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Research Article

SIGNIFICANCE OF URINARY TRACT INFECTION BY ENTEROBACTER, CITROBCATER AND SERRATIA SPECIES AND THEIR ANTIMICROBIAL SUSCEPTIBILITY PROFILE WITH SPECIAL REFERNCE TO INTRINSIC RESISTANCE

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A B S T R A C T

Background: Urinary tract infections (UTIs) are one of the most common bacterial infections affecting humans. Despite advances in antimicrobial therapy, the mortality and morbidity associated with UTIs remain significantly high. This study highlights the significance of *Enterobacter, Citrobacter and Serratia* species in causing urinary tract infection. The knowledge of knowing intrinsic drug resistance of these organisms is important particularly in the management. As most of these isolates are intrinsically resistant to commonly used antimicrobial agents, antimicrobial susceptibility plays a pivotal role in patient care.

Materials and Methods: This is a retrospective analysis from January 2016 to December 2017. Urine samples collected in appropriate sterile manner were screened for polymorphonuclear leucocytes and bacteria by routine microscopic examination. Isolated strains of *Enterobacter, Citrobacter and Serratia* in significant count from MacConkey's agar were identified with Matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS). Antibiotic susceptibility was performed by Vitek Compact™ 2 (Biomeuriux, France) as per CLSI standards establishing MIC (Minimum Inhibitory Concentration).

Results: Of the 402 strains of *Enterobacter,* 334(83.08%) were sensitive, 9(2.23%) strains shown intermediate susceptibility and 59(14.67%) strains found resistant to meropenem. Meropenem has shown good in-vitro susceptibility as compared with imipenem. Of the 238 species of *Citrobacter*, 227(95.37%) were susceptible to Nitrofurantoin, seven (2.94%) strains wereresistant and four (1.68%) strains shown intermediate susceptibility. Of the 402 *Enterobacter*species*,* 133(33.08%) strains were sensitive, 73(18.15%) strains were resistant and 196(48.75%) strains shown intermediate susceptibility. All the 38 strains of *Serratiamarcescens* shown intrinsic resistance to Nitrofurantoin. Of the 238 strains of *Citrobacter* species, 220(92.43%) were susceptible and 18(7.57%) were resistant with ciprofloxacin. Of the 402 *Enterobcater* species, 288(71.64%) were susceptible, 15(3.73%) strains shown intermediate suceptibility and 99(24.63%) were resistant. Of the 38 strains of *Serratia marcescens,* 34(89.47%) were susceptible and only four strains were resistant.

Discussion: The magnitude of health care associated and community acquired urinary tract infections have increased over time considering its potential to cause MDR infections. UTIs caused by *E. aerogenes*, *E. cloacae complex*, *Serraita marcescens*, *Citrobacter koseri* and *C. freundii* are increasing both in hospital and in general community. It is of utmost importance of performing antimicrobial susceptibility testing for these isolates as they are known to be intrinsically resistant to commonly used antimicrobials. Extensive use ofantimicrobial agents as empirical therapy without evidence of culture susceptibility pattern and local antibiogram has resulted in development of drug resistance including multidrug resistant (MDR) organisms.

Conclusion: *E. aerogenes*, *E. cloacae complex*, *Serraita marcescens*, *Citrobacter koseri* and *C. freundii* are now recognised to be clinically important pathogens causing both complicated and uncomplicated urinary tract infections. Early empirical treatment with fluoroquinolones, penicillins and cephalosporins in UTI should be carefully considered. Drugs like cotrimoxazole and nitrofurantoin should be considered as an alternative agent's for treatment of urinary tract infections based on susceptibility pattern and local epidemiological data.

INTRODUCTION

Bacterial infections of the urinary tract are the most common cause of both community acquired and nosocomial infections for patients admitted to health care units.

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Urinary tract infection (UTI) is the third most common infection experienced by humans after respiratory and gastro-intestinal infections. Most cases of urinary tract infections are due to the colonization of the urogenital tract with rectal and perineal flora. The most common organisms implicated are *Escherichia coli, Enterococcus faecalis and Enterococcus faecium, Klebsiella species, Pseudomonas, Acinetobacter* and *Staphylococcus* species. The other organisms like *Citrobacter* species, *Enterobactercloacae complex*, *Enterobacter aerogenes*, and *Serratia* species are less commonly involved in

UTI. Residential care patients, diabetics and those with indwelling urinary catheters or any form of immunocompromised can also colonize with these organisms. Urinary cauterization and its duration in-situ is the single most important predisposing factor for UTI. However, the prognosis and management of urinary tract infections depends on the site of infection and any predisposing factors. UTI may be defined as a condition in which bacteria are established and multiplying within the urinary tract. Diagnosis requires demonstration of bacteriuria with presence of polymorphonuclear leucocytes. Highly immunocompromised patients may not be able to produce leukocyte response. In such patients isolation of urinary pathogens should be reported carefully in view of clinical data. Although the infection and resultant symptoms may be localized, the presence of bacteria in urine places the entire urinary system at risk of invasion by bacteria. Significant bacteriuria is defined as the presence of 100000 or more colony forming units (CFU) per ml of urine[1]. This Kass criteria has been questioned and bacterial counts of 1×10^2 or more organisms per ml particularly when accompanied by pyuria (>10 wbc/mm^3) provide impressive evidence of urinary tract infection in symptomatic young women[2].

This criteria may not be applicable in all situations where urinary pathogens are isolated from immunosuppressed patients and the type of organisms isolated. It is recommended that laboratories should define their cut off values for number of polymorphonuclear leukocytes depending on the diagnosis, underlying co-morbidities and clinical history of the patient. Laboratories should insist on getting relevant clinical history including antimicrobials administered before reporting such results. The Infectious Disease Society of America (IDSA) gave a slightly more relaxed consensus definition requiring 10^3 organisms per ml to diagnose cystitis and 10^4 per ml for pyelonephritis[3].

It is useful to distinguish between upper (kidney) and lower (bladder, prostate and urethra) urinary tract infections. Infections confined to lower urinary tract commonly cause dysuria, frequency and urgency. Pyelonephritis (inflammation of the renal parenchyma) is a clinical syndrome characterized by chills and fever, flank pain and constitutional symptoms caused by bacterial invasion of the kidney. The localization of the site of infection on the basis of symptoms and signs can be inaccurate. Using ureteral catheterization, it has been shown that approximately 50% of women with asymptomatic bacteriuria had infection in their upper tracts[4].

Response to treatment is now used to distinguish between the two upper versus lower urinary tract infections. This is based on the observation that many women with symptoms of cystitis shown by localization studies to be confined to bladder can be cured by a single dose of antibiotic[5].

Recurrence of bacteriuria with the same organism within seven days of single dose therapy was reported to be most often associated with upper tract infection. There is a general agreement that for the best management of patients with urinary tract infections, it is important to distinguish between complicated and uncomplicated infections. Complicated infections include those involving the parenchyma (pyelonephritis or prostatitis) and frequently occur in the setting of obstructive uropathy or after instrumentation. The presence of obstruction, stones or high-pressure vesico-ureteric reflux, perinephric abscess, life-threatening septicemia or a combination of these predispose to kidney damage[6].

Unlike relapse, reinfection does not represent failure to eradicate infection from urinary tract but is due to reinvasion of the system. Prophylactic measures must be initiated. Relapse is a return of infection due to the same micro-organism which is often drug resistant. It is defined as the recurrence of bacteriuria with the same organism within three weeks of completing treatment, which during treatment rendered the urine sterile. Relapse implies that there has been a failure to eradicate the infection. This most often occurs in association with renal scars, stones, cystic disease or prostatitis and in patients with chronic interstitial disease or in those who are immune compromised[7].

The term treatment failure has been used to describe failure to eradicate bacteriuria during treatment and failure to prevent relapse. Factors predisposing to treatment failure are recent antibiotic treatment, Hospital acquired infection, Renal or bladder calculi, Obstructive uropathy, renal cysts, and renal diseases such as reflux nephropathy, chronic interstitial nephropathy, analgesic nephropathy, diabetic nephropathy, sickle cell nephropathy, immunosuppression, and prostatitis.

Asymptomatic bacteriuria is especially common in women as evidenced by a minimum prevalence of 2-4% in young and 10% in elderly women. The cumulative prevalence of asymptomatic bacteriuria in women increases about 1% per decade throughout life regardless of ethnicity and geographic locations. In contrast to women, the occurrence of asymptomatic bacteriuria in men is rare until after 55 years of age, at which time the prevalence increases per decade and approaches the rate in elderly women. Prostatic hypertrophy and increased likelihood of instrumentation account for the bacteriuria in older men[8].

Differences between men and women in the rates of bacteriuria have been attributed to the shorter female urethra and its proximity to the vagina and rectal mucosa and their abundant microbial flora. Symptomatic UTI occur in all age groups. Among newborns and infants, boys are affected more than the girls. When urinary tract is the source of neonatal sepsis, serious underlying congenital anomalies are frequently present. During childhood, persistent bacteriuria with or without repeated symptomatic episodes occurs in a small group (less than 2%) of school-aged girls. Such girls and also school-aged boys with bacteriuria should have a urological evaluation to detect correctable structural abnormalities when UTIs are documented. Sexually active women have a markedly increased risk of cystitis. Vast majority of acute symptomatic infections involve young women. A prospective study demonstrated an annual incidence of 0.5-0.7 episodes per patient year in this group[9].

This study highlights the significance of *Enterobacter, Citrobacter and Serratia* species in urinary tract infection and the need for antimicrobial susceptibility testing. The knowledge of knowing intrinsic drug resistance of these organisms is important particularly in the management of these infections at times which are life threatening. As most of these isolates are intrinsically resistant to commonly used antimicrobial agents, antimicrobial susceptibility plays a pivotal role in the patient care. A small percentage (1% to 3%) may appear susceptible due to method variation, mutation, or low levels of resistance expression. A “susceptible” result

should be viewed with caution and reported accordingly. We must ensure antimicrobial susceptibility test results and identification are accurate and reproducible.

MATERIALS AND METHODS

Urine (midstream, catheterized and suprapubic aspiration) specimens collected from patients with suspected UTI were processed in the Department of Microbiology, Metropolis healthcare limited, Mumbai, India. During the study period (January 2016 to December 2017), *Enterobacter, Citrobacter and Serratia* species isolated in significant counts ($>1\times10^5$ cfu/ml) in pure culture were included in the study. UTI was defined as the presence of any one of the following symptoms: fever, burning, urgency, frequency of micturition, supra pubic tenderness and growth of $>=1\times10^5$ cfu/ml from un-centrifuged urine specimen. Patients undergone suprapubic aspiration, even lesser colony count ($<1\times10^5$ cfu/ml) with presence of polymorphonuclear leucocytes was considered significant and included in the study. The objective of this study was to determine the antibiotic susceptibility pattern of the isolated strains of *Enterobacter, Citrobacter and Serratia* with special reference to intrinsic resistance and to guide clinicians for appropriate antimicrobial therapy for reduction of morbidity & mortality in hospitalized patients. The knowledge of knowing intrinsic drug resistance of these organisms is important particularly in the management of such infections at times which are life threatening. As most of these isolates are intrinsically resistant to commonly used antimicrobial agents, antimicrobial susceptibility plays a pivotal role in patient care. This study was conducted with patients admitted in a tertiary care hospital, developing symptoms of UTI at least after 48 hours of admission. Few patients from community acquired infection with symptoms of UTI have also been included in the study. Cases of urinary tract infection with established nonbacterial aetiology (fungal UTI) excluded from the study.

Urine samples collected in appropriate sterile precautions were screened for pus cells and bacteria by routine microscopic examination followed by plating on MacConkey's agar and Blood agar by T streaking method with an inoculating loop of 4 mm diameter (10 µl of un-centrifuged urine specimen). Inoculated plates were incubated overnight at 37^0c. Isolated colonies of Gram negative bacilli from MacConkey's agar were identified with Matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS). Antimicrobial susceptibility was performed by Vitek Compact™ 2 (Biomeuriux, France) as per CLSI guidelines establishing MIC (Minimum Inhibitory Concentration) of the tested antimicrobials.

Intrinsic Resistance

Intrinsic resistance is defined as inherent or innate (not acquired) antimicrobial resistance, which is reflected in wild-type antimicrobial patterns of all or almost all representatives of a species. Intrinsic resistance is so common that susceptibility testing is unnecessary. For example, *Citrobacter* species are intrinsically resistant to ampicillin. The knowledge of konwing intrinsic resistance mechanisms of organsims is important in following ways: 1) they provide a way to evaluate the accuracy of testing methods; 2) they aid in the recognition of common phenotypes; and 3) they can assist with verification of cumulative antimicrobial susceptibility test data. An "R" (Resistant) occurring with an organism antimicrobial agent combination means that strains should test resistant. A small percentage (1% to 3%) may appear susceptible due to method variation, mutation, or low levels of resistance expression. A "susceptible" result should be viewed with caution and reported accordingly. We must ensure antimicrobial susceptibility test results and identification are accurate and reproducible.

Table 1 Minimum inhibitory concentration (MIC) Breakpoints of antimicrobials

Antimicrobial	MIC µg/ml			Comments
	S	I	R	
Amoxicillin-clavulanate	<=8/4	16/8	>=32/16	
Ampicillin	<=8	16	>=32	-
Piperacillin-tazobactam	<=16/4	32/4-64/4	>=128/4	
Cefazolin	<=2	4	>=8	Breakpoints when cefazolin is used for therapy of infections other than uncomplicated UTIs due to *E. coli, K.pneumoniae,* and *P. mirabilis*. Breakpoints are based on a dosage regimen of 2 g every 8 h.
Cefazolin	<=16	-	>=32	Breakpoints when cefazolin is used for therapy of uncomplicated UTIs due to *E. coli, K. pneumoniae,* and *P. mirabilis*. Breakpoints are based on a dosage regimen of 1 g every 12 h.
Cefepime	<=2	4-8 SDD	>=16	The breakpoint for susceptible is based on a dosage regimen of 1 g every 12 h. The breakpoint for SDD is based on dosing regimens that result in higher cefepime exposure, either higher doses or more frequent doses or both, up to approved maximum dosing regimens.
Cefotaxime	<=1	2	>=4	Breakpoints are based on a dosage regimen of 1 g every 24 h for
ceftriaxone	<=1	2	>=4	Ceftriaxone and 1 g every 8 h for cefotaxime.
Ceftazidime	<=4	8	>=16	Breakpoints are based on a dosage regimen of 1 g every 8 h.
Doripenem	<=1	2	>=4	Breakpoints are based on a dosage regimen of 500 mg every 8 h.
Ertapenem	<=0.5	1	>=2	Breakpoints are based on a dosage regimen of 1 g every 24 h.
Imipenem	<=1	2	>=4	Breakpoints are based on a dosage regimen of 500 mg every 6 h or 1 g every 8 h.
Meropenem	<=1	2	>=4	Breakpoints are based on a dosage regimen of 1 g every 8 h.
Gentamicin	<=4	8	>=16	
Amikacin	<=16	32	>=64	-
Ciprofloxacin	<=1	2	>=4	
Levofloxacin	<=2	4	>=8	-
Norfloxacin	<=4	8	>=16	For testing and reporting of urinary tract isolates only.
Trimethoprim sulfamethoxazole	<=2/38	-	>=4/76	

Adapted from CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 27th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.
S= Susceptible; I= Intermediate; R= Resistant.

Table 2 Organisms depicting intrinsic resistance to various antimicrobial agents

Orgnism/ Antibiotic	Citrobacter freundii	Citrobacter koseri	Enterobacter aerogenes	Enterobacter cloacae complex	Serratia marcescens
Ampicillin	R	R	R	R	R
Amoxicillin- clavulanate	R	-	R	R	R
Ampicillin-Sulbactam	R	-	R	R	R
Piperacillin	-	R	-	-	-
Ticarcillin	-	R	-	-	-
Cephalosporin I: Cefazolin, Cephalothin	R	-	R	R	R
Cephamycins: Cefoxitin, Cefotetan	R	-	R	R	R
Cephalosporin II: Cefuroxime	R	-	R	R	R
Nitrofurantoin	-	-	-	-	R
Polymyxin B	-	-	-	-	R
Colistin	-	-	-	-	R

Adapted from CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 27th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.

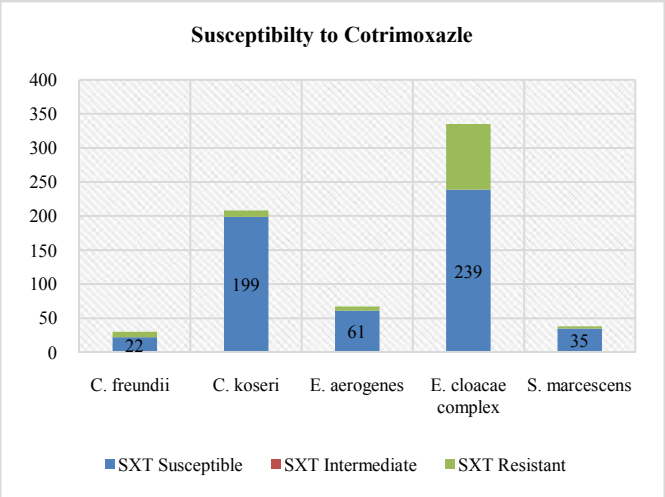
RESULTS

Table 3 Antimicrobial susceptibility pattern of different species of urinary isolates

Organism (N=678) /	*C. freundii* (N=30)			*C. koseri* (N=208)			*E. aerogenes* (N=67)			*E. cloacae complex* (N=335)			*S. marcescens* (N=38)		
Antibiotic	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Amoxicillin-clavulanate	-	-	30	199	3	6	-	-	67	-	-	335	-	-	38
Ampicillin	-	-	30	-	-	208	-	-	67	-	-	335	-	-	38
Piperacillin-tazobactam	25	-	5	203	1	4	59	1	7	286	8	41	-	-	38
Cefazolin	-	-	30	199	-	9	-	-	67	-	-	335	-	-	38
Cefepime	24	-	6	199	2 (SDD)	7	61	2 (SDD)	4	239	12 (SDD	84	35	0	3
Doripenem	25	-	5	204	2	2	64	0	3	203	23	109	36	0	2
Ertapenem	25	-	5	205	1	2	64	0	3	203	23	109	36	0	2
Imipenem	25	1	4	204	2	2	64	2	1	256	26	53	36	0	2
Meropenem	25	1	4	204	2	2	64	2	1	270	7	58	36	0	2
Gentamicin	23	-	7	205	-	3	66	0	1	237	0	98	35	0	3
Amikacin	23	-	7	207	-	1	66	0	1	283	2	50	37	0	1
Ciprofloxacin	21	-	9	199	-	9	61	4	2	227	11	97	34	0	4
Levofloxacin	22	-	8	202	-	6	65	0	2	234	7	94	34	0	4
Cotrimoxazole	22	-	8	199	-	9	61	0	6	239	-	96	35	0	3
Nitrofurantoin	24	3	3	203	1	4	10	47	10	123	149	63	-	-	38
Polymyxin B	30	-	-	208	-	-	67	0	0	335	0	0	-	-	38
Colistin	30	-	-	208	-	-	67	0	0	335	0	0	-	-	38

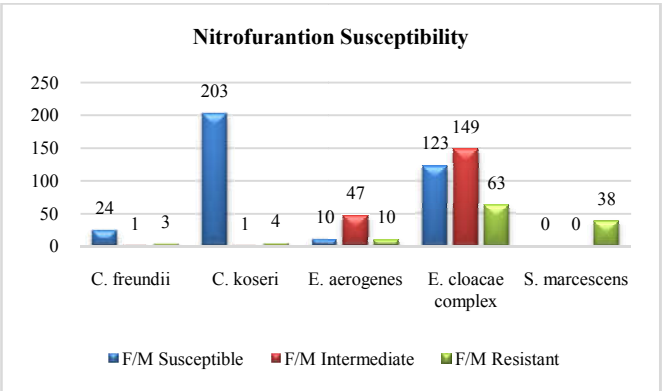
S= Susceptible; I= Intermediate; R= Resistant, SDD- Susceptible Dose Dependent

All the strains of *C. freundii, E. aerogenes, E. cloacae complex* and *S. marcescens* are inherently resistant toampicillin and amoxicillin clavulanic acid and cefazolin except *C. koseri*, which is found sensitive with cefazolin and amoxicillin-clavulanic combination. Thirty-eight strains of *S. marcescens* were inherently resistant with nitrofurantoin, polymyxin B and colistin.



Graph 1 Susceptibility of *Enterobacter, Citrobacter* and *Serratia* species to Cotrimoxazole (SXT).

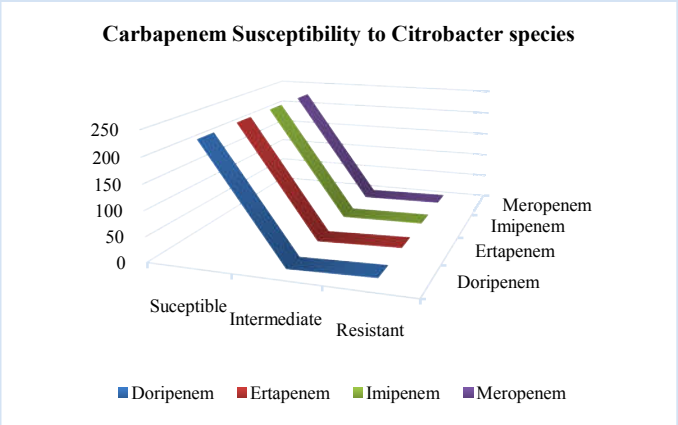
Of the 238 species of *Citrobacter*, 221(92.85%) were susceptible to Cotrimoxazole, and only 17(7.14%) strains were found resistant. Of the 402 *Enterobacter,* 300(74.63%) strains were sensitive and 102(25.37%) strains were resistant. Of the 38 strains of *Serratia marcescens,* 35(92.11%) strains were sensitive and only three (7.89%) strains were resistant. Cotrimoxazole is a good option for treatment of UTIs caused by multidrug resistant (MDR) organisms, which achieves sustainable urinary concentration.



Graph 2 Susceptibility of *Enterobacter, Citrobacter* and *Serratia* species to Nitrofurantoin (F/M)

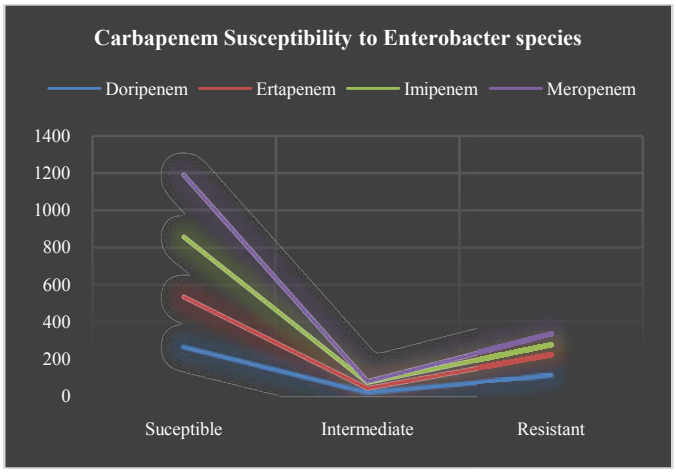
Of the 238 species of *Citrobacter*, 227(95.37%) were susceptible to Nitrofurantoin, seven (2.94%) strains were

resistant and four (1.68%) strains shown intermediate susceptibility. Of the 402 *Enterobacter* species, 133(33.08%) strains were sensitive, 73(18.15%) strains were resistant and 196(48.75%) strains shown intermediate susceptibility. All the 38 strains of *Serratiamarcescens* shown intrinsic resistance to Nitrofurantoin.



Graph 3 Susceptibility of *Citrobacter* species with Carbapenems

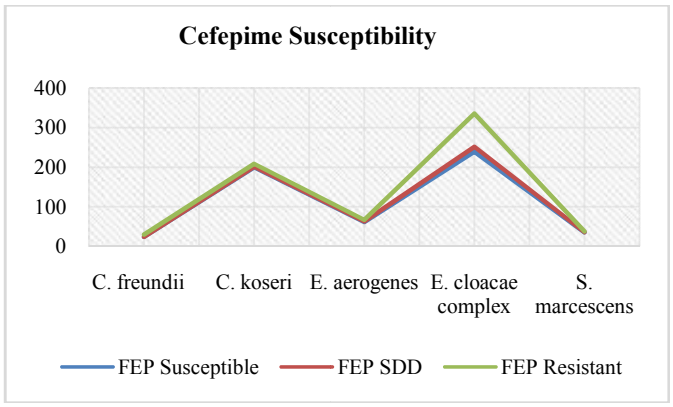
Of the 238 strains of *Citrobacter*, 229(96.21%) were sensitive, 3(1.26%) strains shown intermediate susceptibility and six (2.52%) strains found resistant to imipenem and meropenem. There was no significant difference found in the susceptibility between doripenem and ertapenem in-vitro. In vivo use of doripenem and ertapenem for treatment of UTI needs further evaluation, as these drugs are susceptible to hydrolyzing enzymes produced by *Enterobacteriaceae* family.



Graph 4 Susceptibility of *Enterobacter* species with Carbapenems

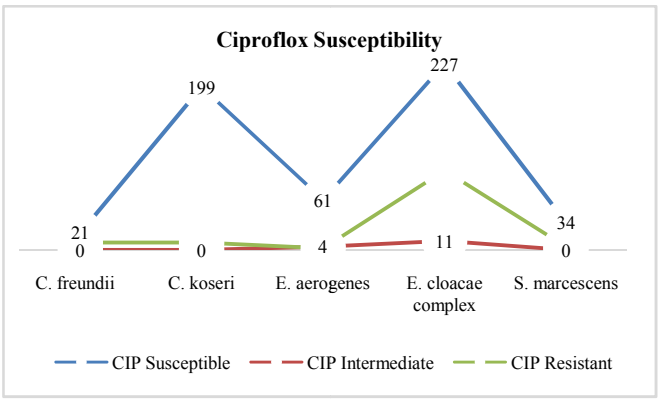
Of the 402 strains of *Enterobacter,* 267(66.41%) were sensitive, 23(5.72%) strains shown intermediate susceptibility and 112(27.86%) strains found resistant to doripenem and ertapenem.

Of the 402 strains of *Enterobacter,* 334(83.08%) were sensitive, 9(2.23%) strains shown intermediate susceptibility and 59(14.67%) strains found resistant to meropenem. Meropenem has shown good in-vitro susceptibility as compared with imipenem.



Graph 5 Susceptibility of *Enterobacter, Citrobacter* and *Serratia* species to Cefepime (FEP)

Of the 238 species of *Citrobacter*, 223(93.69%) were susceptible to Cefepime, 13(5.46%) strains were resistant and two (0.84%) strains were susceptible dose dependent (SDD). Of the 402 *Enterobacter* species, 300(74.62%) strains were sensitive, 88(21.89%) strains were resistant and 14(3.48%) strains were susceptible dose dependent (SDD). Of the 38 strains of *Serratiamarcescens* 35(92.10%) were sensitive and only three (7.90%) were resistant to Nitrofurantoin.



Graph 6 Susceptibility of *Enterobacter, Citrobacter* and *Serratia* species to Ciprofloxacin

Of the 238 strains of *Citrobacter* species, 220(92.43%) were susceptible and 18(7.57%) were resistant with ciprofloxacin. Of the 402 *Enterobcater* species, 288(71.64%) were susceptible, 15(3.73%) strains shown intermediate suceptibility and 99(24.63%) were resistant. Of the 38 strains of *Serratia marcescens,* 34(89.47%) were susceptible and only four strains were resistant.

DISCUSSION

Urinary tract infections (UTIs) are the most common clinical problem worldwide which are caused by microbial invasion of the urinary tract. Urine is said to be normally sterile, that is, free of bacteria, viruses, and fungi. A urinary tract infection is a condition in which one or more parts of the urinary system (the kidneys, ureters, bladder, and urethra) become infected. UTIs are one of the most common bacterial infections in the general population, with an estimated overall incidence rate of 18 per 1000 person per year. It is the most frequent bacterial infection recorded in older people. In addition, UTIs are a major cause of hospital admissions and are associated with significant morbidity and mortality as well as a high economic burden to the healthcare system[10]. In a study performed by *Sammon et al.* 10.8 million patients in the United States visited

an Emergency Department (ED) for the treatment of a UTI between 2006 and 2009. The economic burden of utilizing the ED for the treatment of UTIs is estimated to be $2 billion US dollars annually[11]. UTIs can manifest in a wide clinical range from bacteriuria with limited clinical symptoms to frank bacteraemia and septicaemia[12].

Increasing concern about the use or misuse of antibiotics, resulting in increasing resistance, has highlighted the need for rational pharmacotherapy of common infections in general practice. Relatively little is known about how general practitioners (GPs) actually manage urinary tract infection (UTI). A prospective three vignette-based studies from the United States[13] and several European countries[14] as well as prescribing surveys from the United States[15] and the Netherlands, Norway and Sweden and prescription statistics[16] indicate that management of complicated and uncomplicated cases could be improved with rationale use of antimicrobial agents. Diagnostic tests for identification and susceptibility of urinary pathogens are not always employed appropriately. Second choice antibiotics (e.g. fluoroquinolones, cotrimoxazole and aminoglycosides) are frequently used in some countries and longer treatment courses than recommended are often prescribed[17, 18].In some countries, use of irrational medication, such as antispasmodics or plant extracts, is high.

The understanding of the pathogenesis and epidemiology and resistance mechanisms of organisms causing urinary tract infections can facilitate early recognition and possible prevention and use appropriate antimicrobial therapy. At any age, both sexes may develop symptomatic infections in the presence of risk factors that alter urinary flow. These include: congenital anomalies, renal calculi, ureteral occlusion (partial or total), vesico-ureteral reflux, residual urine in bladder, neurogenic bladder, urethral stricture, prostatic hypertrophy, instrumentation of urinary tract, indwelling urinary catheters, catheterization, urethral dilatation and cystoscopy[19].

A complicated urinary tract infection (cUTI) is an infection associated with a condition, such as a structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defence mechanisms, which increase the risks of acquiring infection or of failing antimicrobial therapy. Associations have been established between UTI and age, pregnancy, sexual intercourse, use of diaphragm and a spermicide, delayed post-coital micturition, menopause and a history of recent UTI. Factors that do not seem to increase the risk of UTI include diet, use of tampons, clothing and personal hygiene including methods of wiping after defecation and bathing practices[20].Bacteria in the enteric flora periodically gain access to the genitourinary tract. Close proximity of anus in women to peri-urethra is a likely factor. Bacterial colonization of periurethral area often precedes the onset of bladder bacteriuria. In the bladder, the organisms multiply, colonize the bladder mucosa and invade mucosal surface. Although urine adequately supports the growth of most uropathogens, the bladder has several mechanisms that prevent bacteriuria. A mucopolysaccaride (urine slime) layer covers the bladder epithelium and prevents colonization. Urine flow and bladder contraction serve to prevent stasis and colonization[21].

Enterobacter Species

The genus *Enterobacter* includes 14 medically important species, the most common are *E cloacae complex, E. aerogenes, E. sakazakii* and *E. gergoviae.* Rarely other species such as *E. hormaechei, E. cancerogenus, E. asburiae* and *E. taylorae* may lead to human infection but in much smaller proportion[22]. Gram negative bacilli are an important cause of hospital acquired infections including bacteremia and septicemia. These organisms are also involved in community acquired infections, especially infections of the urinary tract[23]. *Enterobacter* species can be the etiological agent of respiratory tract infections, skin and soft tissue infections, biliary tract infections, and meningitis and abdominal infections[24, 25, 26].

It is of utmost importance to perform routine culture and antimicrobial susceptibility testing to identify an etiological agent of infectious diseases and to guide clinicians for appropriate antimicrobial therapy. *Enterobacter* species are intrinsically resistant to aminopenicilins, cefazolin and cefoxitin due to the AmpC beta-lactamase production, typically encoded on the chromosome[27]. In the present study, all the strains of *E. aerogenes, E. cloacae complex* are foundinherently resistant toampicillin and amoxicillin-clavulanic acid and cefazolin.The resistance of *Enterobacter* strains to the third generation of cephalosporins is usually caused by the production in excess of AmpC beta-lactamase[28]. ESBL (extended spectrum beta lactamases) are enzymes that hydrolyze the oximino group of the beta-lactamic ring having the ability to inactivate penicillins, oximino cephalosporins and monobactams[29]. Studies showed that the administration of broad-spectrum cephalosporins represent an independent risk factors for resistance[30].

The presence of ESBL producing strains is often associated with therapeutic difficulties because these Gram negative bacilli are often resistant to various classes of antibiotics (e.g. cephems, quinolones, aminoglycosides, tetracyclines, and trimethoprim-sulfamethoxazole) [31, 32].

Carbapenems still represent the best choice for the treatment of infections with ESBL producing strains but the increasing of the resistant strains number is a great concern. Colistin (polymyxin E) is also considered an effective and safe drug for the therapy of severe infections due to multidrug-resistant gram-negative bacteria[33]. Of the 402 strains of *Enterobacter,* 267(66.41%) were sensitive, 23(5.72%) strains shown intermediate susceptibility and 112(27.86%) strains found resistant to doripenem and ertapenem. Of the 402 strains of *Enterobacter,* 334(83.08%) were sensitive, 9(2.23%) strains shown intermediate susceptibility and 59(14.67%) strains found resistant to meropenem. Meropenem has shown good in-vitro susceptibility as compared with imipenem. During the last decade, the emergence and the dissemination of ESBL strains became a concerning problem worldwide[34]. All the physicians should understand the importance of the problem and practice a rational prescribing of antibiotics[35]. Epidemiological surveillance of antibiotic resistance must be performed in hospitals[36].

It has been also analyzed the level of the resistance of *Enterobacter* spp. to the usual quinolones. In our study, of the 402 *Enterobcater* species, 288(71.64%) were susceptible, 15(3.73%) strains shown intermediate susceptibility and 99(24.63%) were resistant to ciprofloxacin. There was no significant difference in the susceptibility between

ciprofloxacin and levofloxacin. Levofloxacin should not be used as an empirical treatment of urinary tract infections as other safer and cheaper drugs like nitrofurantoin and cotrimoxazole can be considered. These drugs achieves sustainable concentration in bladder. In the present study, of the 402 *Enterobacter* species, 300(74.63%) strains were sensitive and 102(25.37%) strains were resistant with cotrimoxazole. With nitrofurantion, 133(33.08%) strains were sensitive, 73(18.15%) strains were resistant and 196(48.75%) strains have shown intermediate susceptibility. We do not know the reason for this high number of intermediate susceptibility with nitrofurantion. Inspite of having intermediate sensitivity it achieves good urinary concentration and can be used as an alternative drug to penicillins and cephalosporins and safely used during pregnancy. Levofloxacin should be reserved for other serious infections including as a second line drug of MDR tuberculosis. The level of resistance is relatively high but these antibiotics can still be used with success in therapy.

Further, we have evaluated the sensitivity of *Enterobacter* strains to aminoglycosides. *E. cloacae* complex found to be more resistant as compared to *E. aerogenes*. Further, amikacin has shown good in-vitro susceptibility in comparison with gentamicin. The etiological spectrum of infections produced by *Enterobacter* species was large, these organisms being most frequent implicated in urinary tract infections (48%). Resistance of *Enterobacter* strains to beta-lactams was high, especially to ampicillin (inherent resistance). The level of resistance to quinolones was relatively high particularly in *E. cloacae complex*, but the role of these antibiotics must not be ignored since they could be still used with success in the therapy of *Enterobacter* infections. The resistance to amynoglicosides was different, being higher in case of gentamicin than for amikacin. The sensitivity of *Enterobacter* spp. to carbapenems and colistin was very high, these antibiotics representing the therapeutic solution even in infections produced by ESBL producing strains. We did not found any strain of *Enterobacter* species resistant to polymyxin B and colistin. The selection of nosocomial resistant *Enterobacter* strains for these antibiotics is however worrying.

Citrobacter Species

Citrobacter species are uncommon causes of infections in neonates, young children, immunocompromised adults & older children[37, 38]. Urinary tract infection by *C. koseri* has been reported to be as high as 12.0% in the year 1969 and the prevalence rate is rising. Invasive procedures like, catheterization helps them to colonize urinary bladder and during intensive chemotherapy this bacterium disseminates to the blood stream to cause severe bacteremia. Intact immunity helps to control the pathogen to certain extent but when the patients are immunocompromised, the situation is grave. The problem is further intensified by the emergence of multidrug resistance *Citrobacter* species resulting into treatment failure. Neonates may acquire the organisms horizontally as nosocomial infections or vertically from the mother at the time of delivery. They are normal inhabitants of the gut and have been clubbed with the coliforms but when host defenses are weak or other factors favor their establishment in other tissues, serious infections may result. An association with virulence markers like the serum resistance, the cell surface hydrophobicity and the killing in the polymorphonuclear leucocytes, which had been studied in *Escherichia coli*, were found to exist in *Citrobacter* spp. leading to its pathogenicity[39].

Citrobacter spp are one of the most misidentified genera in routine laboratory practice. It mimics many other bacteria of the family *Enterobacteriaceae* in colony morphology and biochemical properties. It has been reported in various studies that the prevalence rate of *Citrobacter* spp ranges from as low as 1.0%[40] to as high as 8.23%[41] which is consistent with our study where we report a prevalence rate of 3.6%. A prevalence rate of 2.18% and 1.8% among the uropathogens and in patients of peritonitis respectively was reported in other studies[42, 43] while in our study percentage prevalence in pus, urine and blood was 5.8, 1.7 and 2.0 percent respectively. The affected mean age of 35.5 years (range 3 days-87 years) was reported from an Indian studyComparable results were obtained in our study where we observed maximum isolation from 11-20 years and 31-40 years age range. There are other reports suggesting *Citrobacter* spp. to be an infective agent in extremes of age[44, 45] Male predominance was seen in our study which had been reported by other workers also. In a study conducted by S. Mohanty *et al*, 67.3% *Citrobacter* isolates were from male patients while 32.7% were from female patients.

In the present study, *Citrobacter* UTI were found to be high in elderly age group. These groups constitute large proportion of hospital populations and reduced immunity in these people to fight against infection in general. Similar results were seen in the study conducted by Shih *et al* although Citrobacter species isolated from intra-abdominal infections[46].

In our study all 30 strains of *C. freundii* were resistant with ampicillin, cefazolin and amoxicillin-clavulanic acid combination. All the 208 strains of *C. koseri* were inherently resistant with ampicillin. In our study, *Citrobacter* species isolated from urinary tract, *C. koseri* (N=208) was the most common *Citrobacter* species followed by *C. freundii.* This is not in concordance with other studies which have isolated *C. freundii* as the most common *Citrobacter* species from clinical specimens. Carbapenems are found to be useful drugs for treatment of MDR organisms especially in debilated and immunocompromised persons with life threatening infections. Of the 238 strains of *Citrobacter*, 229(96.21%) were sensitive, 3(1.26%) strains shown intermediate susceptibility and six (2.52%) strains found resistant to imipenem and meropenem. There was no significant difference found in the susceptibility between doripenem and ertapenem in-vitro. In vivo use of doripenem and ertapenem for treatment of UTI needs further evaluation, as these drugs are susceptible to hydrolyzing enzymes produced by *Enterobacteriaceae* family.

None of the strains of *Citrobacter* has shown resistance with Polymyxin B and Colistin. However clinical efficacy of these drugs in treatment of urinary tract infections needs to be evaluated and kept reserved only for severe infections with bacteremia and complicated UTIs. Polymyxin and colistin monotherapy is not advisable due to emergence of drug resistance.

Amoxycillin and ampicillin are often used as oral therapy for Gram negative UTIs, but the high rate of in-vitro and in-vivo resistance (inherent resistance) demonstrated in this study and

others suggests that they should not be used. Trimethoprim and amoxicillin-clavulanate combination are also often prescribed in general practice. This has led to increasing rate of resistance to trimethoprim over the last 10 years and the more recent increase in resistance to amoxicillin-clavulanate, presumably as a result of mechanisms other than production of βeta lactamase[47].

Of the 238 species of *Citrobacter*, 221(92.85%) were susceptible to Cotrimoxazole, and only 17(7.14%) strains were found resistant. Of the 238 species of *Citrobacter*, 227(95.37%) were susceptible to Nitrofurantoin, seven (2.94%) strains were resistant and four (1.68%) strains shown intermediate susceptibility. In this study we found good in-vitro efficacy with cotrimoxazole and nitrofurantoin. These drugs should be preferred over penicillin's, cephalosporin's and carbapenems as they are much cheaper, less toxic, no anaphylactic reactions as seen with penicillin's and cephalosporin's and they are not inactivated by production of Beta lactamases, unless they show in-vitro resistance. Fluroquinolones and aminoglycosides can also be safely considered in treatment of complicated and un-complicated UTIs. Majority of the isolates were found to be susceptible to levofloxacin, ciprofloxacin, and the aminoglycosides. This has important implications as patients in a tertiary care hospital receive aminoglycosides, fluoroquinolones, or a combination of these drugs as empirical therapy or as definitive treatment. The *Citrobacter* isolates resistant to multiple anti-microbial agents have emerged, making it an emerging nosocomial pathogen. The emergence of this usually rare organism as the third most common urinary pathogen, which is resistant to commonly available antibiotics is alarming. The indiscriminate use of antimicrobial agents is possibly the main reason responsible for this situation. Therefore, such studies will guide clinicians to choose accurate empirical treatment options and will help to reduce the mortality and morbidity rates from infections. It is more significant to prevent the resistance development in micro-organisms and to lend the accurate information to clinicians in terms of the use of antibiotics in appropriate period. The magnitude of *Citrobacter* infections have increased over time considering its potential to cause nosocomial infections and the growing numbers of immunocompromised patients in hospitals; *C. koseri* and *C. freundii* being the commonest species isolated. They are usually isolated from patients with wound infections, urinary tract infections and bacteremia. These are monomicrobial in more than half of the cases but polymicrobial infection can also be encountered. *Citrobacter* spp can cause infection in any age group with significant predilection in adolescent and middle age. Infection is seen in both sexes with significant proportion of infection in males. Identification should be done upto species level in all microbiology laboratories to quantitate and assess the real magnitude of these infections.

Serratia Marcescens

Members of the genus *Serratia,* particularly the type species *Serratia marcescens,* is an important cause of health care associated infections especially immunocompromised patients. Taxonomically, the genus *Serratia* is confusing. Currently there are 14 recognized species, with 2 subspecies, in the genus. First described in 1819, *S. marcescens* was thought to be a non-pathogen for years, although sporadic reports in the medical literature implicated that the organism could cause opportunistic infections. Since many strains of *S. marcescens* have red pigment, and the organism was assumed to be nonpathogenic, it was used as a tracer organism in medical experiments and as a biological warfare agent.

It is known now, however, that *Serratia* species are commonly found in water and soil and are also associated with plants, insects, and animals. Water appears to be a natural environment for several species, including *S. marcescens, S. fonticola, S. grimesii, S. liquefaciens, S. plymuthica, S. rubidaea,* and *S. ureilytica*[48, 49, 50]. *S. marcescens, S. liquefaciens, S. proteamaculans, S. grimesii,* and *S. plymuthica* were found in river water in one study, with the predominant species being S. marcescens, followed by S. liquefaciens[51]. In the meantime, *S. marcescens* was revealed to be a pathogen capable ofcausing a full spectrum of clinical disease, from urinary tractinfections (UTIs) to pneumonia. *S. marcescens* is now an accepted known clinical pathogen, and MDR isolatesare prevalent. Many of the other members of the genus, though, are rarely isolated in clinical microbiology labs and hence may not be recognized readily by laboratory personnel. Because *Serratia* species are intrinsically resistant to a large number of antibiotics, there are fewer treatment options for these organisms than for many other bacteria. Multi drug resistant *Serratia* strains are routinely isolated from human clinical infections, and highly resistant strains have been causative agents in many outbreaks. Health care providers may empirically treat suspected *Serratia* infections with piperacillin-tazobactam, a fluoroquinolone, an aminoglycoside, and/or a carbapenem and then modify treatment based on actual antimicrobial susceptibility test results when available. Therapy with piperacillin-tazobactam, an aminoglycoside, and/or a carbapenem is usually successful in treating serious *Serratia* infections.

Aminoglycoside-modifying enzymes are the most common mechanism of aminoglycoside resistance in bacteria. These enzymes modify their targets, aminoglycosides, by adding either an acetyl group (N-acetyltransferases [AAC]), a phosphate group (O-phosphotransferases [APH]), or a nucleotide (O-nucleotidyltransferases [ANT]). The antibiotic then does not bind to the ribosome target. The aminoglycoside-modifying enzymes are usually acquired by bacteria via genes on plasmids. Aminoglycoside resistance in bacteria can also occur because of alteration of the ribosome target, cell impermeability, or efflux. Another type of enzyme, a 16S rRNA methylase called RmtB, has been identified in S. marcescens[52].

In a survey published in 1985, 19.2% of aminoglycoside resistant Gram-negative rods in the United States were *Serratia* isolates[53]. The same survey also found that 42.7% of the examined aminoglycoside resistant Gram-negative rods from Japan, Korea, and Formosa were *Serratia* isolates. In another study, antimicrobial sensitivities of a large number of Gram-negative rod isolates that were recovered from ICU patients from hospitals throughout the United States from 1993 to 2004 were examined. *S. marcescens* was the sixth most commonly isolated organism, representing 5.5% of all Gram-negative rods from the study. Another recent study evaluated amikacin resistance in Enterobacteriaceae isolates from 1995 to 1998 and 2001 to 2006 from a university hospital in South Korea. In this study, 7.5% of *S. marcescens* isolates were resistant to amikacin, and most of the resistant strains were isolated from 2001 to 2006. Many nosocomial outbreaks in

both pediatric and adult patients have occurred with *S. marcescens* strains resistant to one or more aminoglycosides[54, 55, 56].

In the present study, of the 38 isolates of *S. marcescens,* 35 isolates were susceptible with gentamicin and 37 were isolates were sensitive with amikacin. To establish the local antmicrobial susceptibility pattern, this number is too less to compare with similar studies conducted. We need to study on large number of isolates from clinical specimens and from multiple health centers nationwide with community involvement.

B-Lactams susceptibility in Serratia Species

Serratia species are intrinsically resistant to several β-lactam antibiotics, including penicillin G, ampicillin, amoxicillin, amoxicillin-clavulanate, cefuroxime, and narrow-spectrum cephalosporins. All *Serratia* species are sensitive to carbapenems, although some *S. marcescens* strains have been identified that harbor chromosomal carbapenemases. In addition, most of the members of the genus *Serratia* carry a chromosomal ampC gene, and there have been several descriptions of strains acquiring plasmid mediated extended-spectrum β-lactamases (ESBLs). AmpC β -lactamases are classified as either group 1 enzymes by the Bush scheme or class C enzymes by the Ambler scheme. They hydrolyze primarily cephalosporins, including the cephamycins, although these enzymes have activity against the penicillins and aztreonam. The chromosomal ampC genes of *S. marcescens* and several other members of the Enterobacteriaceae are inducible by various β lactam antibiotics by a complex mechanism that involves cell wall recycling. Typically, the expression of AmpC is low from *S. marcescens* and other members of the Enterobacteriaceae. Induction of the chromosomal ampC gene causes an increase in AmpC β -lactamase production and increases the MICs of several β -lactams. Strong inducers of ampC in enteric bacteria such as *S. marcescens* include cefoxitin, imipenem, ampicillin, amoxicillin, benzylpenicillin, and narrow-spectrum cephalosporins, including cephalothin and cefazolin. Broad-spectrum cephalosporins, such as ceftazidime, cefotaxime, and ceftriaxone, and other β -lactams, including cefepime, cefuroxime, and aztreonam, are weak inducers. Overexpression of AmpC β -lactamase in *S. marcescens* and other Enterobacteriaceae, however, is most often due to a mutation or deletion in the induction/ cell wall recycling pathway[57, 58]. An outbreak of a multiply antibiotic resistant *S. marcescens* clone occurred in Italy from 2001 to 2002 and may have been due to ampC derepression or induction. The outbreak occurred among 13 patients, and 12 of the patients had been treated with various β-lactams before isolation of *S. marcescens*. The *S. marcescens* clone in this cluster was resistant to penicillins, aztreonam, and expanded- and broad-spectrum cephalosporins and was sensitive to carbapenems and cefepime[59]. The prevalence of ESBLs in *S. marcescens* varies. In Taiwan, 12.2% of *S. marcescens* strains recovered from clinical specimens over about a 6 month period from 2001 to 2002 produced ESBLs. All of the ESBLs from this study were identified as CTX-M-3, and 33% of the patients with ESBL-producing *S. marcescens* died[60].

Carbapenem susceptibility in Serratia species

Carbapenems such as imipenem and meropenem are important antibiotics, since they are often used to treat severe infections caused by Enterobacteriaceae organisms resistant to broad spectrum cephalosporins. Carbapenem resistance is uncommon in *Serratia* species[61, 62]. A carbapenemase, eventually called SME-1, was first found in two *S. marcescens* isolates in 1982 in England[63]. These isolates were both resistant to imipenem and had reduced sensitivity to meropenem. In addition, the two isolates were fully sensitive to broad-spectrum cephalosporins. Since then, two other SME type enzymes have been described: SME-2 and SME-3[64]. Plasmid mediated class B metallo- β -lactamases have also been identified in *S. marcescens*. The metallo- β -lactamases hydrolyze carbapenems, are not inhibited by β-lactamase inhibitors, are inhibited by metal ion chelators, and have zinc ions at the active site. There are several plasmid borne metallo- β -lactamase genes, and the first found in *S. marcescens* encoded an IMP-1 enzyme. This enzyme, produced from an *S. marcescens* strain with high-level resistance to several β -lactam antibiotics, including imipenem and meropenem, was recovered from a patient in 1991 in Japan[65]. In the present study, of the 38 isolates of *S. marcescens,* 36 have shown in-vitro susceptibility to doripenem, ertapenem, imipenem and meropenem. An outbreak of meropenem resistant *S. marcescens* in 2005 occurred in South Korea among nine different patients. None of the isolates carried a carbapenemase, and resistance to carbapenems was probably due to overproduction of the chromosomally encoded AmpC enzyme and to loss of outer membrane protein F (OmpF) [66].

Quinolone susceptibility in Serratia Species

Quinolones target DNA gyrase and topoisomerase IV[67]. DNA gyrase, encoded by gyrA and gyrB, is a type II topoisomerase that is essential for DNA replication and transcription. In general, *Serratia* species are often fairly sensitive to quinolones. In the present study, Of the 38 strains of *Serratia marcescens,* 34(89.47%) were susceptible and only four strains were resistant with ciprofloxacin. No significant difference in susceptibility was found between ciprofloxacin and levofloxacin.Sheng and others, however, found that fluoroquinolone sensitivity decreased in *S. marcescens* and other Gram-negative bacteria from the mid1980s to the late 1990s in Taiwan. For example, 99% of *S. marcescens* isolates recovered from 1985 to 1986 were sensitive to ciprofloxacin, but only 80% of isolates from 1996 to 1997 were sensitive to ciprofloxacin[68]. In the two studies of *Serratia* susceptibilities performed by Stock and others, all of the *Serratia* species tested were sensitive to the quinolones, although reduced sensitivities were observed with some strains of *S. marcescens* and *S. rubidaea*. When quinolone resistance in *Serratia*species does occur, it can be by a variety of mechanisms, as with other Gram negative rods, and has most often been described for *S. marcescens*. *S. marcescens* has chromosomal determinants for quinolone resistance and also may develop resistance by acquiring plasmids or by mutation. Alterations in gyrA have commonly been shown to be involved in quinolone resistance[69]. Efflux pumps are a common cause of quinolone resistance, especially in Gram-negative bacteria. Three different chromosomally mediated efflux pumps of the resistance nodulation cell division (RND) family have been identified in *S. marcescens*[70].

Trimethoprim-Sulfamethoxazole susceptibility in Serratia Species

Trimethoprim and sulfamethoxazole together they act synergistically to inhibit folic acid synthesis in bacteria. First used in combination in 1968, Sulfamethoxazole inhibits dihydropteroate synthetase (DHPS), an enzyme that catalyzes the formation of dihydrofolate from para-aminobenzoic acid. Trimethoprim acts on the next step of the pathway, by inhibiting the enzyme dihydrofolate reductase (DHFR); this enzyme catalyzes the conversion of dihydrofolate into tetrahydrofolate[71]. *Serratia* species are generally thought to be susceptible to trimethoprim-sulfamethoxazole. Of the 38 strains of *Serratia marcescens,* 35(92.11%) strains were sensitive and only three (7.89%) strains were resistant. Cotrimoxazole is a better option for treatment of UTIs caused by multidrug resistant (MDR) organisms, as it achieves sustainable urinary concentration.There are some limitations to our study. We retrospectively collected data from electronic medical records through epicenter. It was difficult to obtain all characteristics for analyzing risk factors such as comorbidity, previous antibiotics use and history of recurrent UTI due to unrecorded information. This study was conducted only in a single standalone laboratory. Therefore, it is difficult to reflect the overall characteristics of all the organisms involved in pathogenesis of UTIs. This study suggests the need for further large-scale nationwide surveillance on the epidemiology and antimicrobial susceptibility of UTIs.

CONCLUSION

The magnitude of health care associated and community acquired urinary tract infections have increased over time considering its potential to cause MDR infections and the growing numbers of immunocompromised patients in hospitals. *E. aerogenes*, *E. cloacae complex*, *Serraita marcescens*, *Citrobacter koseri* and *C. freundii* are now recognised to be clinically important pathogens causing both complicated and uncomplicated urinary tract infections. These are monomicrobial in more than half of the cases but polymicrobial infection can also be encountered. It is of utmost importance of performing antimicrobial susceptibility testing for these isolates as they are known to be intrinsically resistant to commonly used antimicrobials. Early empirical treatment with fluoroquinolones, penicillins and cephalosporins in UTI should be carefully considered. The proportion of ESBLs in UTI has increased to a high. Amikacin and piperacillin-tazobactam can be considered for empirical treatment as alternatives to carbapenems in patients at risk for ESBL. Other drugs like cotrimoxazole and nitrofurantoin should be considered as an alternative agent's for treatment of urinary tract infections based on susceptibility pattern and local epidemiological data.

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Conflict of Interest
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