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# Species distribution of Enterobacteriaceae and non-Enterobacteriaceae responsible for urinary tract infections at the Zainoel Abidin Hospital in Banda Aceh, Indonesia

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[2]Department of Microbiology, Faculty of Medicine, Universitas Syiah Kuala. Jl. Teuku Tanoh Abee, Kopelma Darussalam, Syiah Kuala, Banda Aceh 24415, Aceh, Indonesia. Tel.: +62-651-7555591, ♥email: wildamahdani@unsyiah.ac.id

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**Abstract.** *Suhartono S, Mahdani W, Hayati Z, Nurhalimah N. 2021. Species distribution of Enterobacteriaceae and non-Enterobacteriaceae responsible for urinary tract infections at the Zainoel Abidin Hospital in Banda Aceh, Indonesia. Biodiversitas 22: 3313-3318.* Urinary tract infection (UTI) is an infection that occurs along the urinary tract caused by pathogenic bacteria. Enterobacteriaceae and non-Enterobacteriaceae are generally normal flora originating from the large intestine and vaginal mucosa. This study aimed to assess the distribution of Enterobacteriaceae and non -Enterobacteriaceae pathogens that cause UTI based on species diversity, patient age, gender, and hospital units, and to evaluate their antibiotic sensitivity to uropathogens in ZAH. In total, there were 284 isolates classified as UTI pathogens with 178 Enterobacteriaceae isolates dominated by *Escherichia coli* and 107 non-Enterobacteriaceae isolates. Non- Enterobacteriaceae consisted of 77 isolates of Gram-positive dominated by *Enterococcus faecalis* and *Enterococcus facium,* and 29 isolates of Gram-negative dominated by *Acinetobacter baumannii*. The highest UTI ratio was found in the elderly (56-65 years), namely 66.2% Enterobacteriaceae and 33.8% non-Enterobacteriaceae isolates. Based on gender, females were infected with Enterobacteriaceae (66.86%) and non-Enterobacteriaceae (37.41%). Most of UTI patients in the internal medicine unit were infected with Enterobacteriaceae (55.36%) and non-Enterobacteriaceae (44.64%). Amikacin, meropenem, and levofloxacin were antibiotics that had high sensitivity against Enterobacterial and non-Enterobacterial uropathogens. The emergence of Gram-positive uropathogens need to be concerned as these groups start emerging. It is also important to monitor regularly the antibiotic susceptibility of bacterial UTI pathogens to ensure the efficacy of current UTI treatments and minimize the UTI incidence in nosocomial settings.

**Keywords:** Antibiotic susceptibility, Enterobacteriaceae, non-Enterobacteriaceae, Urinary Tract Infection

**Abbreviations:** UTI: Urinary tract infection

## INTRODUCTION

Urinary tract infections (UTI) are one of the most common infectious diseases in humans, which have significant clinical and financial impacts (Medina and Castillo-Pino 2019). UTI is characterized by the presence of pathogenic microbes in the urinary tract and is classified according to the site of infections. For example, infection in the bladder is known as cystitis, in the kidney known as pyelonephritis, or in the urine known as bacteriuria (Foxman et al. 2000). These infections occur asymptomatically or symptomatically with wide spectrum of symptoms ranging from mild irritation to bacteremia, sepsis, and even death. Furthermore, UTI also produces considerable financial burdens in clinical settings. During UTI incidences among women from 1970-1990 in the United States, UTI is estimated to annually cost approximately $1.6 billion in community-acquired settings and $424–451 million in clinical settings, owing primarily to medical costs i.e. outpatient physician visits, antimicrobial prescriptions, and hospitalization, and nonmedical costs i.e. travel expenses (Foxman 2002). A recent study signifies that the economic burden of UTI might increase up to 29% when patients were infected with antibiotic-resistant UTI pathogens (Iskandar et al. 2021).

Many factors contribute to UTI including bacterial invasion, abnormalities of urinary tract anatomy and function, and the host immune status. *Enterobacteriaceae* is the most common uropathogenic bacteria in terms of bacterial invasion, accounting for more than half of UTI incidences (Kucheria 2005). Several non-Enterobacteriaceae such as *Staphylococcus aureus*, *Salmonella sp*., and *Pseudomonas* sp., are also known as pathogenic bacteria that cause UTI especially those suffering from chronic diseases, such as diabetes mellitus (Ahmad et al. 2020). It was expected that as the number of symptomatic UTI cases requiring antimicrobial therapy increases, the population of highly susceptible patients will increase, resulting in an increased risk of antimicrobial resistance among common uropathogens (Foxman et al. 2000). This raises concerns regarding the prevalence of the pathogenic bacteria associated with the increase in UTI cases at the Zainoel Abidin Hospital, Banda Aceh, Indonesia. The objectives of the present study were to evaluate and determine the distribution of Enterobacteriaceae and non-Enterobacteriaceae bacterial UTI pathogens based on species diversity, patients' age, genders, and hospital units, and to determine antibiotic sensitivity.

## MATERIALS AND METHODS

### Sample collections

Clinical samples of uropathogenic bacteria were isolated from the urine of inpatients and outpatients in the Zainoel Abidin Hospital (ZAH) Banda Aceh, Indonesia from February to December 2020. All urine samples were assessed for their quality including delivery time of delivery i.e., not exceed than 2 hours at room temperature, urine volume in sample vials i.e., 5-20 cc, and sampling locations. All the samples were labeled with the information of clinical sample types, age, gender, and ward types.

### Uropathogenic bacterial isolation, observation, and identification

All urine samples were subjected to direct microscopic observation and indirect or culture observation. For direct observation, a loopful of urine samples was performed for Gram staining and directly observed under a microscope with 1000 x magnification. For culture observation, 1 µL of the samples was inoculated using an inoculation loop to plates containing culture media of blood agar (Merck, Germany) and MacConkey agar (Merck, Germany). The plates were incubated for 24 hours at 37 ºC before they were Gram-stained and observed for morphological characters macroscopically and microscopically.

Additional identification and antibiotic susceptibility were conducted using VITEK® 2 Compact (Biomeriux, Lyon, France). A pure uropathogenic bacterial colony recovered from the clinical samples was suspended in NaCl 0.45% equivalent to 1.8-2.2 McFarland Standard solution before the suspension was inoculated into appropriate cassettes of GN (Gram-negative), GP (Gram-positive), and AST (antimicrobial susceptibility testing) for identification and antimicrobial susceptibility, respectively.

Ethical Clearance Approval for this study was obtained from the Ethical Clearance Committee for Health Research, Faculty of Medicine, Universitas Syiah Kuala with registration number 327/EA/FK-RSUDZA/2020.

### Statistical analysis

The species distribution of Enterobacterial and non-Enterobacterial uropathogenic isolates were descriptively analyzed based on patients' ages, gender, and hospital units. All data were tabulated using Microsoft Excel to generate descriptive information in tables or charts. Statistical analysis was performed using the Chi-square test or Fisher's exact test when appropriate. All tests were performed using XLStat 2020 (Addinsoft, New York, USA, $p \leq 0.05$ on two-tailed were considered as statistically significant.

## RESULTS AND DISCUSSION

### Uropathogenic bacterial isolation, observation, and identification

In total, there were 284 isolates recovered from urine samples and identified as uropathogens. Of all isolates, there were 177 isolates of Enterobacteriaceae and 107 isolates of non-Enterobacteriaceae. There were 29 species of uropathogenic bacteria, in which nine species were identified as Enterobacteriaceae, and 20 species were identified as non-Enterobacteriaceae. The two highest numbers of Enterobacteria were *Escherichia coli* and *Klebsiella pneumoniae* with a distribution of 121 (42.6%) and 36 (12.7%) of the total uropathogens, respectively. *Enterococcus faecalis* and *Enterococcus facium*, were found as the two most prevalent Gram-positive non-Enterobacteriaceae and *Acinetobacter baumannii* of Gram-negative non-Enterobacteriaceae with distributions of 37 (13%), 23 (8.1%), and 10 (3.5%), respectively (Table 1).

**Table 1.** Species distribution of Enterobacteriaceae (n = 177) and non-Enterobacteriaceae (n = 107) in urine samples from February – to December 2020 at the Zainoel Abidin Hospital (ZAH) Banda Aceh, Indonesia

| Enterobacteriaceae | n | % | Non- Enterobacteriaceae | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Gram-positive | n | % | Gram-negative | n | % |
| *Escherichia coli* | 121 | 42.6 | *Enterococcus faecalis* | 37 | 13 | *Acinetobacter baumannii* | 10 | 3.5 |
| *Klebsiella pneumoniae* | 36 | 12.7 | *Enterococcus facium* | 23 | 8.1 | *Pseudomonas aeruginosa* | 6 | 2.1 |
| *Enterobacter cloacea* | 7 | 2.5 | *Staphylococcus haemolyticus* | 5 | 1.8 | *Pseudomonas putida* | 6 | 2.1 |
| *Citrobacter freundii* | 5 | 1.8 | *Staphylococcus aureus* | 4 | 1.4 | *Aeromonas hydrophyla* | 2 | 0.7 |
| *Enterobacter aerogenes* | 3 | 1.1 | *Streptococcus agalactiae* | 3 | 1.1 | *Pseudomonas fluorescens* | 1 | 0.4 |
| *Enterobacter asburiae* | 2 | 0.7 | *Staphylococcus sciuri* | 1 | 0.4 | *Stenotrophomonas maltophilia* | 1 | 0.4 |
| *Serratia liquefaciens* | 1 | 0.4 | *Staphylococcus hominis* | 1 | 0.4 | *Sphingomonas paucimobilis* | 1 | 0.4 |
| *Citrobacter amalonaticus* | 1 | 0.4 | *Enterococcus sp.* | 1 | 0.4 | *Acinetobacter juni* | 1 | 0.4 |
| *Proteus hauseri* | 1 | 0.4 | *Enterococcus avium* | 1 | 0.4 | *Burkholderia cepacia* | 1 | 0.4 |
| *Providencia stuartii* | 1 | 0.4 | *Enterococcus gallinarum* | 1 | 0.4 | | | |
| Subtotal | 177 | 62.3 | | 77 | 27,1 | | 30 | 10,6 |

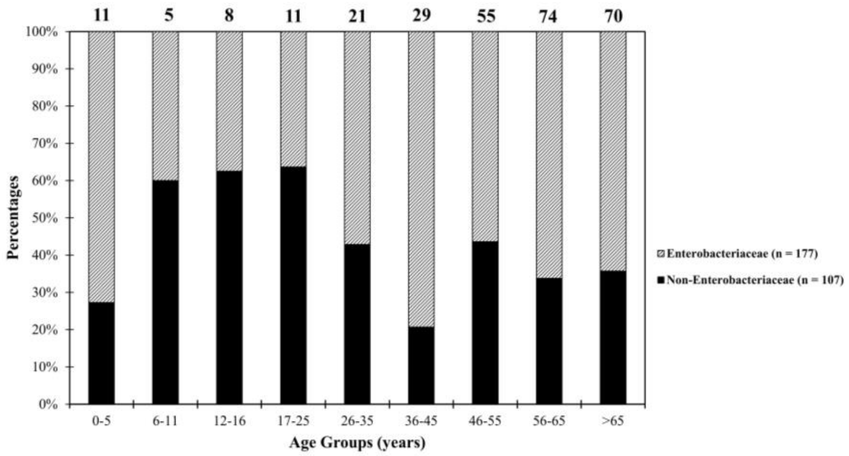


**Figure 1.** The frequency of occurrence (%) Enterobacterial uropathogenic bacteria (n=177) and non-Enterobacterial uropathogenic bacteria (n=107) from patients in different age groups at the Zainoel Abidin Regional Hospital in Aceh, Indonesia from February – December 2020. The numbers in the column are the total number of isolates recovered from each age group. Based on the Chi-square test of independence, the isolates and the patient age group were independent ($P$ = 0.149).

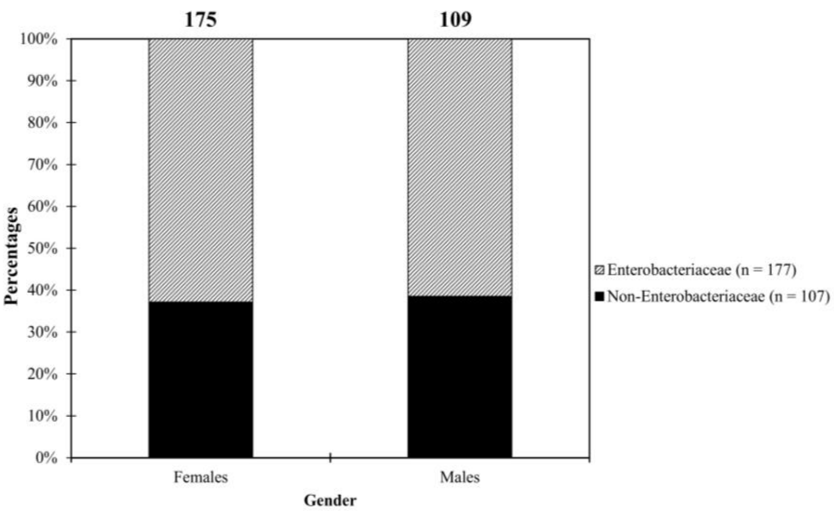


**Figure 2.** Frequency of occurrence (%) uropathogenic Enterobacteria (n=177) and uropathogenic non-Enterobacteria (n=107) from patients of different gender in the Zainoel Abidin Regional Hospital in Aceh, Indonesia from February to December 2020. Numbers above each column are the total number of isolates recovered from each gender. Based on the Chi-square test of independence, the isolates and the patients' gender were independent ($P$ = 0.814).

**Distribution of uropathogenic bacteria based on age groups, genders, and hospital units**

The results showed that uropathogenic bacterial isolates of both Enterobacteriaceae and non-Enterobacteriaceae were found prevalently in patients 46 years or older (Figure 1). However, there was no significant relationship between the family of uropathogenic isolates (Enterobacteriaceae and non-Enterobacteriaceae) and the age of the patient. The distribution of the uropathogens showed that increasing age results in the increase of urinary tract infections risk. Children under the age of 17 were less likely to have the infections.

Results on gender showed that females (175 cases) were more susceptible to UTI than males (109 cases) (Figure 2). There was no significant relationship between the family of uropathogenic isolates (Enterobacteriaceae and non-Enterobacteriaceae) and the patient's gender. Uropathogenic bacterial isolates of both Enterobacteriaceae and non-Enterobacteriaceae had almost the same proportion in both genders. The number of uropathogenic bacterial isolates was predominantly recovered from patients treated in the internal medicine units (112 isolates or 39% of the total isolates) (Figure 3). The number of uropathogenic bacteria in the internal medicine ward was almost two folds than those isolated from a surgical unit or nearly the same as the combination of non-surgical unit and outpatient unit. There was no significant relationship between the types of uropathogenic isolates (Enterobacteriaceae and non-Enterobacteriaceae) and the hospital units.

**Table 2.** Antibiotic susceptibility of uropathogenic Enterobacteria (n=177) and uropathogenic non-Enterobacteria (n=107) from patients in the Zainoel Abidin Regional Hospital in Aceh, Indonesia from February – December 2020

| Antibiotics | Enterobacteriaceae | | Non-Enterobacteriaceae | | Chi-2[a] | *p-values*[b] |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| Amikacin | 125 | 70.62 | 27 | 25.23 | 54.351 | < 0.0001 |
| Amoxicillin | 11 | 6.21 | 34 | 31.78 | 32.928 | < 0.0001 |
| Ampicillin | 5 | 2.82 | 54 | 50.47 | 92.462 | < 0.0001 |
| Cefotaxime | 23 | 12.99 | 4 | 3.74 | 6.571 | 0.010365 |
| Cefoxitin | 88 | 49.72 | 1 | 0.93 | 73.207 | < 0.0001 |
| Ceftazidime | 39 | 22.03 | 10 | 9.35 | 7.410 | 0.006486 |
| Gentamicin | 90 | 50.85 | 4 | 3.74 | 66.285 | < 0.0001 |
| Levofloxacin | 29 | 16.38 | 19 | 17.76 | 0.102 | 0.749 |
| Meropenem | 121 | 68.36 | 33 | 30.84 | 37.107 | < 0.0001 |
| Levofloxacin | 106 | 59.89 | 33 | 30.84 | 22.046 | < 0.0001 |

[a] Chi-square calculated for comparison of susceptibility in Enterobacteriacea versus Non-Enterobacteriaceae
[b] P value generated from the chi-square

Table 2 summarizes that amikacin, meropenem, and levofloxacin were antibiotics possessing high sensitivity against uropathogenic Enterobacteria, with sensitivity percentages of 70.62%, 68.36%, and 59.89%, respectively. On the other hand, ampicillin is the only antibiotic exhibiting high sensitivity against uropathogenic non-Enterobacteriaceae with 50.47% sensitivity.

## Discussion

The results in this study showed that Enterobacteriaceae remains the major causative agent for urinary tract infections. Similar to other previous studies (Moroh et al. 2018), *E. coli* and *K. pneumoniae* are the most prevalent Enterobacteriaceae responsible for urinary tract infections. Uropathogenic Enterobacteriaceae, such as *E. coli* harbor some virulence factors including adhesive organelles such as type 1, P, and S pili which facilitate the attachment and invasion of microorganisms to the uroepithelial cells and cause diseases (Mulvey 2002). The indiscriminate and extensive use of antibiotics resulted in the resistance of uropathogenic bacteria to antibiotic resistance, namely extended-spectrum beta-lactamases (ESBLs) and multi-drug resistance (Mazzariol et al. 2017; Yamasaki et al. 2021). The results also showed an increase in the number of Gram-positive uropathogens especially *Enterococcus faecalis* and *Enterococcus facium*. Several previous studies showed the emergence of non-Enterobacteriaceae, i.e., *Enterococcus faecalis* and *Enterococcus facium* as primary causative agents for urinary tract infections (Parameswarappa et al. 2013; Shrestha et al. 2019; Rostkowska et al. 2020). Therefore, *Enterococcus faecalis* and *Enterococcus facium* are projected in contributing to the rapid increase of multidrug resistance due to their intrinsic resistance plus genetic diversity, including resistance to the well-known synthetic drugs to prevent urinary tract infections such as nitrofurantoin (Zhang et al. 2021).

Intrinsic host factors, i.e., age and gender, also contribute to the severity of urinary tract infections. The incidence of UTI is directly proportional to age because of the decline in physiological function including immunosenescence due to aging which causes susceptibility to infections and is often accompanied by severe complications. The incidence of UTI increases in patients aged 40 years and over with the highest peak in the 50-59year age group in long-term care facilities and communities (Matthews and Lancaster 2011). Several predisposing factors cause UTI in elderly people, including prostate problems in men, postmenopausal estrogen deficiency in women, exposure to nosocomial pathogens, and comorbidities such as diabetes mellitus is widely associated with an increased incidence of UTI (Ahmad et al. 2020; Rodriguez-Mañas 2020). In terms of gender, similar to previous findings by Kurniawati and Auliyanah (2021), women are more likely to have urinary tract infections compared to men in all age groups. The high rate of UTI incidence in women is primarily due to the anatomical proximity of the rectum and the urinary tract in women in addition to the shorter female urethra so that the bacteria can more easily reach the bladder (Shiralizadeh et al. 2018). Other factors may include the history of prior UTI, sexual activity, pregnancy, and physiologic and anatomic abnormalities in the urinary tract (Guglietta 2017).

In the current study, the highest number of uropathogenic bacterial isolates were recovered from patients in the internal medicine ward compared to other hospital units. It may be associated with the patients treated in internal medicine who were generally geriatric patients with comorbidities, including UTI risk factors. Besides, patients in the internal medicine units usually undergo rehabilitation or prolonged bed rests tend to have increased risks urological system including urinary retention, urinary tract infections (UTIs) and kidney stones (Knight et al. 2019). Patients in the internal medicine room usually receive invasive medical devices such as urinary catheters, thereby increasing the incidence of UTI. Urinary catheterization is the most likely risk factor to develop UTI prevalence including the development of multidrug-resistant uropathogens (Tenney et al. 2018).

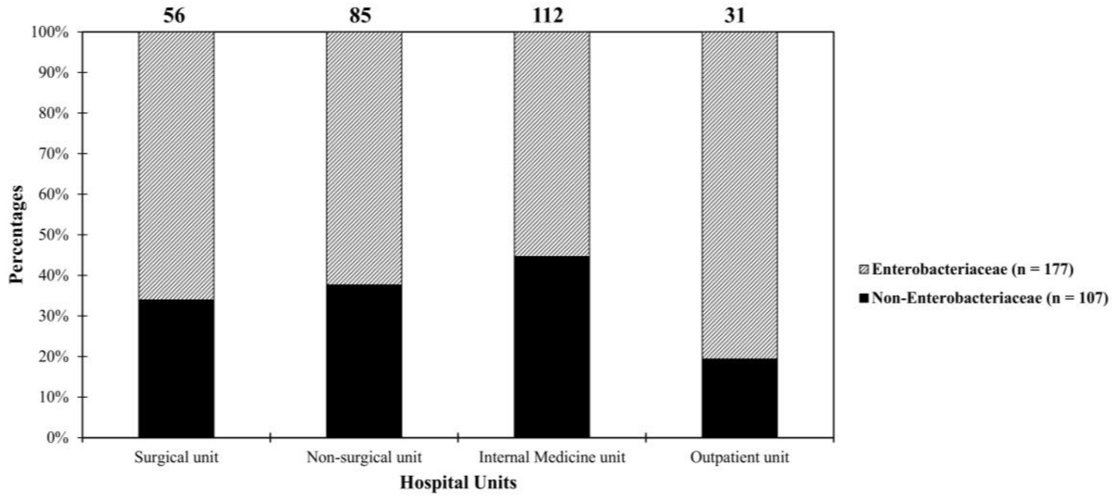


**Figure 3.** Frequency of occurrence (%) uropathogenic Enterobacteria (n=177) and uropathogenic non-Enterobacteria (n=107) from patients in different hospital units at the Zainoel Abidin Regional Hospital in Aceh, Indonesia from February to December 2020. Numbers above each column are the total number of isolates recovered from each hospital unit. Based on the Chi-square test of independence, the isolates and the hospital units were independent ($P = 0.069$).

The results of antibiotic susceptibility showed that amikacin, meropenem, and levofloxacin were antibiotics that possess high sensitivity against Enterobacterial and non-Enterobacterial uropathogens. A study by Cho et al. (2016) demonstrated that amikacin remains the feasible therapeutic option to treat UTI, including antibiotic-resistant uropathogens. Meropenem, or in combination with vaborbactam, also continues to be the best option for empiric treatment for patients with complicated UTIs (Baldwin et al. 2008; Burgos et al. 2018). Like previous drugs, levofloxacin is also effective in treating a broad range of Gram-positive, Gram-negative, and atypical bacterial pathogens causing UTI (Bientinesi et al. 2020).

Overall, Enterobacteriaceae remains the most dominant uropathogens, however, the occurrences of Gram-positive uropathogenic bacteria are noteworthy as these groups are beginning to emerge alongside their Gram-negative of Enterobacteriaceae and non-Enterobacteriaceae. The antibiotic susceptibility of UTI bacterial pathogens is also important to be monitored regularly to ensure the effectiveness of current UTI treatments and minimize the UTI incidence in nosocomial settings.

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