

## Isolate Gram Negative Bacteria Resistant Antibiotics Carbapenems in Maternal Urine Pregnant

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### ABSTRACT

Pregnant women with bacterial uria, more than half have infections with antibiotic- resistant organisms. This pattern of resistance has a real clinical impact because pregnant women with antibiotic-resistant Gram Negative lower urinary tract infections are estimated to be 2-3 times more likely to develop pyelonephritis. Antibiotic resistance is common among pathogenic bacteria that cause urinary tract infections. Enterobacteriales are frequently encountered pathogens that cause community-associated infections, such as urinary tract infections. Urinary tract pathogenic bacteria are generally caused by *Escherichia coli*, *Staphylococcus aureus* *Klebsiella sp*, *Escherichia coli* is a common cause of bacteriuria symptomatic and asymptomatic. In the era of multidrug-resistance, appropriate diagnosis and treatment must be given to avoid complications in pregnant women and prevent antibiotic resistance. Antibiotic-resistant bacteria pose a serious threat to the mother and fetus because it is difficult to obtain safe antibiotics. Increased bacterial resistance of urinary tract pathogens may complicate the selection of appropriate drugs. This study aimed to determine the sensitivity of carbapenem antibiotics to bacterial isolates from the urine of pregnant women. This type of research is descriptive observational research, where the sample used is urine Pregnant. A urine specimen sample is inoculated to in Brain Heart Infusion Broth (BHIB) media, next inoculated to MacConkey agar medium. Isolate bacteria from MacConkey To be done Gram examination and sensitivity test. Sensitivity test use method diffusion the Kirby-Bauer disc uses an antibiotic disc group Carbapenems namely Meropenem (MER) 10ug. Data in the form of mark sensitivity form resistant (R), Intermediate (I) and Sensitive (S) of antibiotic group, participant data processed use SPSS application. This study obtained there were 5 ( 20 %) Gram Negative bacteria that resistant antibiotic meropenem (MER) from group Carbapenems. There is isolate Gram Negative bacteria from urine pregnancy that resistant to antibiotics meropenem from group carbapenemia. Type of group carbapenems the is the antibiotic.

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### INTRODUCTION

The immune system in pregnant women is reduced during pregnancy, making them susceptible to bacterial infections. Bacteria found in urine during pregnancy can be classified as asymptomatic bacteria, upper Urinary Tract Infection (UTI) or lower UTI. (Glaser & Schaeffer, 2015) about 10% women pregnant experience infection channel urinary . (Szweda & Józwick, 2016), and around 2% to 15% of incidents bacteriuria asymptomatic in all pregnancy . (Smaill & Vazquez, 2019)

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Bacteriuria Asymptomatic is bacteriuria without specific symptoms of acute urinary tract infection (Smaill & Vazquez, 2019). Bacterial screening in pregnant women needs to be carried out to determine the presence of bacteriuria early in pregnancy (Glaser & Schaeffer, 2015).

Pathogenic bacteria in the urinary tract are generally caused by *Staphylococcus sp* (Ndamason et al., 2019), *Escherichia coli*, *Staphylococcus aureus* (Awoleke et al., 2015), *Klebsiella sp* (Muharram et al., 2014). *Escherichia coli* is a common cause of bacteriuria symptomatic and asymptomatic. (Kalinderi et al., 2018) A bacteria that rarely causes urinary tract infections is *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Enterobacter sp*. Whereas Gram positive microorganisms that cause UTIs include; *Streptococcus*, *Staphylococcus aureus*, *Staphylococcus saprophyticus* and *Staphylococcus haemolyticus* (Ndamason et al., 2019).

Based on research from Rosana (Rosana et al., 2020) who conducted research on pregnant women in Jakarta found that bacteriuria Asymptomatic disease was found in 10.5% of 715 pregnant women. *Escherichia coli* is the main causative factor (26.7%), *Klebsiella pneumoniae* (20%), *Streptococcus agalactiae* (9.3%), *Enterobacter cloacae* (5.3%), *Enterococcus faecalis* (5.3%), *Staphylococcus saprophyticus* (4%), *Acinetobacter baumannii* (4%). The occurrence of this infection can be caused by reflux conditions vesicourethral, urinary tract obstruction, use of new urethral instruments, and septicemia. *E. coli* can be found in urine samples from UTI patients. (Widianingsih & Jesus, 2018).

UTI and bacteriuria asymptomatic disease during pregnancy has a negative impact on the mother and fetus (Mansouri et al., 2019), if left undiagnosed and treated appropriately it can cause acute disease, pyelonephritis and low birth weight in babies. (Lumbiganon et al., 2010) preeclampsia, premature birth, intrauterine growth restriction, premature rupture of membranes (Nurfaizah et al., 2020), birth defects and possible miscarriage (Ledan, 2020).

UTIs can be prevented, urinary tract tests, such as urine culture or DNA sequence-based analysis, can be used to improve antenatal screening in pregnant women. (Kalinderi et al., 2018) Infections can come from bacteria feces, and hygienic habits, as well as sexual behavior (Badran et al., 2015). UTI screening is very important in pregnant women (Azami et al., 2019).

Surveillance and patterns of antimicrobial resistance are important to reduce the consequences of bacteriuria symptomatic and asymptomatic, as well as resistant bacteria in pregnant women (Gessese et al., 2017). Antibiotic-resistant bacteria pose a serious threat to the mother and fetus because it is difficult to obtain safe antibiotics.

The types of antibiotics that are resistant are Ampicillin (Sáez-López et al., 2016), Erythromycin, Tetracycline Chloramphenicol and Penicillin. The most recommended antibiotic for treating urinary tract infections in pregnant women is Ceftriaxone (Aristo Parut, 2015) In the era of multidrug-resistance, appropriate diagnosis and treatment must be given to avoid complications in pregnant women (Ndamason et al., 2019).

Bacteriuria in pregnancy should be treated, the choice of antimicrobial should reflect maternal and fetal safety. After treatment, patients should be closely followed due to the risk of recurrent bacteriuria. (Glaser & Schaeffer, 2015) However Bacteriuria Asymptomatics do not always require antibiotic treatment, as their excessive use can lead to the emergence of antibiotic (Hoffmann et al., 2021).

Based on the description above, the researchers hypothesized whether the bacterial isolates in the urine of pregnant women were still sensitive to antibiotics. The specific aim of this study was to determine the sensitivity of carbapenem class antibiotics to Gram Negative bacterial isolates in the urine of pregnant women.

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## MATERIALS/METHOD

Types of research This is study observational descriptive. Collection Urine sample from Mother pregnant carried out in the work area Binanga Community Health Center (PKM). Regency Mamuju . Urine sample Mother pregnant entered in receptacle sterile. A urine specimen sample is inoculated to in Brain Heart Infusion Broth (BHIB) media. Incubated at 37 ° C for 24 hours. inoculated onto MacConkey Agar media. Colonies that grow on MacConkey agar media are subjected to Gram staining and sensitivity testing. Sensitivity testing was carried out using the Kirby-Bauer disk diffusion method using a Carbapenem class antibiotic disk, namely the antibiotic Meropenem (MER) 10ug. A barrier zone is formed interpreted according to Clinical and Laboratory Standards Institute CLSI guidelines. Data in the form of mark sensitivity form resistant (R), Intermediate (I) and Sensitive (S) of group antibiotics, participant data processed use SPSS application

## RESULTS AND DISCUSSION

Research result to isolation and sensitivity test antibiotics in urine pregnant can taken in a number of table as following :

**Table 1.** Characteristics of Pregnant Women

	Description	Frequency (n=25)	Percentage (%)
Body Weight (Kg)	<40	3	12
	40-50	2	8
	51-60	7	28
	>61	13	52
Age Pregnancy (week)	<12	4	16
	12-24	3	12
	24-36	14	56
	>36	4	16
Work	IRT	20	80
	Civil servants	2	8
	Private	3	12
Marriage to -	1	22	88
	2	3	12
Level of education	Bachelor	7	28
	elementary school	2	8
	Junior High School	3	12
	high school	13	52
Gravida	1	7	28
	2-3	13	52
	4-5	4	16
	>5	1	4

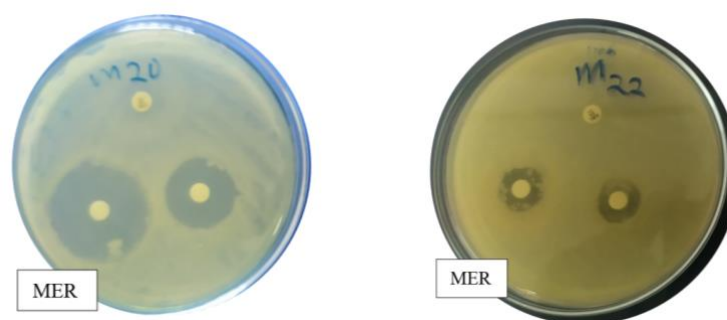
**Table 2.** Antibiotic sensitivity test on MacConkey media bacterial isolates

Antibiotics			Resistance diameter (mm)	n (%)
Meropenem (MER)	10	ug	=<22 (R)	5 (20%)
			23-27 (I)	3 (12%)
			>=26 (S)	17 (68%)
			Total	25 (100%)

Description: R=Resistant, I=Intermediate, S=Sensitive The results of the sensitivity test on 25 bacterial isolates from MacConkey Agar media showed that 5 (20%) were resistant to the antibiotic Meropenem.



**Figure 1.** Bacterial colonies on MacConkey Agar media



**Figure 2.** Sensitivity Test Meropenem (MER) antibiotics in isolates Gram Negative Bacteria

Pregnancy cause some physiological and hormonal changes. In the first and second trimester of pregnancy, it occurs enlargement ureter, this process continues until childbirth. Increased plasma volume causes a decrease in urine concentration during pregnancy and an increase in bladder volume. As a result of these changes, bacteria will more easily travel to

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the urethra and kidneys, which can cause the development of bacteriuria (Ndamason et al., 2019).

In this study, from 25 urine samples from pregnant women, after inoculation on BHIB enrichment media, they were then inoculated onto specific MacConkey Agar media. MacConkey Agar media is a medium used to grow Gram Negative bacteria. In MacConkey agar media there is growth of bacterial colonies

Bacteria in urine during the pregnancy period can be classified as asymptomatic bacteria. There is an estimated 2% to 15% incidence of bacteriuria asymptomatic in all pregnancies. Urinary tract pathogenic bacteria are generally caused by *Staphylococcus sp.*, (Ndamason et al., 2019), *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella sp.* *Escherichia coli* is a common cause of bacteriuria symptomatic and asymptomatic (Szweda & Jóźwik, 2016) Bacteriuria Asymptomatic is bacteriuria without specific symptoms of acute urinary tract infection (Smaill & Vazquez, 2019). Bacterial screening in pregnant women needs to be carried out to determine the presence of bacteriuria early in pregnancy (Glaser & Schaeffer, 2015) Urinary tract pathogenic bacteria are generally caused by *Escherichia coli*, *Staphylococcus aureus* (Awoleke et al., 2015), *Klebsiella sp* (Muharram et al., 2014). *Escherichia coli* is a common cause of symptomatic and asymptomatic bacteriuria (Kalinderi et al., 2018).

Infection Channel Urinary (UTI) section on or UTI section lower (Glaser & Schaeffer, 2015). Infection This This is because the immune system of pregnant women is reduced during pregnancy, making them susceptible to bacterial infections. UTIs are caused by a variety of pathogens, including Gram-negative and Gram-positive bacteria, as well as fungi. According to UTI epidemiology, uropathogenic E.coli (UPEC) is the main pathogenic factor causing UTI, approximately 75% of uncomplicated UTI cases; however, there are less common pathogens, such as *Klebsiella pneumoniae* (*K. pneumoniae*), *Enterococcus faecalis* (*E. faecalis*), group B *Streptococcus*, *Proteus mirabilis* (*P. mirabilis*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. Aureus*), and other pathogenic bacteria cause opportunistic UTIs (Zhou et al., 2023).

Based on study from Rosana (Rosana et al., 2020) who conducted research on pregnant women in Jakarta found that bacteriuria Asymptomatic disease was found in 10.5% of 715 pregnant women. *E. coli* is the main causative factor (26.7%), *Klebsiella pneumoniae* (20%), *Streptococcus agalactiae* (9.3%), *Enterobacter cloacae* (5.3%), *Enterococcus faecalis* (5.3%). The occurrence of this infection can be caused by reflux conditions vesicourethral, urinary tract obstruction, use of new urethral instruments, and septicemia. *E. coli* can be obtained in urine samples from UTI patients. (Widianingsih & Jesus, 2018). In research by Mastuti Widianingsih, it was identified that the bacteria contained *E. coli*, *Klebsiella spp.* Positive results for *E. coli* are indicated by small round colonies, semi- mucoid elevations, and positive lactose fermentation on MacConkey Agar media (Widianingsih & Jesus, 2018).

Urinary tract infections (UTIs) are one of the most common bacterial infections worldwide, occurring in community and healthcare settings. Uropathogenic *Escherichia* (UPEC) is the most common causative agent for both uISK and cISK, followed by other pathogenic microorganisms. Additionally, the incidence of UTIs caused by multidrug resistance (MDR) is increasing, resulting in a significant increase in the spread of antibiotic resistance and the economic burden of these infections (Mancuso et al., 2023). *Escherichia* uropathogenic agents (UPECs) are the main causative agents of UTIs. UPEC strains can survive in epithelial urothelial cells, thereby acting as a reservoir of quiescent intracellular bacteria (Zaglia et al., 2022).

UTIs can be prevented, urinary tract tests, such as urine culture or DNA sequence-based analysis, can be used to improve antenatal screening in pregnant women (Kalinderi et

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al., 2018). Infection can come from fecal bacteria, and hygienic habits, as well as sexual behavior (Badran et al., 2015). UTI screening is very important in pregnant women (Azami et al., 2019).

UTI can be a factor causing other complications such as premature rupture of membranes, premature birth, low birth weight babies, intrauterine fetal growth (Yan et al., 2018), UTI and bacteriuria asymptomatic disease during pregnancy has a negative impact on the mother and fetus (Mansouri et al., 2019), if left undiagnosed and treated appropriately it can cause acute disease. and low birth weight in babies (Lumbiganon et al., 2010), preeclampsia, premature birth, intrauterine growth restriction (Kalinderi et al., 2018), premature rupture of membranes (Infection et al., 2020) (Nurfaizah et al., 2020), birth defects and possible miscarriage (Ledan, 2020).

Based on Table 2, the results of the antibiotic sensitivity test Meropenem 10 ug showed that there were 5 (20%) bacterial isolates from MacConkey Agar media is resistant Meropenem. The presence of bacterial isolates originating from the urine of pregnant women giving resistant results is a serious problem for health. The spread of antibiotic resistance is a major health problem that must be considered because it has a significant impact on the health of individuals in society (Jalil & Al Atbee, 2022). Surveillance and patterns of antimicrobial resistance are important to reduce the consequences of bacteriuria symptomatic and asymptomatic, as well as resistant bacteria in pregnant women (Gessese et al., 2017). Antibiotic-resistant bacteria pose a serious threat to the mother and fetus because it is difficult to obtain safe antibiotics.

The types of antibiotics that are resistant are Ampicillin (Sáez-López et al., 2016), Erythromycin, Tetracycline Chloramphenicol and Penicillin. The most recommended antibiotic for treating urinary tract infections in pregnant women is Ceftriaxone (Aristo Parut, 2015). In the era of multidrug-resistance, appropriate diagnosis and treatment must be given to avoid complications in pregnant women (Ndamason et al., 2019)

It is important to know local epidemiological data for appropriate initial treatment. There is increasing resistance to antimicrobial agents, especially antibiotics of first choice in the treatment of cystitis (Tano et al., 2022). The incidence of UTIs caused by multidrug resistance (MDR) is increasing, resulting in a significant increase in the spread of antibiotic resistance and the economic burden of these infections (Mancuso et al., 2023).

Based on research by Ndamason et al., 2019 that the most common urinary tract pathogen is *Staphylococcus sp.* in pregnant women it was 45% and in non-pregnant women it was 38.89%. *Staphylococcus bacteria sp.* shows resistance to Amoxicillin (AMO; 55.56%) and Chloramphenicol (CHL; 100%) in pregnant and non-pregnant women respectively. that bacterial agents are significantly associated with increased resistance to antibiotics, such as AMO (55.56%) by *Staphylococcus sp.*, DOX (33.33%) by *Staphylococcus aureus*, AMO (80%), CEP (80%), GEN (40%), and NOR (60%) by *Escherichia*, and NOR (75%), CIP (75%) by *Klebsiella sp.* in pregnant women. The most common urinary tract pathogen is *Staphylococcus sp.* with 45% and 38.89% in pregnant and non-pregnant women respectively. *Staphylococcus sp.* shows resistance (Ndamason et al., 2019).

The most common pathogens causing UTIs are gram-negative bacteria, including *Escherichia*, *Klebsiella spp.*, *Citrobacter spp.*, and *Pseudomonas spp.* For the treatment of UTI, beta-lactam antibiotics are usually recommended for the treatment of infections caused by Gram-Negative bacteria, Gram-negative pathogens often develop resistance to cephalosporins and combinations of beta-lactamase inhibitors, mainly by producing various beta-lactamases. Inappropriate choice of antibiotics can cause problems such as persistence

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of infection, recurrence, or reinfection, resulting in increased health care costs from long hospital stays (Ezure et al., 2022).

The level of resistance to third generation cephalosporins is also very high, namely 22%. Resistance to carbapenems is low. However, superiority of nitrofurantoin was found, which provides rational support for the usefulness of nitrofurantoin as an empiric therapeutic (Haindongo et al., 2022)

Of pregnant women with bacteriuria, more than half have at least one infection with an antibiotic-resistant organism. This pattern of resistance has a real clinical impact because pregnant women with antibiotic-resistant Gram-negative lower urinary tract infections are estimated to be 2-3 times more likely to develop pyelonephritis. (Denoble et al., 2022)

Enterobacterales are frequently encountered pathogens that cause community-associated infections, such as urinary tract infections. ESBL-producing Enterobacterales are increasingly associated with community-acquired infections in the US and worldwide. Carbapenems are preferred for the treatment of invasive ESBL-producing Enterobacterales infections. However, carbapenem resistance is also increasingly observed in Enterobacterales (Shrestha et al., 2022).

In research by Jalil MB et al, isolates were obtained *E. Coli* was highly resistant to ceftriaxone (89.0% of isolates), ampicillin (86.6%), levofloxacin (82.9%), cefotaxime (79.3%), aztreonam (74.4%), tazidime (68.3%) and gentamicin, piperacillin, and trimethoprim-sulfamethoxazole, 54.9 and 53.7%, respectively. Isolate *E. coli* was found to be relatively less resistant to imipenem (2.4%), cefepime (34.1%), and ciprofloxacin (35.4%). *E. coli* and *K. pneumoniae* of clinical isolates showed high resistance to many antibiotics in UTI patients. (Jalil & Al Atbee, 2022)

ESBL is considered a major pathogen contributing to antimicrobial resistance. Among 444,281 isolates *E. coli* from urine samples tested in 1013 laboratories, the average prevalence of ESBL-producing *E. coli* was 3.0% (Paumier et al., 2022).

Bacteriuria in pregnancy must be treated, the safety of the mother and fetus is a concern when selecting antibiotics. After treatment, patients should be closely followed due to the risk of recurrent (Glaser & Schaeffer, 2015). However Bacteriuria asymptomatics do not always require antibiotic treatment, as their excessive use can lead to the emergence of resistant strains. Treatment of asymptomatic bacteriuria aims to treat the infection. The urinary tract bacterial isolate must be sensitive to the selected antibiotic, the duration of treatment must be adequate, compliance must be ensured, and the drug must have favorable pharmacokinetic parameters. Treatment must be safe during pregnancy, for both the mother and the developing fetus. Increasing bacterial resistance of urinary tract pathogens may complicate the selection of appropriate drugs, especially in resource-poor settings, where facilities for urine culture and antimicrobial susceptibility testing are limited (Smaill & Vazquez, 2019). Appropriate use of antibiotics can help overcome the problem of the emergence of antibiotic resistance (Hoffmann et al., 2021)

## CONCLUSIONS

There is isolate Gram Negative bacteria from urine pregnancy that resistant to antibiotics meropenem from group carbapenemia. Type of group carbapenems the is the antibiotic

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