

## Resistance Patterns of *Escherichia coli* and *Klebsiella pneumoniae* Bacteria Against Amikacin, Ceftazidime, Meropenem, Nitrofurantoin Antibiotics in Elderly Patients with UTI in Dr. Soetomo General Hospital Surabaya

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### ABSTRACT

**Introduction:** Urinary tract infection (UTI) is an infection that involves the urinary tract, including the urethra, bladder, ureter, and kidneys. UTI is caused by microorganisms that breed in the urinary tract which are supposed to be free of microorganisms. Two bacteria that cause UTI in general are *Escherichia coli* and *Klebsiella pneumoniae*. UTI can occur at any age but generally occurs in the elderly. UTI caused by gram-negative bacteria can be killed with several examples of antibiotics namely amikacin, ceftazidime, meropenem and nitrofurantoin. These antibiotics found resistance to the bacteria that cause the UTI. This research is to determine the resistance patterns of *Escherichia coli* and *Klebsiella pneumoniae* bacteria against amikacin, ceftazidime, meropenem, nitrofurantoin antibiotics in elderly patients with UTI in Dr. Soetomo Surabaya January-June 2017 period.

**Methods:** A descriptive retrospective study in accordance with the logbook data of Clinical Microbiology Installation at Dr. Soetomo General Hospital Surabaya. Data from this study were taken from all populations that met the inclusion criteria. The results are presented by tables.

**Results:** There are 163 elderly patient data which diagnosed with urinary tract infection. *Escherichia coli* resistance pattern against ceftazidime (75.6%), nitrofurantoin (12.6%) and meropenem (2.4%). Meanwhile, *Klebsiella pneumoniae* against ceftazidime (72.2%), nitrofurantoin (55.6%), meropenem (11.1%) and amikacin (2.8%).

**Conclusion:** There were resistance numbers of *Escherichia coli* and *Klebsiella pneumoniae* bacteria against antibiotics amikacin, ceftazidime, meropenem, nitrofurantoin in elderly patients with UTI.

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## Introduction

Urinary tract infection (UTI) is an infection that involves the urinary tract, including the urethra, bladder, ureter, and kidneys. UTI is caused by microorganisms that multiply in the urinary tract which are supposed to be free of microorganisms<sup>1</sup>. Two bacteria that cause UTI in general are *Escherichia coli* and *Klebsiella pneumoniae*<sup>2</sup>. In Ethiopia also found gram-negative bacteria for UTI patients in the first order, namely *Escherichia coli* (33.3%) followed by *Klebsiella pneumoniae* (19%)<sup>3</sup>. Whereas in France, *E. coli* (73%) and *Klebsiella spp.* (6%)<sup>4</sup>.

UTI can occur at any age but generally occurs in the elderly. This infection is the second highest infection after respiratory infection in elderly patients<sup>5</sup>. Elderly patients often cannot explain or report complaints that they experience clearly. This causes the infection is often overlooked so that patients experience delays in treatment and can cause complications in the form of sepsis. In addition, all infectious diseases can accelerate the progress of dementia which is a condition in which the ability of a person's brain to decline. Therefore, UTI disease needs to be identified and treated quickly<sup>6</sup>.

UTI caused by gram-negative bacteria can be killed with several examples of antibiotics such as aminoglycosides such as amikacin, cephalosporins such as ceftazidime, carbapenem such as meropenem, and nitrofurantoin synthesis such as nitrofurantoin. Excessive treatment with antibiotics for UTI is suspected remains a significant problem and causes various negative consequences including the development of microorganisms that are resistant to antibiotic drugs<sup>7</sup>.

Amikacin found resistance to several strains gram-negative bacteria associated with the antibiotic enzyme<sup>8</sup>. Ceftazidime which extends across the blood-brain barrier is also still misused for the treatment of gram-negative bacterial infections whereas this can lead to resistance<sup>9</sup>. Active or sensitive nitrofurantoin to fight *Escherichia coli* strains was found to be resistant to gram-negative bacteria<sup>10</sup>. The carbapenem antibiotic group including meropenem has begun to be resistant to Enterobacteriaceae<sup>11</sup>. Therefore, the researchers wanted to know the clarity of the resistance patterns of *Escherichia coli* and *Klebsiella pneumoniae* bacteria against the antibiotics amikacin, ceftazidime, meropenem, and nitrofurantoin whether they have experienced resistance or are still sensitive to their use in elderly patients with UTI, especially in Dr. Soetomo January 2017-June 2017 period.

## Methods

This research was a descriptive retrospective. The independent variables were *Escherichia coli* bacteria, *Klebsiella pneumoniae* bacteria, age, UTI patient, while the dependent variables were amikacin, ceftazidime, meropenem, and nitrofurantoin.

This research used logbook data with inclusion data (data on male and female patients aged  $\geq 60$  years, data on elderly patients suffering from UTI, data on elderly patients suffering from UTI with the causes of the bacteria *Escherichia coli* and *Klebsiella pneumoniae*, antibiotic data for amikacin, ceftazidime, meropenem and nitrofurantoin, treated in the period January - June 2017) and exclusion data (patient data that is not complete). The population was patients data of UTI in elderly in Dr. Soetomo General Hospital Surabaya January 2017-June 2017 period. The research sample was taken from the population of patients who were suitable with the inclusion criteria in Dr. Soetomo General Hospital Surabaya in January 2017-June 2017 period which has been done by urine culture test and antibiotic resistance test and recorded in logbook data at the Clinical Microbiology Installation at Dr. Soetomo General Hospital Surabaya. This research took place in Clinical Microbiology Installation at Dr. Soetomo General Hospital Surabaya with January 2017-June 2017 period. The results of this research were presented by tables.

## Results

Table 5.1 Distribution of Research Subject Patterns Based on Gender

Gender	<i>n</i> (Amount)	% (Percentage)
Male	76	46.7
Female	87	53.3
Total	163	100.0

In table 5.1 shows that from 163 patient data obtained a few more subjects of women who suffer from UTI as many as 87 patient data (53.5%) compared to male subjects which amounted to 76 patient data (46.7%).

Table 5.2 Distribution of Age Subject Research Patterns

Age	<i>n</i> (Amount)	% (Percentage)
60-70	109	66.9
71-80	44	27
81-90	10	6.1
Total	163	100.0

In table 5.2 shows that the data of UTI patients in elderly aged  $\geq 60$  years is 163 patient data. The most data of UTI patients were in the 60-70 year age group, which were 109 patient data (66.9%).

Table 5.3 Distribution of Research Subject Patterns Based on Bacteria Causes of UTI

In table 5.3 shows that the bacteria that cause UTI in the elderly were found to be the most, namely *Escherichia coli* bacteria with 127 isolates (78%) followed by *Klebsiella pneumoniae* with 36 isolates (22%).

Table 5.4 Distribution of Research Subject Patterns Based on *Escherichia coli* Bacteria on Amikacin, Ceftazidime, Meropenem and Nitrofurantoin Antibiotics in UTI Patients

Antibiotic	<i>Escherichia coli</i> (n=127)					
	R	%	I	%	S	%
Amikacin	0	0	1	0.8	126	99.2
Ceftazidime	96	75.6	0	0	31	24.4
Meropenem	3	2.4	0	0	124	97.7
Nitrofurantoin	16	12.6	9	7.1	102	80.3

In Table 5.4 shows that the resistance pattern of *Escherichia coli* bacteria to ceftazidime antibiotics has the highest resistance level (75.6%). The next highest followed by nitrofurantoin antibiotics (12.6%), meropenem (2.4%). Whereas for antibiotics amikacin does not have a resistance number (0%).

Antibiotic	<i>Klebsiella pneumoniae</i> (n=36)					
	R	%	I	%	S	%
Amikacin	1	2.8	0	0	35	97.2
Ceftazidime	26	72.2	0	0	10	27.8
Meropenem	4	11.1	0	0	32	88.9
Nitrofurantoin	20	55.6	6	16.7	10	27.8

Table 5.5 Distribution of Research Subject Patterns Based on *Klebsiella pneumoniae* Bacteria on Amikacin, Ceftazidime, Meropenem and Nitrofurantoin Antibiotics in UTI Patients

In Table 5.5 shows the resistance pattern of *Klebsiella pneumoniae* bacteria to ceftazidime antibiotics has the highest resistance rate (72.2%). Then the next highest followed by nitrofurantoin antibiotics (55.6%), meropenem (11.1%) and amikacin (2.8%).

## Discussion

The results showed that the data of patients with subjects of women who suffered from UTI were slightly more than male subjects. The dominant UTI in women can be caused by differences in the anatomical structure of a woman's urethra shorter than a man's, making it easier for bacteria to enter the woman's bladder. Female bladder is also closer to the anus which makes susceptible bacteria move from the anus to the urethra<sup>12</sup>.

The results of the study explained that every elderly population starting from 60 years to 90 years had data that they included UTI patients. UTI is one of the most common infections in geriatric or elderly patients. UTI can occur at certain times that occur in the elderly. This infection is the second highest infection after respiratory infection in the elderly<sup>13</sup>.

Bacteria	n	%
	(Amount)	(Percentage)
<i>Escherichia coli</i>	127	78.0
<i>Klebsiella pneumoniae</i>	36	22.0
Total	163	100.0

The most bacteria found in elderly patients with UTI are *Escherichia coli* bacteria followed by *Klebsiella pneumoniae*. The most common bacteria that causes UTI is *Escherichia coli* then the second most bacterial, *Klebsiella pneumoniae*<sup>14</sup>. This is due to the large intestine and perineal area functioning as a reservoir for pathogenic bacteria such as *Escherichia coli*<sup>15</sup>. In addition, most of the UTIs involving the bladder or kidneys in a healthy host are caused by the small number of type O antigens that can produce colonization and cause infection. *Escherichia coli* bacteria are used for uropathogenic and can produce cytotoxic hemolysin then cause tissue invasion.<sup>15</sup>

The pattern of resistance of *Escherichia coli* bacteria obtained from the results of this study shows the highest resistance results, namely *Escherichia coli* bacteria against ceftazidime antibiotics. The next highest followed by the antibiotic nitrofurantoin and antibiotics meropenem. Whereas antibiotics amikacin does not have resistance numbers. The resistance of *Escherichia coli* bacteria to ceftazidime antibiotics can be caused by *Escherichia coli* bacteria which have been found to have a resistance mechanism in the Extended-Spectrum Beta-Lactamase (ESBL) with porin impermeability and efflux pump activity<sup>16</sup>. Antibiotic resistance of nitrofurantoin to *Escherichia coli* bacteria is associated primarily with the presence of mutations in the chromosomal nitroreductase gene (*nfsA* and *nfsB*) involved in converting drugs into toxic compounds. In addition, nitrofurantoin resistance can also be caused by the presence of the *oqxAB* gene mediated by plasmids<sup>17</sup>.

The resistance mechanism of carbapenem antibiotics is caused by carbapenemase production and also due to deletion or loss of outer protein membranes<sup>18</sup>. Amikacin can actively fight against *Escherichia coli* by transporting through the cytoplasmic membrane which in the process depends on the available oxygen. This antibiotic also has a bactericidal effect on gram-negative bacteria including *Escherichia coli* so that amikacin in its use is sensitive to *Escherichia coli*.<sup>19</sup> This study explains that the resistance pattern of *Escherichia coli* bacteria to ceftazidime, nitrofurantoin and meropenem in elderly patients with UTI can be known to cause the resistance in general, which is caused by mutations in genes, changes in permeability (membranes and porins), production of enzymes that can damage antibiotics, changes of efflux pump activity and the use of antibiotic abuse.

The resistance pattern of *Klebsiella pneumoniae* bacteria obtained from the results of this study shows that the highest level of resistance of *Klebsiella pneumoniae* is against ceftazidime antibiotics.

The next highest sequence is followed by nitrofurantoin, meropenem, and amikacin antibiotics.

The resistance of ceftazidime against *Klebsiella pneumoniae* can be caused by the extended-spectrum beta-lactamase gene (ESBL) which is a beta-lactamase that has mutations and can damage ceftazidime antibiotics by ceftazidime binding to bacterial enzymes ( $\beta$ -lactamase) which can hydrolyze the ring  $\beta$ -lactam and deactivate the antibacterial properties of ceftazidime antibiotics.

Nitrofurantoin resistance is caused mainly by the presence of mutations in *nfsA* or *nfsB* which both will affect nitroreductase which is not sensitive to oxygen so that nitrofurantoin resistance can increase. In addition, the presence of the *oqxAB* gene in *Klebsiella pneumoniae* can increase its resistance to the antibiotic nitrofurantoin<sup>20</sup>. The resistance of meropenem against *Klebsiella pneumoniae* caused by the NDM-1 gene which is a carbapenemase gene encoding<sup>21</sup>. In addition, the OXA-181 enzyme can affect carbapenemase so meropenem resistance against *Klebsiella pneumoniae* can also occur<sup>22</sup>.

Mechanism resistance of amikacin against *Klebsiella pneumoniae* caused by the enzymatic modification of the drug, modification of ribosomal target and decreased intracellular antibiotic accumulation by changing the permeability of the outer membrane, decreased transport of the inner membrane or active efflux<sup>23</sup>. Among all the mechanism resistance, the most common amikacin mechanism resistance caused by the production of aminoglycoside-modifying enzymes<sup>23</sup>. This study explains that the resistance pattern of *Klebsiella pneumoniae* bacteria against ceftazidime, nitrofurantoin, meropenem and amikacin in elderly UTI patients in general can be caused by the production of enzymes that can damage antibiotics, inhibited peptidoglycan synthesis, modification of ribosomal targets, changes in permeability membranes, decreased membrane transport and mutations in genes.

## Conclusion

Based on this research, the number of data for elderly patients suffering from UTI is 163 patient data. The number of data for elderly patients of women with UTI was a little more than 87 patient data (53.3%) compared to the data of 76 elderly male patients (46.7%). The bacteria that cause UTI in the most elderly are *Escherichia coli* bacteria with a total of 127 isolates (78%) followed by *Klebsiella pneumoniae* with 36 isolates (22%). *Escherichia coli* bacteria are resistant to antibiotics with the highest resistance number of ceftazidime (75.6%), nitrofurantoin (12.6%) and meropenem (2.4%). Whereas amikacin antibiotics do not have resistance numbers (0%).

*Klebsiella pneumoniae* bacteria are resistant to antibiotics with the highest resistance number of ceftazidime (72.2%), nitrofurantoin (55.6%), meropenem (11.1%) and amikacin (2.8%).

## CONFLICT OF INTEREST

The author stated there is no conflict of interest

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