

Original Research Paper

Multidrug Resistant Uropathogens among Egyptian Pregnant Women

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Abstract: Urinary Tract Infections (UTIs) in pregnancy is a common medical problem associated with significant increase in the risk of fetal morbidity and mortality. The effective appropriate antimicrobial agent is a major concern as many effective antimicrobial groups cannot be used due to their potential toxicity to the fetus as well as the increasing rates of Multidrug-Resistant (MDR) strain isolation. This cross-sectional study was conducted on women attending the antenatal care of Zagazig University. This study aimed to estimate prevalence of various uropathogens in UTI among the pregnant women and determine their antimicrobial resistance patterns. Clean catch mid-stream urine samples were obtained, complete microbiological examination and antibiotic susceptibility testing were carried out. More than half of culture positive samples was obtained from asymptomatic pregnant women. Asymptomatic bacteriuria was more common among primigravida, women of low socioeconomic class and with history of previous Cesarean section. Gram negative bacterial isolates were the most prevalent (71%). The most frequently isolated pathogens were: *E. coli* 34%, *K. pneumoniae* 26% and *S. saprophyticus* 23%, among the total Gram negative isolates, 95.0% were MDR. Meropenem was the antibiotic with the highest susceptibility rate (96%) on *E. coli* isolates, followed by nitrofurantoin (74%) and tobramycin (72%). Recommendations: Urine culture and sensitivity must be the role as MDR pathogens are increasing, rationalization of antibiotic administration is a must.

Keywords: MDR, Bacteriuria, Pregnancy

Introduction

Urinary Tract Infection (UTI) in pregnancy is a major challenge for physicians. The extensive structural and functional changes in the urinary tract during pregnancy increase the risk of UTI. These changes include ureteral dilatation, increased volume of urinary bladder along with decreased its tone, increased urinary stasis and ureterovesical reflux (Duarte *et al.*, 2008). Pregnancy-induced biochemical changes; glucosuria, amino acids and hormone degradation products and pH changes are also condemned (Jeyabalan and Lain, 2007; Jolley and Wing, 2010).

Urinary tract infection is a clinical condition where inflammatory response of urothelium due to bacterial invasion occurs, which is usually associated with bacteriuria, however, in pregnancy UTIs are classified as

symptomatic and asymptomatic bacteriuria (Fasalu Rahiman *et al.*, 2015)

Asymptomatic Bacteriuria (ASB); bacteria present in the urine without evident symptoms, or Symptomatic Bacteriuria (SB); bacteria invade urinary tract tissues inducing an inflammatory response and causing symptoms. Pregnant women with untreated ASB have a significant risk of developing acute pyelonephritis later during pregnancy (Smaill and Vazquez, 2007).

Bacteriuria in pregnancy either asymptomatic or symptomatic is associated with a 50% increase in the risk of low birth weight and a significant increase in the risk of premature delivery, fetal mortality, chronic renal failure, pre-eclampsia, hypertension, anemia and postpartum sepsis (Farkash *et al.*, 2012; Dash *et al.*, 2013). The prevalence of UTI in pregnancy is variable worldwide, with a range of 2%-10 in different parts of

the world (Mathia *et al.*, 2004; Borchert *et al.*, 2008), however, some countries have higher prevalence (Onoh *et al.*, 2013; Mohamed *et al.*, 2017).

The species of isolated uropathogens are relatively limited, with the eternal leadership of *Escherichia coli* as a major cause accounting for 75%--90% of uncomplicated UTI isolates. Other players are involved; *S. saprophyticus*, *Klebsiella pneumoniae*, *Proteus mirabilis* and group B *Streptococci* (Mukherjee *et al.*, 2014; Bose and Revankar, 2018).

With the emergence of drug resistance and particularly the Extended Spectrum Beta Lactamase (ESBL) production by Gram negative bacteria and Methicillin Resistance in *Staphylococcus* species (MRSA), antibiotic options for treating pregnant woman with bacteruria become limited (Thapa *et al.*, 2015; Bose and Revankar, 2018). Multidrug-Resistant (MDR) strains are defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (Magiorakos *et al.*, 2012). In developing countries, where self medication practice and irrational antibiotic use are common, MDR represent a major concern.

This study was conducted to find out the prevalence of various uropathogens in UTI among the pregnant women and their antimicrobial resistance patterns and to determine the prevalence of MDR isolates in these subjects.

Methodology

Study Design

A cross-sectional study during the period from January 2018 to January 2019 was conducted on pregnant women attending the antenatal care clinic of Zagazig University Hospital. Participants were excluded if they had antimicrobial drug therapy in the preceding 2 weeks prior to sample collection. Informed written consent was obtained from each patient prior to sample collection. Detailed history highlighting the following items was gathered: Age, complaint, period of gestation, parity and previous caesarian sections. Ethical approval was obtained from Zagazig University IRB committee.

Sample Size

The required sample size was calculated using single population formula (Charan and Biswas, 2013).

The calculated sample size (n = 304) was rounded off to 400.

Microbiological Specimen Processing

Participants were instructed to obtain a clean-catch midstream urine samples. Sample were collected in a sterile container and cultured on Cysteine Lactose Electrolyte Deficient agar (CLED) in addition to nutrient agar, using a calibrated drop delivering 0.001 mL of urine.

Inoculated plates were incubated at 37°C degree overnight. The cultured plates were examined and bacterial colonies were counted. Identification of bacterial growth was done depending on cultural morphology and Gram staining. Gram positive cocci were subjected to catalase, coagulase and DNase tests, in cases of Staphylococcal isolates, novobiocine sensitivity was tested and subculture on Mannitol salt agar. Gram negative rods were identified by the following biochemical reaction; oxidase, urease, citrate utilization, indole and fermentative profile on triple sugar agar. Significant bacteriuria was considered when 10⁵ colony forming units per ml urine of one or two isolate (s) was obtained. Wet film examination using high power lens was carried out with reporting of the followings: Pus cells, red blood cells, epithelial cells and crystals.

Antibiotic Susceptibility Testing

Antimicrobial susceptibility was tested for bacterial isolates by modified Kirby Bauer test Agar. A loop full of bacteria was taken from pure colony and was transferred to a tube containing 5 mL nutrient broth and mixed gently until it formed a homogenous suspension. The turbidity of the suspension was then adjusted to the optical density of a McFarland 0.5 tubes measured at 500 nm absorbance in order to standardize the inoculum size. A sterile cotton swab was then dipped into the suspension and the excess fluid was removed by gentle rotation of the swab against the surface of the tube. Bacterial suspension was evenly distributed over the entire surface of Mueller-Hinton plates using the swab by successive 90° rotation movement and keeping Petri dish lids in place, the antimicrobial discs were evenly distributed on the inoculated plates. The selection of antibiotic tested is guided by Clinical Laboratory Standard CLSI (2017), US Food and Drug Administration (FDA) categories of medications in pregnancy and the type of isolated bacteria regarding Gram staining. Gram-negative bacterial isolates were tested against the following antimicrobials amoxicillin-clavulanic acid, cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, cefuraxime, meropenem, nitrofurantoin, piperacillin tazobactam, tobramycin, trimethoprim-sulphamethoxazole.

Gram positive organisms were tested against the following antimicrobial agents: Azithromycin, erythromycin, clindamycin, cefoxitin, linezolid, trimethoprim-sulphamethoxazole, nitrofurantoin, gentamycin, rifampicin, vancomycin.

Antibiotic discs used were supplied by (Oxoid UK).

The plates were then transferred to incubator at 37°C for 18-24 h. Diameter of the zone of inhibition around the disc was measured to the nearest millimeter using a metal caliper and the isolate were classified as sensitive and resistant. (Intermediate agents are considered resistant) (CLSI, 2017).

ESBL Detection

Isolates with zone diameters less than 25 mm for ceftriaxone and less than 22 mm for ceftazidime were subsequently confirmed for ESBL production via double-disc synergy test (DDST). Amoxy-clavulanic acid (20/10 µg) disc was placed in the center of ceftazidime (30 µg) and cefotaxime (30 µg) discs with center to center distance of 25-30 mm. After overnight incubation at 37°C, confirmation of ESBL producing pathogen was assessed when the zone of inhibition around ceftazidime and cefotaxime was expanded by at least 5 mm by the presence of clavulanic acid. *E. coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 were used as negative and positive controls for ESBL production, respectively (CLSI, 2017).

MRSA Detection

Staphylococcal isolates separately tested on additional MH agar plates against cefoxitin 30 ug and incubated at 33-35°C; ambient temperature for 24 h to detect mecA-Mediated Oxacillin Resistance.

Statistical Methods

Data were analyzed using OpenEpi, Version 3, data expressed in percentage, Chi square test was used to analyze qualitative data. Significant results obtained when *P* value is ≤0.05.

Results

Out of the 400 examined urine samples, 182 samples revealed significant bactruria, this amounted to a 45% positive culture rate. Only 78 (43%) positive samples belonged to participants with UTI symptoms (fever, dysurea, frequency). The remaining 104 (57%) positive samples were considered as ASB. Socio-demographic

and clinical criteria of participants with positive cultures are displayed in table 1.

Bacterial Isolates

Types and prevalence of isolated organisms are displayed in Table 2. Gram negative pathogens accounted for 71% (n:130) of the isolated organisms (n:182) of positive culture samples. *E. coli* (62) 34%, *K. pneumoniae* (48) 26%, *S. saprophyticus* (40) 23%, *Morganella* (9) 5%, *Streptococci* (8) 5%, *Pseudomonas* (7)3%, *Enterobacter* (2) 1%, *Enterococci* (2)1%, *Proteus* (2) 1%, Methicillin Resistant *S. aureus* (MRSA) (2) 1%.

Antibiotic Resistance Pattern

Regarding Gram negative isolates, meropenem was the antibiotics with maximum sensitivity (Fig. S1), about 96% of the isolated *E coli* was meropenem sensitive, susceptibility rate of *E coli* isolates toward other agents was as follow: Nitrofurantoin (74%), tobramycin (72%), Azteronam (68%), cefepime (63%), ceftriaxone (55%). *K. pneumoniae* species showed high resistance rates (80-100%) to most tested agents, azteronam showed the highest susceptibility rate in such isolates. Among the total Gram negative isolates, 95% (124/130) were MDR. There were no isolates sensitive to all antibiotics tested (Table S1 and Fig. S2).

Prevalence of ESBL producing gram negative isolates demonstrated in Table 3.

Twenty nine (47%) isolates of *Escherichia coli* and 21 (44%) isolates of *Klebsiella pneumoniae* were ESBL producers (Figure 1) The total ESBL producing isolates among gram negative pathogens was 50 (38%).

In isolates of some Gram negative bacteria (*Morganella*, *Pseudomonas*, *Proteus*, *Enterobacter*), 100% resistance rates were detected toward some agents; amoxicillin-clavulanic acid, cefazolin, cefepime, ceftazidime (Fig. 2S).

Table 1: Socio-demographic, obstetric and clinical variables of pregnant women with culture positive results

	SB No: 78		ASB No: 104		X ²	P
Parity					9.7	0.007*
Primigravida	20	26%	56	54%		
Primipara	31	40%	37	36%		
Multipara	27	34%	11	10%		
Age					3.6	0.16
19-27	23	29%	21	20%		
28- 35	37	48%	47	45%		
36- 43	18	23%	36	35%		
Previous CS					4.6	0.03*
Yes	46	59%	77	74%		
No	32	41%	27	26%		
Socioeconomic state					2.4	0.2
Low	45	58%	71	68%		
Moderate	21	27%	19	18%		
High	12	15%	14	14%		

Table 2: Types and prevalence of bacterial isolates

Organism	SB (78)	ASB (104)	Total (182)
<i>E. coli</i>	23	39	62
<i>K. pneumonia</i>	17	31	48
<i>S. saprophyticus</i>	13	27	40
<i>Morganella</i>	7	2	9
<i>Streptococci</i>	7	1	8
<i>Pseudomonas</i>	5	2	7
<i>Enterobacter</i>	1	1	2
<i>Proteus</i>	1	1	2
<i>Enterococci</i>	2	0	2
MRSA	1	1	2
Total	78	104	182

Table 3: Prevalence of ESBL producing gram negative isolates

Organism	Number (%)	ESBL producer (%)
<i>E. coli</i>	62	29 (47%)
<i>K. pneumonia</i>	48	21 (44%)
<i>Morganella</i>	9	0
<i>Pseudomonas</i>	6	0
<i>Enterobacter</i>	2	0
<i>Proteus</i>	2	0
Total	130	50 (38%)

Table 4: Antibiogram of the most prevalent Gram positive isolates

Agent	CON n: 42		Streptococci n: 8	
	R	S	R	S
AZM	32 (76%)	10 (34%)	4 (50%)	4 (50%)
E	38 (90%)	4 (10%)	6 (75%)	2 (25%)
Clind	26 (62%)	16 (38%)	8 (100%)	0 (0%)
Ceph	36 (86%)	6 (14%)	6 (75%)	2 (25%)
FEP	36 (86%)	6 (14%)	5 (62%)	3 (38%)
FOX	24 (57%)	18 (43%)	3 (38%)	5 (62%)
LiZ	2 (5%)	40 (95%)	0 (0%)	8 (100%)
SXT	34 (81%)	8 (19%)	7 (88%)	1 (12%)
F	10 (23%)	32 (77%)	7 (88%)	1 (12%)
Mem	4 (10%)	38 (90%)	1 (12%)	7 (88%)
Gen	26 (62%)	16 (38%)	5 (63%)	3 (37%)
Rif	14 (33%)	28 (67%)	7 (88%)	1 (12%)

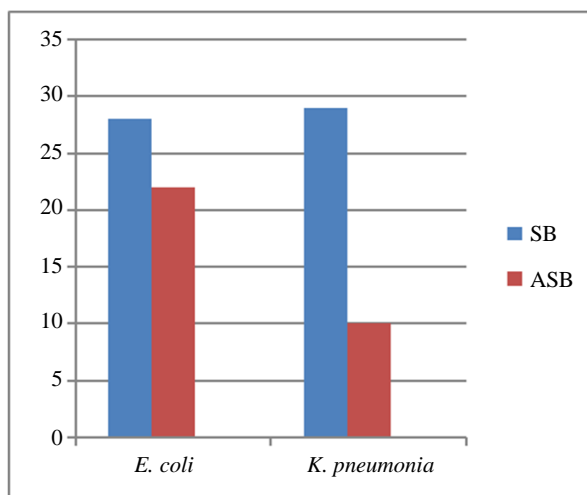


Fig. 1: Distribution of ESBL and non ESBL isolates among SB and ASB, chi square: 0.64, P: 0.2

Linezolid showed the maximum sensitivity in Coagulase negative staphylococci (CON) isolates, while erythromycin showed the highest resistance rates, however, streptococcal isolates were noticed to have more resistance to clindamycine than erythromycin. High levels of single and multiple antimicrobial resistances against commonly prescribed drugs were observed (Table 4).

Discussion

The effective appropriate antimicrobial agent is a problematic issue in pregnancy as many antimicrobial groups cannot be used; quinolones, tetracyclines due to their potential toxicity to the fetus (Matuszkiewicz-Rowińska *et al.*, 2015). With the emergence of drug resistance and particularly the ESBL production by Gram negative bacteria and methicillin resistance in Staphylococcus species, antibiotic options for treating pregnant woman with bacteruria are limited (Thapa *et al.*, 2015; Bose and Revankar, 2018).

In the current study, a 45% positive culture rate was reported, this is a higher rate than those obtained from previous studies carried out by different researchers in the same governorate (Dimetry *et al.*, 2007), the prevalence of laboratory confirmed UTI in pregnant was estimated to be 30.29% in neighboring regions (Suez governorate) in Egypt (Mohamed *et al.*, 2017). Similar findings were obtained in Yemen and Bangaldish (Almushait *et al.*, 2013), however Indian (Manjula *et al.*, 2013) and Nigerian (Onoh *et al.*, 2013) studies reported slightly raised rates (49.4% and 46.5% respectively). This variation may be explained by the differences in characteristics of study populations, environmental conditions and methodology.

In the this study, more than half of culture positive samples was obtained from asymptomatic pregnant women. Asymptomatic bacteriuria in pregnancy was more common among primigravida (54%) compared to multigravida, however, Dash *et al.* (2013), reported that majority (54.4%) of the subjects they tested were multipara. This discrepancy could be explained by absence of routine urine culture in Egypt, so primigravida especially in rural communities are more prone to ASB. These findings highlight the importance of urine culture in the antenatal care practice to pick up the affected pregnant and giving the appropriate therapy.

Previous Caesarian section was associated with higher risk of ASB (74%), The past decade had witnessed a great increase in the prevalence of CS in Egypt (52%), which suggests that cesarean delivery might be overused or used for inappropriate indications (The Population Council, 2018).

ASB was more prevalent in women of low socioeconomic class (68%) although not statically

significant. These findings are similar to those obtained by (Kerure *et al.*, 2012; Bose and Revankar, 2018).

Gram-negative bacteria were more prevalent with a noticed predominance of *E. coli* and *K. pneumonia*. Similar findings have been reported in Ethiopia (Derese *et al.*, 2016). This is a cardinal finding that had been previously noted by many other studies in different countries (Moyo *et al.*, 2010; Dash *et al.*, 2013; Onoh *et al.*, 2013). As *E. coli* have a normal presence in the bowel, infection could occur by contamination of the urethra by fecal matter due to poor and difficult hygiene, the anatomical proximity to the genito-urinary area in womans and the urinary stasis induced by pregnancy (Farkash *et al.*, 2012; Huttner *et al.*, 2015). About 38% of Gram negative isolates was ESBL producers, this ratio is higher than those obtained by other authors Iqbal *et al.* (2014; Thapa *et al.*, 2015). This higher rate could be explained by the irrational antibiotic use and self-medication practice especially with broad spectrum antibiotics that could be easily obtained in many regions in Egypt without medical prescriptions.

Most Gram negative isolates were resistant to more than three antibiotic classes. The antibiotic susceptibility patterns of Gram Negative bacteria showed that meropenem, azreonam and nitrofurantoin were effective in more than half of these isolates. These findings are in agreement with an Indian study (Bose and Revankar, 2018) stated that meropenem was the most sensitive antibiotic (84%), followed by cefaperazone (73.1%) and nitrofurantoin (69.2%). The antibiotic with the overall highest sensitivity pattern in this study was meropenem, however, nitrofurantoin showed an appreciated sensitivity rates in *Proteus, morganella, E coli* and CoNs, these findings are quite similar to those obtained by (Onoh *et al.*, 2013), so nitrofurantoin could be a good option in the management of UTI in pregnancy, especially when the isolated organism has good sensitivity to nitrofurantoin. Results from systematic review and meta-analysis of 27 controlled clinical trials revealed that nitrofurantoin appears to have good clinical and microbiological efficacy for UTI caused by common uropathogens, with clinical cure rates varying between 79% and 92% (Huttner *et al.*, 2015).

Ceftazidime, cephazolin and amoxicillin-clavulanic acid had the higher resistance rates. Similar findings was reported by Bose and Revankar (2018). The resistance rates of amoxicillin-clavulanic acid in Gram negative isolates were found to be 65-100%, with overall rate of 82%, this could be explained by the irrational use of the drug due to its easy rout of administration and relatively low price.

Among the total Gram negative isolates, 95.0% (124/130) were MDR, this figure is higher than that obtained by Thapa *et al.* (2015) in Nepal (72%), however other studies revealed higher isolation rate of MDR (Alemu *et al.*, 2012; Gessese *et al.*, 2017). The high prevalence of MDR reported in our study might be due

to the easily obtained, non-prescribed drugs. Although bacterial resistance is a natural phenomenon, its current high and dangerous rate usually is related to the misuse of antimicrobial drugs, failure to adhere to standard treatment guideline and inadequate or absence of stringent antimicrobial drug resistance surveillance program.

Conclusion

Multidrug resistant bacteria is a major health problem especially among pregnant woman. Urine culture and sensitivity must be included in the antenatal care practice to detect ASB and administer accurate treatment.

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Author's Contributions

Wafaa Salah Metwally: Study idea and design, microbiological processing of the specimen, analysis of laboratory data, writing and editing the manuscript, corresponding author.

Walid Mohamed Elnagar: Patient selection and history taking, analysis of clinical data, writing and editing the manuscript.

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Supplement Material

Table S1: Antibigram of Gram negative isolates

Antibiotic	<i>E. coli</i> n: 62		<i>K. pneumoniae</i> n: 48		<i>Morganella</i> n: 9		<i>Pseudomonas</i> n: 7		<i>Proteus</i> n:2		<i>Enterobacter</i> n:2		Total n: 130 Resistant isolates to each antibiotic
	R	S	R	S	R	S	R	S	R	S	R	S	
AMC	40 (65%)	22 (35%)	46 (96%)	2 (4%)	9 (100%)	0 (0%)	7 (100%)	0(0%)	2 (100%)	0(0%)	2 (100%)	0(0%)	106 (81%)
CZ	54 (87%)	8 (13%)	48 (100%)	0 (0%)	9 (100%)	0 (0%)	7 (100%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	0 (0%)	122 (94%)
FEP	23 (37%)	39 (63%)	43 (90%)	5 (10%)	9 (100%)	0 (0%)	7 (100%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	0 (0%)	86 (66%)
CAZ	56 (90)	6 (10%)	48 (100%)	0 (0%)	9 (100%)	0 (0%)	7 (100%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	0 (0%)	124 (95%)
CRO	28 (45%)	34 (55%)	39 (81)	9 (19%)	6 (66%)	3 (34%)	7 (100%)	0(0%)	1 (50%)	0 (0%)	2 (100%)	0 (0%)	82 (63%)
CTX	39 (63%)	23 (37%)	37 (77%)	11 (23%)	8 (88%)	1 (12%)	7 (100%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	0 (0%)	94 (72%)
MEM	4 (6%)	58 (94%)	40 (83%)	8 (17%)	0 (0%)	100 (100%)	7 (100%)	0 (0%)	0 (0%)	2 (100%)	1 (50%)	1 (50%)	51 (39%)
AZT	20 (32%)	40 (68%)	30 (63)	18 (37%)	2 (22%)	7 (78%)	5 (71%)	2 (29%)	0 (0%)	2 (100%)	2 (100%)	0 (0%)	58 (45%)
F	16 (26%)	46 (74%)	35 (73%)	13 (27%)	6 (66%)	3 (34%)	4 (57%)	3 (43%)	0 (0%)	2 (100%)	2 (100%)	0 (0%)	63 (48%)
TAZ	30 (49%)	32 (51%)	43 (90%)	5 (10%)	8 (88%)	1 (12%)	4 (57%)	3 (43%)	1 (50%)	1 (50%)	2 (100%)	0 (0%)	88 (68%)
TOB	17 (28%)	45 (72%)	42 (88%)	6 (12%)	6 (66%)	3 (34%)	5 (83%)	2 (17%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)	70 (54%)
SXT	45 (72%)	17 (28%)	44 (92%)	4 (8%)	6 (66%)	3 (34%)	7 (100%)	0 (0%)	0 (0%)	2 (100%)	2 (100%)	0 (0%)	103 (79%)

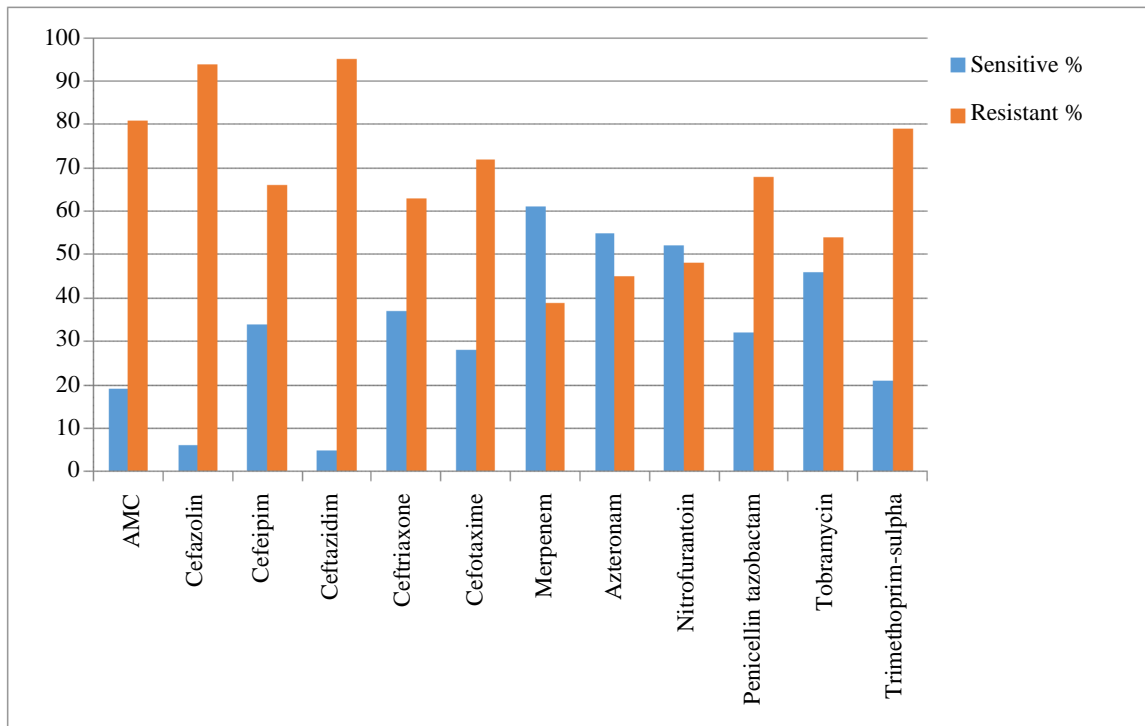


Fig. S1: Percentage of sensitive and resistant isolates toward antibiotics

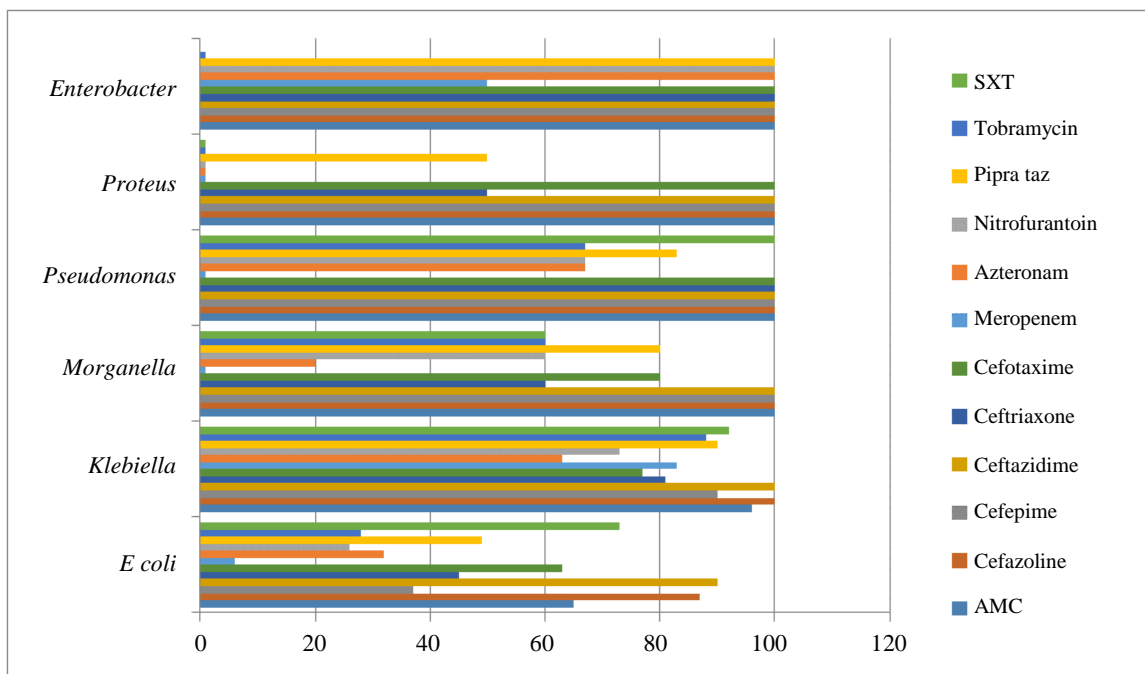


Fig. S2: The resistance rate of individual Gram negative bacteria to the tested antimicrobials