	0 (0)
K. aerogenes	4 (100)	0 (0)
E. fergusonii	1 (100)	0 (0)
Escherichia sp.	1 (100)	0 (0)
Kluyvera sp.	1 (100)	0 (0)
P. penneri	1 (50)	0 (0)
P. alcalifaciens	1 (100)	0 (0)
P. alcaligenes	1 (100)	0 (0)
P. putida	2 (100)	0 (0)
S. marcescens	1 (100)	0 (0)
S. odorifera	1 (100)	0 (0)
Total	342	95 (27.94)

(%)$^{\phi}$ is the number of gram-negative isolates or species which were tested for carbapenem-resistant phenotypes divided by total of respective gram-negative isolates which recovered from the urine culture; (%)$^{\phi\phi}$ is the number of gram-negative isolates with carbapene- resistant phenotypes divided by total of respective gram-negative isolates which were tested for carbapenem-resistant phenotypes; Bacteria with “sp.” means that the isolate identification was only up to genus level

During the study period, a total of 199 (58.70%) ESBL-producing gram-negative bacteria were identified from those isolates. We identified that 57 (42.22%) *E. coli* phenotypically exhibited the characteristic of ESBL-producing bacteria. Other gram-negative bacteria were also often phenotypically presented as ESBL-producing bacteria; those including *Pseudomonas* sp. (49 (89.09%)), *P. aeruginosa* (35 (85.37%)), and *K. pneumoniae* (20 (52.63%)). *Enterobacter* sp., *Klebsiella* sp., *K. aerogenes*, and *P. fluorescens* were less identified as ESBL-producing bacteria accounted for 7 (58.33%), 5 (62.5%), 4 (100%), and 3 (75%) isolates respectively. Other bacteria were also shown as ESBL producers, but they are limited in number (TABLE 2).

Carbapenem-resistant Gram-negative bacteria identified from the urine culture

This study recorded that among Gram-negative bacteria which isolated and tested against carbapenem (meropenem), resistance was identified in 27.94% of them (TABLE 3). Although some bacteria isolates revealed a relatively high percentage of carbapenem resistance, this research sample size is limited. Among Gram-negative bacteria isolates tested against carbapenem, *Pseudomonas sp.*, *E. coli, K. pneumoniae, P. aeruginosa, Enterobacter* sp., *Klebsiella* sp., *P. fluorescens,* and *Serratia* sp. were relatively common as carbapenemase producers which accounted for 27 (45%), 23 (17.04%), 10 (26.32%), 10 (24.39%), 5 (41.67%), 4 (50%), 3 (75%), 2 (100%) isolates, respectively.

DISCUSSION

This study described the UTI's etiology and their resistance against antibiotics by observing their phenotypic characteristics as ESBL-producing and or carbapenemase-producing bacteria. This data can serve as local surveillance in Yogyakarta that enables benefits in diagnostic and antimicrobial stewardship programs.[12] This study showed of all recovered isolates from urine culture, Gram-negative bacteria were identified as the predominant (74.78%) uropathogens, whereas Gram-positive bacteria and fungi were represented only in 14.44% and 10.78%, respectively. This finding was similar to a study from East China (2021) that conducted urine culture from 1760 UTIs patients, and reported uropathogens which consisted of 90.5% Gram-negative bacteria, 9.3% Gram-positive bacteria, and 0.2% fungi.[13] In Indonesia, a study of asymptomatic UTI in pregnant women revealed that Gram-negative bacteria (72%) were more frequently isolated from their urine culture, as compared to Gram-positive bacteria (28%).[14] A study in Surabaya, Indonesia also reported similar result, Gram-negative (59.67%) and Gram-positive (14.51%) bacteria, as well as fungi (*Candida* sp.) (25.81%) were identified in the urine culture of diabetic patients with UTI.[15]

Gram - positive bacteria as uropathogens

The East China study reported *E. faecalis* as the most prevalent (31.7%) gram-positive bacteria, then followed by *S. agalactiae* (24.4%), *S. saprophyticus* (18.3%), *E. faecium* (9.1%) and others (16.5%).[13] Our study has slightly different pattern, we reported *Enterococcus* sp., *S. aureus*, and *E. faecalis* as the majority (95.52% in total) of Gram-positive bacteria identified from urine culture, whereas *S. agalactiae* was only accounted for 2.99% of Gram-positive bacteria involved in UTIs. A study in Jakarta revealed that *S. agalactiae* (33.33%), *E. faecalis* (19.04%), and *S. saprophyticus* (14.28%) were the frequently identified gram-positive bacteria of asymptomatic UTI in pregnant women.[14] In Surabaya, *E.*

faecalis (66.66%) was the gram-positive bacteria which frequently isolated from urine culture of diabetic patients with UTI.[15]

This study found that *S. pneumoniae,* which is commonly associated with respiratory or central nervous infection, was detected in a urine sample from a patient with UTI.[16] This extraordinary finding came from a patient who also suffered from *S. pneumoniae* bacteraemia, as suggested by the positive results of two blood cultures (also yielded *S. pneumoniae*) which accompanied the urine culture. Although uncommon, in Munich, Germany, *S. pneumoniae* as urinary tract pathogen was reported in a 82-year-old man with pyelonephritis and urosepsis.[16] Pneumococcosuria where *S. pneumoniae* identified as an agent of infection in urinary tract was scarce.[17] A study at the Department for Infectious Diseases, University Hospital of Heidelberg, reported that 26 urine samples from 18 different patients (age of 3-72 years) contained *S. pneumoniae* between January 2010 and December 2014.[17] The literature suggested that in children, *S. pneumoniae* is rarely identified from urine samples (less than 1%).[18]

Gram - negative bacteria as uropathogens

Escherichia coli was accounted for 75-95% of uropathogens in UTIs all over the world.[19] A study in Japan which included a total of 2049 UTI patients reported that 1682 (82.1%) of UTIs were caused by gram-negative bacteria. It comprised *E. coli* (93.3%), *Klebsiella* sp. (6.2%), and *P. mirabilis* (0.5%).[20] Interestingly, a meta-analysis study in Iran found comparable finding among pregnant women, that *E. coli* and *Klebsiella* were the common gram-negative bacteria causing UTIs which accounted for 61.6% and 13.9% respectively.[21] Similarly, the study in US Veterans Affairs medical centers (in Minnesota and Texas) highlighted that *E. coli* was a predominant uropathogen which accounted for 40.7%.[22]

A study of asymptomatic UTI in pregnant women in Indonesia reported that the gram-negative bacteria which frequently isolated in the urine culture were *E. coli* (37.04%) and *K. pneumoniae* (27.78%).[14] In Surabaya, a study of UTI in diabetic patients reported that the gram-negative bacteria which frequently isolated in the urine culture were *E. coli* (54.05%), *A. baumannii* (10.81%), and *Enterobacter* spp. (8.10%).[15] Similarly, our study reported that *E. coli* was the most prevalent (38.9%) gram-negative bacteria recovered from UTIs, however the second and third most frequent gram-negative uropathogens were *Pseudomonas* sp. (17.29%) and *P. aeruginosa* (12.10%) respectively. We also found a various species of other gram-negative bacteria which involved in UTIs comprising *K. pneumoniae* (10.95%), *Enterobacter* sp. (3.45%), *P. mirabilis* (2.88%), and others (14.43%).

ESBL producing Gram - negative bacteria

Our study highlighted that gram-negative bacteria were the major pathogen (74.78%) causing UTIs, and around 59% of those isolates shared similar phenotypic trait as ESBL producer. ESBLs are defined as a rapidly evolving group of enzymes produced by certain bacteria that can hydrolize extended spectrum cephalosporin.[23,24] These enzymes found to be effective against one or more of third and fourth generation of cephems (such as ceftazidime, ceftriaxone, cefotaxime, cefepime), extended spectrum penicillin (i.e. piperacillin), and monobactam (i.e. aztreonam) but are inhibited by clavulanic acid or tazobactam.[23-25] Therefore the presence of ESBLs in gram-negative bacteria warrant special attention due to the associated risks of

antibiotic therapy failure.[26]

ESBL-producing *Enterobacteriaceae* (i.e. *E. coli, K. pneumoniae*, *Enterobacter* sp., *Proteus* sp.) are the most prevalent causative agents of UTIs.[25] They can be a major threat to the global public as their resistance against β-lactam antibiotics leads to treatment failure in many infections.[25] While our study reported 42.22% ESBL-producing *E. coli* in the urine of UTI patients, a study in Jordan (2019) reported a higher proportion (62%).[27] A systematic review in Ethiopia reported a high rate of ESBL-producing gam-negative bacteria among clinical samples with a pooled rate of 50.1% among different species and varied in the groups of *Klebsiella* spp. (65.7%), *Enterobacter* spp. (62.2%), *Salmonella* spp. (48.4%), *E. coli (*47.0%), *Citrobacter* spp. 46.8%, *Providencia* spp. (43.8%), *Proteus* spp. (28.3%), *P. aeruginosa* (17.4%), *Acinetobacter* spp. (9.4%), and other Gram-negative bacteria (20.8%).[28]

A five-year global surveillance by "SMART program" (2015-2019) reported that the prevalence of non-carbapenem-resistant ESBL-producing *Enterobacteriaceae* was 30% globally, and exceeded 50% in India, Thailand, Vietnam, China, Russia, Mexico, Kenya, and Kuwait.[25] The SMART program estimated that the prevalence of non-carbapenem-resistant ESBL-producing *K. pneumoniae* was 25.4% globally, and more than 40% in Portugal, Chile, Ecuador, Guatemala, Mexico, Israel, Kenya, Morocco, Lithuania, and Kuwait.[25] They also reported that the prevalence of non-carbapenem-resistant ESBL-producing *E. coli* increased significantly ($p < 0.05$) in Asia (excluding China), Australia, New Zealand, and Latin America.[25] Furthermore, the non-carbapenem-resistant ESBL-producing *K. pneumoniae* prevalence increased significantly ($p< 0.05$) in Latin America, USA, and Canada.[25] Unfortunately, no data from Indonesia was included in the SMART surveillance.[25]

A retrospective study in Bali, Indonesia (2019-2020) revealed that ESBL-producing *E. coli* (56.32%) and *K. pneumoniae* (54%) were identified in the urine culture of patients with UTI and chronic kidney disease.[29] Another study in Medan reported that ESBL-producing *E. coli* was contributed to 8.4% of urine associated catheter infections in adult patients who admitted into the intensive care unit from July to August 2018.[30] Differences in clinical settings, study period, study population, and methods might modify the result, thus explaining the heterogeneity of the ESBL-producing bacteria prevalence worldwide.[28]

ESBLs are enzymes encoded in plasmids and can be easily transferred to other bacteria.[31] Apart from ESBL-producing *Klebsiella* and *E. coli*, our study also reported a relatively high prevalence of ESBL-producing Gram-negative bacteria, including non-lactose-fermenting bacteria such as *P. aeruginosa*, *Pseudomonas* spp., and a wide variety of other Gram-negative bacteria causing UTIs.[32] These bacteria have also been reported as the causative pathogen in UTIs, especially in health-care associated UTIs.[32]

Carbapenem - resistant in Gram - negative bacteria

Carbapenems have a β-lactam ring that differs from penicillins by replacing the sulphur atom at C-1 with a carbon atom and adding a double bond between C-2 and C-3.[33] In addition to this characteristic, the side chain of carbapenemis in the trans position instead of the cis- position, making this drug insensitive to the effect of β-lactamases.[33] Carbapenems were previously effective in treatening-drug resistant (MDR) bacteria, including ESBL-producing bacteria which resistant to penicillin and cephalosporins.[34] Unfortunately, the acquisition of carbapenemase genes causes these bacteria to be able to

hydrolize carbapenem, leaving a limited choice of antibiotic treatment for MDR bacteria.[35]

Carbapenemase emergence and spread have increased dramatically over the last decade following its discovery in *K. pneumoniae* in the US in 1996.[34,36] The increasing prevalence of carbapenem-resistant gram-negative bacteria as the cause of infections is a global threat, hence the WHO highlighted those pathogens, particularly carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *P. aeruginosa* (CRPA) and carbapenem-resistant *A. baumanii* (CRAB) in the global priority list of pathogens in 2017.[37] Carbapenem-producing bacteria surveillance is an important strategy to control its spread and enable a positive impact for public health.[38]

Carbapenem-resistant bacteria in this study were reported in 95 (27.94%) of gram-negative bacteria isolated from urine cultures of UTI samples. Our study identified various percentage of carbapenem resistance among different bacterial species isolated from UTI patients, including *Klebsiella* sp. (50%), *K. pneumoniae* (26.32%), *E. coli* (17.04%), *Pseudomonas* sp. (45%), *Enterobacter* sp. (41.67%), *P. fluorescens* (75%), and many more as described in TABLE 3. A review study comprising data mostly from Asia, North America, and Europe (2017) reported that proportion of carbapenem-resistant *Enterobacteriaceae* in community setting was ranged from 0 to 29.5% with the highest proportion of carbapenem- resistant *Enterobacteriaceae* was identified in Asia.[39] In Taiwan, the prevalence of carbapenem-resistant *P. aeruginosa* was increasing from 12% in 2012–2015 to 19-23% in 2018–2021.[40] Surveillance of carbapenem resistance, especially in patients with UTI is remain scattered and fragmented, moreover various surveillance models were adapted to fit with the requirements and capacities of each setting or country.[41] Furthermore, developing countries struggle with political and social dilemmas due to weak laboratory capacity, poor health systems governance, lack of health information systems, and limited resources.[41,42] Despite the challenges, a local antibiogram or data regarding uropathogen and its susceptibility pattern is important to inform local treatment guidelines and promote antimicrobial stewardship program.[43]

Study limitation

This study has limitations, including the small sample size of each bacteria species, limited clinical information, and the passive nature of a secondary laboratory records.

CONCLUSION

This study highlighted the profile of bacteria associated with UTIs in Yogyakarta during 2007-2022 that could be useful for antimicrobial stewardship. The recovery proportion of pathogen of urine culture from UTIs patients was relatively high (55.11%), and like other studies in the world, gram-negative bacteria was the most prevalent pathogen isolated from urine of UTI cases. *Escheriachia coli* and bacteria in the genus *Pseudomonas* and *Klebsiella* were the most frequently identified in this population. In addition, this study revealed the high proportion of ESBLs- and carbapenemase-producer among gram-negative bacteria associated with UTIs. Future study is required to refine the epidemiology of bacteria that cause UTI in developing countries or limited-resource region, especially in Yogyakarta.

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