Original article

Multidrug resistant uropathogens: Some scope today, no hope tomorrow!!!

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Abstract:

Introduction: Multidrug resistant urinary pathogens are on a rise in the hospitals posing a tough challenge to the physicians at large. As they are resistant to most of the drugs available in the hospital, empirical treatment protocols have been rendered almost ineffective. Antibiotic susceptibility testing of urinary isolates helps to choose appropriate antibiotics and monitor epidemiological trends. The aim of the present study was to determine the prevalence of various urinary pathogens in a tertiary care hospital, determine their susceptibility patterns and to suggest possible treatment options in the context of present scenario.

Methods: This study was conducted in the Department of Microbiology of a super specialty hospital in New Delhi. Study design was retrospective. Eight hundred and five uropathogens isolated from 3,931 urine samples cultured over a period of one year (October 2014 - October 2015) were included in the study. The samples had been received from both in-patients and out-patients of the hospital. All these isolates had been identified by appropriate biochemical tests and Antibiotic susceptibility testing was performed by Kirby Bauer method as per the CLSI guidelines.

Observations and results: Eight hundred and five (805) urinary pathogens had been isolated in significant counts ($>10^5$cfu/ml) from 3930 urine samples cultured. The most prevalent isolate was Escherichia coli (34.16%) followed by Klebsiella spp. (18.76%) and Enterococcus spp. (15.40%). Other bacterial isolates were Proteus spp. (8.20%), Pseudomonas aeruginosa (7.95%), Staphylococcus aureus (3.98%), Acinetobacter spp. (3.11%), Morganella spp. (2.61%), Citrobacter spp. (2.48%), CoNS (1.99%) and Enterobacter spp. (1.37%). Majority of these isolates were Multidrug resistant. Eighty to Ninety percent of the gram negative bacteria viz E.coli, Enterobacter spp., Proteus spp., Pseudomonas spp. and Citrobacter spp. were susceptible to Imipenem. 72-96% of E.coli, Enterobacter spp. and Pseudomonas spp. were sensitive to Nitrofurantoin and Piperacillin-Tazobactam. All the gram positive cocci, S. aureus, CoNS and Enterococcus spp. were sensitive to Teicoplanin and Linezolid.

Conclusion: In view of high degree of MDRs amongst the uropathogens, clinicians are left with very few therapeutic options. Judicious use of reserve wonder drugs, strengthening the infection control program and implementation of a proper antibiotic policy are our only saviours.

Keywords: Multidrug resistance, uropathogens

Introduction:

Urinary tract infections are responsible for a lot of sickness amongst people in the community as well as patients in the health care settings.[1] Like most of the

developing countries, India also faces the problem of inadequacy of laboratory facilities for culture of urine samples and antibiotic susceptibility testing. This often leads to incorrect diagnosis and irrational

antibiotic usage, thereby facilitating the emergence of antibiotic resistance.[2] While the culture and sensitivity reports are still awaited, empirical antibiotic therapy is commonly started in most instances for the treatment of urinary tract infections This ever mounting problem of antibiotic resistance has strictly limited our treatment options leading to therapeutic failure most of the times.[3]

To combat this surfacing problem of antibiotic resistance, regular monitoring of the resistance trends needs to be done to bring about an improvement in our empirical treatment protocols.

Aims & Objectives:

The aim of this study was to determine the prevalence patterns of various urinary pathogens and their antibiotic sensitivity in order to suggest the treatment options in the context of present scenario.

Material & Methods:

A one year retrospective study was conducted in the Department of Microbiology by analysis of Laboratory records during a period of one year i.e. from October 2014 to October 2015.

Three thousand nine hundred and thirty one (3931) midstream urine samples had been received in the laboratory from patients admitted in ICUs, Wards and those attending OPDs. Microscopic examination of the urine had been done; and the uncentrifuged urine sample was inoculated onto Blood agar and MacConkey's agar with a calibrated loop delivering 0.001mL of urine. Eight hundred and five uropathogens (non-repetitive strains) isolated had a colony count of $\geq 10^5$ CFU/ ml which was considered as "significant". To rule out colonization only the isolates that showed ≥ 1 pus cell per 7 high power field in the wet mount examination of an uncentrifuged urine sample were included.[4] These microorganisms had been identified according to colony morphology, gram-stain reaction and standard microbiological procedures.[5,6] Antibiotic sensitivity testing of isolated organism had been done on Muller Hinton Agar by Kirby-Bauer disc diffusion method in accordance to the CLSI guidelines.[7]

Antibiotic discs used for Gram Negative Bacteria included Nitrofurantoin (300μg), Ciprofloxacin (5μg), Ofloxacin (5μg), Norfloxacin (5μg), Gentamicin (10μg), Cotrimoxazole (1.25/23.75μg), Amoxicillin+ Clavulanate (50/10μg), Piperacillin+Tazobactam (100/10μg), Cefotaxime (10μg), Ceftriaxone (30μg), Cefuroxime (30μg), Cefoperazone (75μg), Cefpirome (30μg), Imipenem (10μg), Meropenem (10μg).

Additional drugs for Non-fermenters included Amikacin (30μg), Cefepime (30μg), Ceftazidime (30μg), Ceftazidime+Clavulanate (30/10μg), Tobramycin (10μg), Ticarcillin+Clavulanate (75/10μg), Levofloxacin (5μg). For Gram positive cocci antibiotics tested were Nitrofurantoin (300μg), Ciprofloxacin (5μg), Ofloxacin (5μg), Norfloxacin (5μg), Gentamicin (10μg), High level Gentamicin (120μg), Cotrimoxazole (1.25/23.75μg), Amoxicillin-Clavulanate (50/10μg), Cephalexin (30μg), Linezolid (30μg), Teicoplanin (30μg)**.** Cefoxitin (30μg) was used as a marker for Methicillin Resistance in S. aureus and CoNS.

Observations & results:

Eight hundred and five (805) urinary pathogens had been isolated in significant counts (>10^5 cfu/ml) from the cultured samples. Of these 677 isolates were a part of monomicrobial and 128 isolates were one of strains in bimicrobial infections. The most prevalent isolate was Escherichia coli (34.16%) followed by Klebsiella spp. (18.76%) and Enterococcus spp. (15.40%). Other bacterial isolates were Proteus spp. (8.20%), Pseudomonas aeruginosa (7.95%),

Staphylococcus aureus (3.98%), Acinetobacter spp. (3.11%), Morganella spp. (2.61%), Citrobacter spp. (2.48%), Coagulase Negative Staphylococcus spp. (CoNS) (1.99%) and Enterobacter spp. (1.37%).

On studying the pattern of isolation of various uropathogens in relation to patient's gender, it was found out that majority of the uropathogens (viz E.coli, Klebsiella spp., Pseudomonas spp. Enterococcus spp. and Staphylococcus spp.) were isolated more from females rather than males and CoNS were isolated from female patients only (figure 1). Distribution of isolated pathogens amongst various patient care areas showed that E.coli was the only pathogen which was isolated uniformly from ICU, ward and OPD patients whereas rest of the gram negative isolates (viz Klebsiella spp., Pseudomonas aeruginosa, Proteus spp., Citrobacter spp., Acinetobacter spp. and Morganella spp.) were isolated mostly from ICUs (figure 2). Staphylococcus aureus and CoNS strains were the predominant isolates from OPD patients and almost nil from ICUs. On analyzing the susceptibility pattern of the members of Enterobacteriaceae family, it was found that majority of them were multidrug resistant (i.e. resistant to three or more than three class of antibiotics). Most of the isolates showed least susceptibility to 1st and 3rd generation Cephalosporins (0-22%), while susceptibility to other antibiotics ranged from 7-46% to Amoxicillin-clavunate, 9-22% to Cotrimoxazole, 15-46% to Meropenem and 10-43% to Fluoroquinolones. Majority of the isolates were highly susceptible to Imipenem (80-96%), Piperacillin-tazobactam (72-88%), Nitrofurantoin (50-87%) and Gentamicin (40-64%) as shown in figure 3.

Among the non-fermenters, all Acinetobacter spp. isolates were multidrug resistant showing <20% susceptibility to Cephalosporins, Fluoroquinolones, Tobramycin, Ticarcillin-clavulanate, Aminoglycosides and Meropenem while 32% were susceptible to Piperacillin-tazobactam and Imipenem. However, Pseudomonas aeruginosa isolates showed better susceptibility to Piperacillin-tazobactam (95.31%), Imipenem (87.50%), Amikacin (75%), Gentamicin (57.81%) and Tobramycin (39.06%), but less susceptibility was seen to drugs like Ticarcillin-clavulanate (7.81%), Cephalosporins (23-28%) and Meropenem (29.69%) (figure 4).

About eighty three percent Staphylococcus aureus isolates and 69.23% of CoNS isolates were Methicillin sensitive. Staphylococcus aureus and CoNS isolates showed excellent susceptibility to Linezolid (100% respectively) Nitrofurantoin (100% and 83.33% respectively), Gentamicin (83.33% and 68.75% respectively), and Amoxicillin-clavulanate (72% and 87.50% respectively), however, isolates were less susceptible to Norfloxacin (58.62% and 43.75% respectively), Cotrimoxazole (52.17% and 75% respectively) and Cephalexin (50% and 68.75% respectively) (figure 5).

The susceptibility of Enterococcus spp. isolates towards the various antibiotics tested was even less, 8.62% for Ciprofloxacin, 11.02% for Norfloxacin, 20% for High level Gentamicin, 37% for Amoxicillin-clavalanate and 39% for Nitrofurantoin (figure 6). These isolates were highly sensitive to Teicoplanin (74.38%) and Linezolid (100%).

Discussion:

The present study was aimed to determine the prevalence of various uropathogens. Significant growth was obtained in 20.48% (805/3930) of the urine samples cultured. The reasons for such a low positivity rate may be due to the fact that majority of urine samples were received from patients admitted

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to ICUs or wards who were already on antibiotic therapy. Majority of the urine samples that showed significant growth were from females (445 from females and 360 from males) which was similar to the findings made by most of the authors like Rangari et al[8], Chowdhury et al[9] and Rudramurthy et al[10] (Table 1). This can be explained on the basis of the anatomy of female urethra and the physiological and hormonal changes that favor the development of UTIs in females.[11]

In our study the isolation of gram negative bacterial isolates was more than that of the gram positive bacterial isolates which corroborated with similar findings in other studies.[12,13,14]

Escherichia coli was the most common gram negative bacteria isolated followed by Klebsiella spp., Proteus spp., Pseudomonas spp., Acinetobacter spp., Morganella spp., Citrobacter spp. and Enterobacter spp. These findings also correlate with that observed in other studies.[12,13,15,16] Predominantly isolated gram positive cocci in our study included Enterococcus spp.,followed by Staphylococcus aureus and CoNS which was similar to that described by Yadav et al, 2015.[12]

On analyzing the susceptibility pattern of the members of Enterobacteriaceae family, it was found that majority of them were multidrug resistant (MDR) (i.e. resistant to three or more than three class of antibiotics). Most of the isolates showed least susceptibility to 1st and 3rd generation Cephalosporins (0-22%), while susceptibility to other antibiotics ranged from 7-46% for Amoxicillin-clavulanate, 9-22% to Cotrimoxazole, 15-46% to Meropenem and 10-43% to Fluoroquinolones. These observations are similar to the observations made by various other authors as shown in Table 2, except that some authors like Chowdhury et al[9] reported dissimilar

findings, who in their study found the E.coli isolates to be 45% to 51% susceptible to 3rd gen Cephalosporins and Fluoroquinolones in comparison to 14.70% to 28% in other studies including ours (Table 2). Susceptibility to Aminoglycoside was also variable when compared with other studies by Rudramurthy et al[10], Pattanayak et al[17] and Rangari et al[8] which showed 23% to 33.33% sensitivity in comparison to 61.82% to 74.20% shown by other authors including us (Table 2). Gross difference in Meropenem susceptibility pattern was seen in the study by Chowdhury et al[9] who observed that 99.50% E.coli isolates were sensitive to Meropenem while in the present study it was only 15-46%. Studies World over have shown that the selective pressure arising from the overuse of an antimicrobial agent is the major determinant factor for the emergence of resistant strains.[18,19] Increased resistance has recently been noted against 3rd generation Cephalosporins by gram negative bacilli. This could be explained by the recent trend of increased usage of cephalosporins in the hospitals for empirical therapy for a variety of infections in most patients.[20,21] The very high rates of resistance to Cotrimoxazole in this study and worldwide could be because it is one of the current standard drugs used for acute uncomplicated bacterial cystitis in women; for respiratory tract infections, gastrointestinal tract infections, infections by Pneumocystis jiroveci and prophylaxis in neutropenic patients.[22,23] Many authors have reported increasing resistance to fluoroquinolones in uropathogens which may be ascribed to increased prescription of fluoroquinolones and its extensive use in the treatment of UTIs.[24]

Majority of the isolates were highly susceptible to Imipenem (80-96%), Piperacillin-tazobactam (72-88%), Nitrofurantoin (50-87%) and Gentamicin (40-

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64%) as shown in figure 3. But some studies have shown a difference in observations like Pattanayak et al[17] who reported only 42.40%, 50% and 45.50% susceptibility to Piperacillin-tazobactam, Nitrofurantoin and Imipenem respectively (Table 2). The reason for this variation could be that the author had included very few isolates for testing (60 E.coli isolates in comparison to 274 isolates in our study). Interestingly, in our study we observed a unique susceptibility pattern shown by all the Gram negative isolates in being susceptible to one carbapenem (Imipenem) while being resistant to another carbapenem (Meropenem) as shown in figure 7; this unique susceptibility phenotype was also reported in a study done by by Harino et al[25] from Japan where they identified some Klebsiella pneumoniae isolates resistant to all β-lactams except imipenem which they designated as ISMRK strains (for Imipenem susceptible Meropenem resistant Klebsiella). They explained that this phenotype may due to double production of a metallo-β-lactamase, IMP-6, and the extended-spectrum β-lactamase (ESBL) CTX-M-2.[25] In another study by Pai et al, they elucidated that such kind of carbapenem resistance occurs by several mechanisms working in a concert like efflux pumps (e.g. Mex AB-OprM system) or loss of porin channels (e.g. OprD) and production of β-lactamases.[26]

Among the non-fermenters, all Acinetobacter spp. isolates were multidrug resistant showing <20% susceptibility to Cephalosporins, Fluoroquinolones, Tobramycin, Ticarcillin-clavulanate, Aminoglycosides and Meropenem while 32% were susceptible to Piperacillin-tazobactam and Imipenem. However, the susceptibility of Pseudomonas aeruginosa isolates was highest to Piperacillin-tazobactam (95.31%), followed by Imipenem

(87.50%), Amikacin (75%), Gentamicin (57.81%) and Tobramycin (39.06%), but less susceptibility was seen to drugs like Ticarcillin-clavulanate (7.81%), Cephalosporins (23-28%) and Meropenem (29.69%) (figure 4).

About eighty three percent (83%) Staphylococcus aureus isolates were Methicillin sensitive (MSSA) while 69.23% CoNS isolates were sensitive to Methicillin (MSCONS). Staphylococcus aureus and CoNS isolates showed excellent susceptibility to Linezolid (100% respectively) followed by Nitrofurantoin (100% and 83.33% respectively), Gentamicin (83.33% and 68.75% respectively), and Amoxicillin-clavulanate (72% and 87.50% respectively). However these bacterial isolates were less susceptible to Norfloxacin (58.62% and 43.75% respectively), Cotrimoxazole (52.17% and 75% respectively) and Cephalexin (50% and 68.75% respectively) (figure 5). The Enterococcus spp isolates were highly sensitive to Teicoplanin (74.38%) and Linezolid (100%) while the susceptibility of the isolates towards the various other antibiotics tested was very less viz 8.62% for Ciprofloxacin, 11.02% for Norfloxacin, 20% for High level Gentamicin, 37% for Amoxicillin-clavalanate and 39% for Nitrofurantoin (figure 6). These finding were similar to the observations made by Rangari et al[8] but the study by Pattanayak et al[17] showed dissimilar results by finding 100% susceptibility to Amoxicillin-clavalanate and only 25% to Linezolid in their isolates (Table 3).

Conclusion:
To summarize, Escherichia coli and Enterococcus spp. were the commonest uropathogen in this study. Members of the Enterobacteriaceae family showed significant resistance to the commonly prescribed oral drugs, especially the ones that are sold over the

counter like Cotrimoxazole and Fluoroquinolones. The 3rd generation Cephalosporins and Aminoglycosides have also become grossly ineffective against these uropathogens. The most promising drugs effective against these gram negative bacilli in our setup are Imipenem, Nitrofurantoin and Piperacillin-Tazobactam. Teicoplanin and Linezolid remain the wonder drugs in the treatment of Gram positive infections in the present scenario. In order to win the battle against the rising problem of antibiotic resistance, the need of hour is to use the reserved drugs judiciously, decide the antibiotic therapy in accordance to the antibiotic susceptibility reports, build congenial rapport amongst the clinicians and the microbiologist for therapeutic decision making as regards timely escalation and de-escalation of therapy, implement a proper antibiotic policy and strengthen the infection control program.

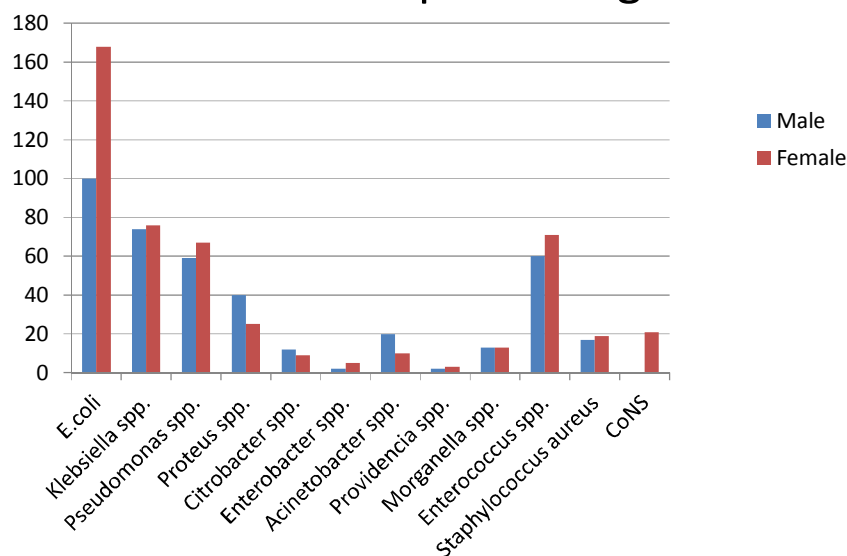## Distribution of isolated pathogens in relation to patient's gender:

Figure 1
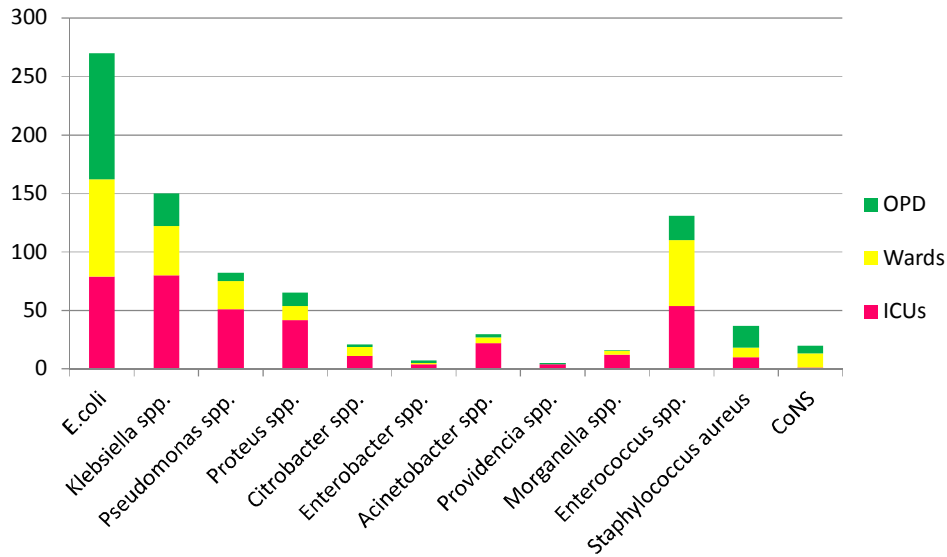
Uropathogens isolated Vs patient care areas:

Figure 2

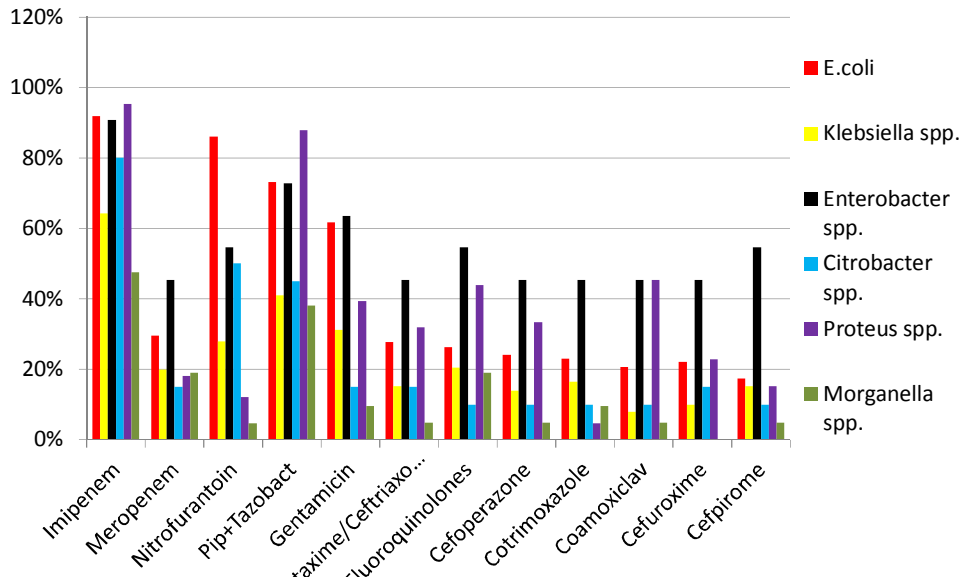## Susceptibility pattern of Enterobacteriaceae bacterial isolates:-
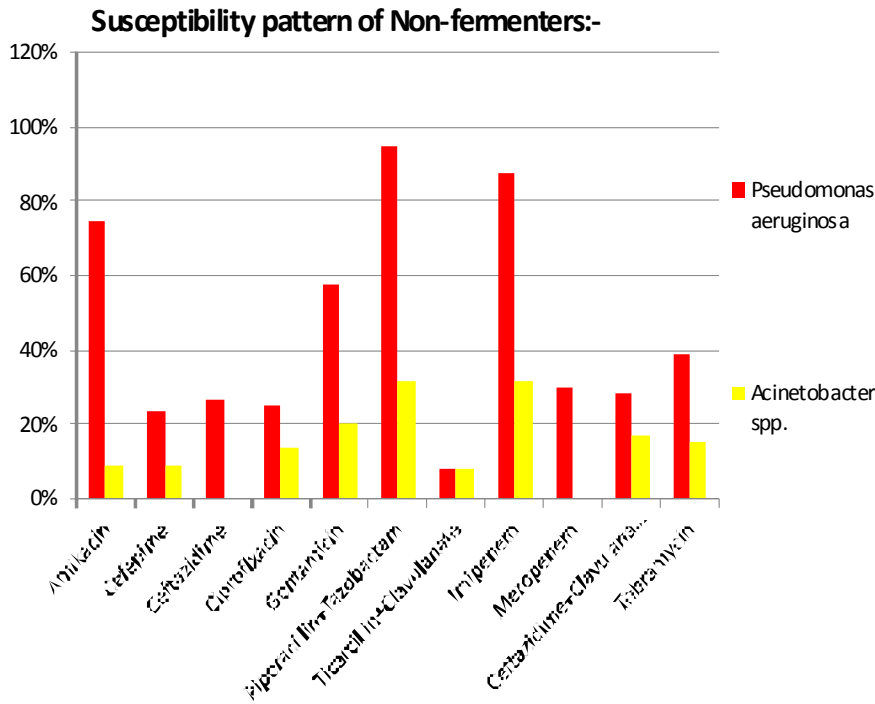

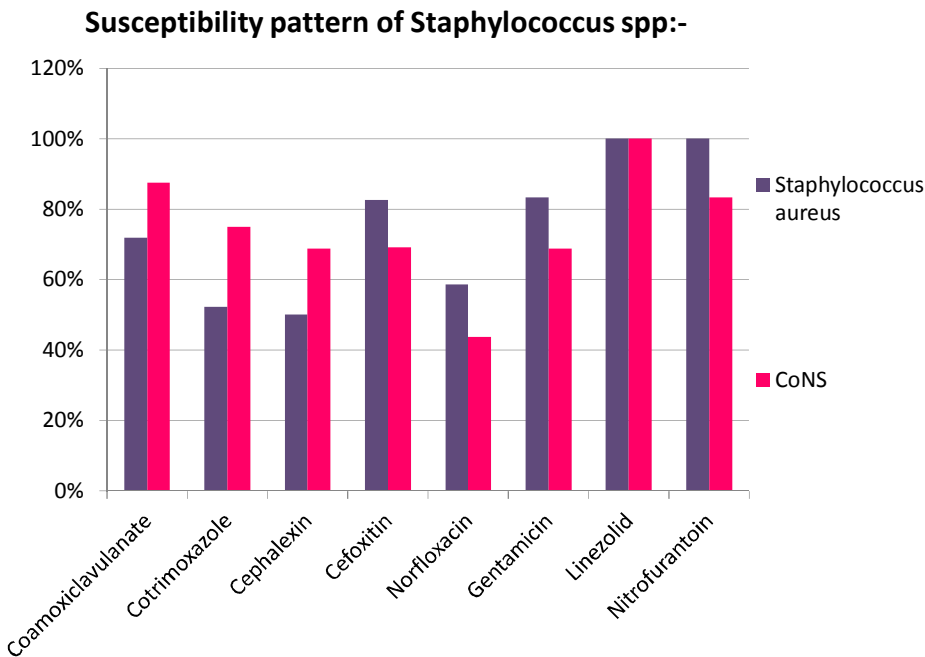**Figure 3**

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Figure 4

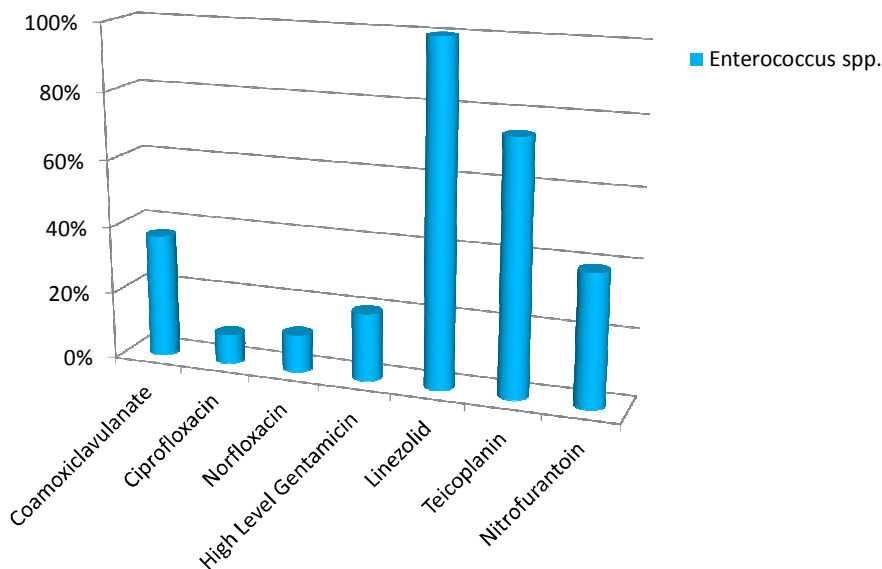**Figure 5**

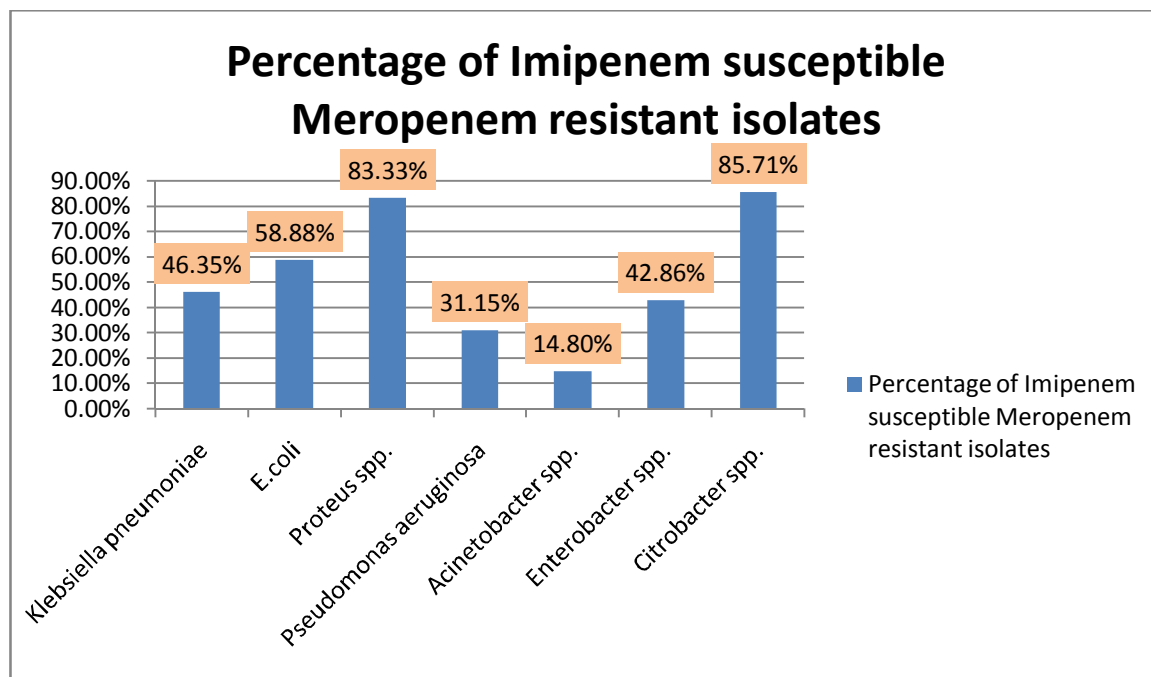**Susceptibility pattern of Enterococcus spp. :-**

Figure 6

Figure 7

Table 1: Pattern of isolation of uropathogens in males and female patients in various studies:								
Isolated Bacteria	Present study		Rudramurthy et al, 2015[10]		Rangari et al, 2015[8]		Chowdhury et al, 2015[9]	
	Male (n=360) %	Female (n=445) %	Male (n=24) %	Female (n=53) %	Male (n=137) %	Female (n=163) %	Male (n=180) %	Female (n=327) %
E.coli	37.31	62.69	19.2	80.8	35	65	33.65	66.35
Klebsiella spp.	49.33	50.67	21.4	78.6	40	60	40.54	59.46
Pseudomonas spp.	46.83	53.17	83.3	16.7	55	45	57.14	42.86
Proteus spp.	61.54	38.46	66.7	33.3	49	51	-	-
Citrobacter spp.	57.14	42.86	0	100	75	25	66.66	33.33
Enterobacter spp.	28.57	71.43	-	-	-	-	0	100
Acinetobacter spp.	66.67	33.33	28.6	71.4	70	30	-	-
Providencia spp.	40	60	-	-	-	-	-	-
Morganella spp.	50	50	-	-	-	-	-	-
Enterococcus spp.	45.80	54.20	35.7	64.3	32	68	-	-
Staphylococcus aureus	47.22	52.78	100	0	22	78	-	-
CoNS	0	100	0	100	33	67	-	-

Table 2: Pattern of Antibiotic susceptibility among E.coli isolates in various studies:						
Antibiotics	Present study n= 274	Bijapur et al, 2015[27] n=96	Rangari et al, 2015[8] n=180	Pattanayak et al year, 2013[17] n=60	Chowdhury et al, 2015[9] n=418	Rudramurthy et al, 2015[10] n=26
Cefpirome	17.45%	-	-	-	-	-
Cefuroxime	22.18%	21.00%	-	11.30%	-	-
Coamoxiclav	20.73%	39.00%	-	20.00%	-	-
Cotrimoxazole	22.91%	31.00%	13.33%	28.10%	26.10%	27.00%
Cefoperazone	24.00%	-	-	-	-	-
Fluoroquinolones	26.18%	28.00%	22.22%	14.70%	51.00%	23.70%
Cefotaxime/ Ceftriaxone	27.64%	23.00%	-	25.50%	45.70%	23.10%
Gentamicin	61.82%	73.00%	33.33%	23.60%	74.20%	30.00%
Piperacillin-Tazobactam	73.09%	85.00%	62.78%	42.40%	-	-
Nitrofurantoin	86.18%	75.00%	97.22%	50.00%	80.40%	80.76%
Meropenem	29.45%	-	-	-	99.50%	-
Imipenem	92.00%	100%	98.89%	45.50%	99.50%	-

n= No. of E.coli isolates tested

Table 3: Pattern of Antibiotic susceptibility among Enterococcus species isolates in various studies:			
Antibiotics	Present study N=123	Rangari et al, 2015[8] N=60	Pattanayak et al, 2013[17] N=4
Ciprofloxacin	8.62%	5.33%	0%
Norfloxacin	11.02%	20%	-
Coamoxiclav	37%	-	100%
High level Gentamicin	20%	9.33%	25%
Nitrofurantoin	39%	73.33%	-
Teicoplanin	74.38%	-	-
Linezolid	100%	74.67%	25%

N= No. of Enterococcus spp. isolates tested

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