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KEY WORDS: UTI, MDR organisms causing UTI, E coli, bacterial etiology of UTI, Hospital acquired UTI

MICROBIOLOGY AND DRUG RESISTANCE PATTERN IN CLINICALLY SIGNIFICANT ISOLATES OF URINE FROM MEDICAL WARDS OF A TERTIARY CARE HOSPITAL IN NORTH INDIA.

Dr Saqib Rishi Senior Resident, Department Of Microbiology, Government Medical College, Srinagar Kashmir India.

Dr Nahid Nahvi Professor, Department Of Microbiology, Government Medical College, Srinagar Kashmir India.

Dr Arshid Rasool Wani Pg Scholar, Department Of Anaesthesiology, ASCOMS Jammu India.

Dr Iqra Majid* Department Of Microbiology, Government Medical College, Srinagar Kashmir India. *Corresponding Author

ABSTRACT

Urinary tract infections (UTIs) are one of the most common bacterial infections encountered in clinical practice both in community and hospital settings in all age groups. It is the second most frequently occurring infection in general population after upper respiratory tract infection .Urinary tract infections (UTIs) are the leading cause of Gram negative sepsis in hospitalized patients and are the origin for about half of all hospital acquired infections caused by urinary catheters and are associated with considerable cost in terms of morbidity and economic and research expenditure. **Material And Methods:** This prospective cross sectional study was carried out in the Department of Microbiology of Government Medical College, Srinagar. A total of 800 patients were taken up for the study. The sample falling under the set inclusion criteria were selected from the urine specimen received in the laboratory for urine culture and sensitivity from Hospitalized patients (IPD). Culture and sensitivity reports and patient data obtained from hospital records was analyzed for this study. **Results:** Out of 800 samples taken up for the study 208 (26%) were culture positive and 592 (74%) were negative. 208 positive samples 125(60.10%) were females and 83(39.90%) were males. female predominance was observed with 71% whereas 29% males were affected by UTI. UTI was predominantly in females of age group (21-40 yrs). most common organism isolated on culture was Escherichia coli(43.26%) both in short stay patients (<48hrs hospital stay) /OPD 22.59% as well as in IPD (>48hrs hospital stay) 20.67%.E.coli was isolated from patients of both uncomplicated and complicated UTI. The second most common organism isolated in our study was Enterococcus faecalis(22.59%), the rate of isolation was much higher 18.75% in inpatients (>48hrs hospital stay) and only 3.84% in OPD/short stay patients (<48hrs hospital stay). In our study Enterococcus spp ranked second amongst uropathogens, in IPD patients isolation rate was almost 5 times higher. Pseudomonas spp was 1 isolate in OPD (0.48%) and 6 (2.88%) in IPD, Acinetobacter 3 (1.44%), Proteus 1 (0.48%) found only in hospitalized patients (stay >48hrs). E.coli showed following sensitivity pattern 96.7% to nitrofurantoin, 93.3% to imipenem, 90.0% to amikacin, 75.6% to gentamycin, 73.3% to cefoperazone-salbactam and meropenem both, 68.9% to pipercillin tazobactam.The sensitivity to TMP-SMX was 45.6%, and to ceftriaxone and cefipime was only 22.2% and 21.1% respectively. The organism also showed resistance to drugs like levofloxacin 82.2% and ciprofloxacin 76.7%.Enterococcus faecalis isolated in our study was sensitive to Vancomycin 95.74% followed by Linezolid (93.6%), Nitrofurantoin (78.7%), HL-Amikacin (74.5%),HL-Gentamycin (70.2%). Enterococcus faecalis showed resistance to drugs commonly used to treat UTI i.e. 91.5% resistant to Ciprofloxacin and 89.4% resistant to Levofloxacin. **Conclusion:** Gram negative bacteria were most predominant microorganisms resulting in more than 50% infections causing urinary tract infection. In our study we have seen that Gram positive cocci especially Enterococcus result in UTI in a significant proportion of patients. In our study Enterococcus spp ranked second amongst uropathogens, in IPD patients isolation rate was almost 5 times higher. The implementation of antibiotic stewardship programs is crucial to minimize resistance. Appropriate antibiotics need to be prescribed based on the antibiotic susceptibility testing which will be narrow spectrum, effective and less expensive with least side effects.

INTRODUCTION:

Urinary tract infection (UTI) is defined as microbial invasion of any of the tissues of the urinary tract extending from the renal cortex to urethral meatus[1]. The term urinary tract infection encompasses a variety of clinical entities, including asymptomatic bacteriuria (ASB), cystitis, prostatitis, and pyelonephritis[2]. Clinically, UTIs are categorized as uncomplicated or complicated. Uncomplicated UTIs typically affect individuals who are otherwise healthy and have no structural or neurological urinary tract abnormalities .These infections are differentiated into lower UTIs (cystitis) characterized by dysuria, frequency, urgency, and occasionally suprapubic tenderness and upper UTIs (pyelonephritis) characterized by flank pain, tenderness, or both, and fever, often associated with dysuria, urgency, and frequency. Several risk factors are associated with cystitis, including female gender, a prior UTI, sexual activity, vaginal infection, diabetes, obesity and genetic susceptibility. Complicated UTIs are defined as UTIs associated with factors that compromise the urinary tract or host defense, including urinary obstruction , urinary retention caused by neurological disease, immunosuppression, renal failure, renal transplantation, pregnancy and the presence of foreign bodies such as calculi, indwelling catheters or other drainage devices[3&4]. In general, infection in men, pregnant women, children, and patients who are hospitalized or in health care associated settings may be considered complicated. Complicated hospital acquired urinary tract infections (UTIs) are generally caused by multidrug resistant organisms. Urinary tract infections (UTIs) can recur in the form of relapses or re-infections. Relapse of bacteriuria refers to a recurrence of bacteriuria with the same infecting microorganism that was present before therapy was started. This is caused by the persistence of the organism in the urinary tract. Re-infection on the other hand is a recurrence of bacteriuria with a microorganism different from the original infecting bacterium. Re-infection may occur with the same microorganism, which may have persisted in the vagina or

feces and can be mistaken for a relapse[5].

Urinary tract infection (UTI) is associated with multiplication of organisms in the urinary tract[1]. The ability of the urinary tract to defend against microbial infections is dependent on its normal anatomic structure and its functional physiological state. The forward flow of urine is one of the important factors for the maintenance of a healthy urinary tract. Any structural or functional process that interrupts the flow of urine leads to urine stasis, and hence to Urinary tract infection (UTI)[6]. Also the urethra has resident microbiota that colonize its epithelium in the distal portion; these organisms are Coagulase-negative staphylococci (excluding Staphylococcus saprophyticus) Viridans and non-hemolytic streptococci Lactobacilli (adult females) Diphtheroids (Corynebacterium spp.) Nonpathogenic (saprobic) Neisseria spp. (adult women) Anaerobic cocci Propionibacterium spp. (adult patients)Commensal Mycobacterium spp. Commensal Mycoplasma spp. Yeasts (pregnant, adult females).The resident microbiota predominantly Lactobacilli produce lactic acid, which creates a low pH condition that is highly unfavorable for the growth and colonization by uropathogenic microbes and hence is one of the major host defenses, as alterations in resident flora are considered a predisposing factor to UTIs[5]. Potential pathogens, primarily Enterobacteriaceae and least likely yeasts may be present as transient colonizers. Whole of the urinary tract above the urethra is sterile in a healthy human and urine thus formed remains sterile. Uropathogenic microbes possess various virulence factors that enhance their ability to colonize and invade the urinary tract. Some of these virulence factors include increased adherence to vaginal and uroepithelial cells by bacterial surface structures (adhesins), pili (P [PAP] type 1), and multiple types of fimbriae; the production of alpha-hemolysin (inhibits the production of protective cytokines), cytotoxic necrotizing factor (CNF), an auto transported protease (Sat), aerobactin (iuc), and a siderophore receptor (iroN); and resistance to serum-killing activity[1].Urinary tract infection (UTI) is defined as microbial invasion of any of the tissues of the urinary tract extending from the renal cortex to urethral meatus[1].The term urinary tract infection encompasses a variety of clinical entities, including asymptomatic bacteriuria (ASB), cystitis, prostatitis, and pyelonephritis[2]. Both urinary tract infection (UTI) and asymptomatic bacteriuria (ASB) denote the presence of bacteria in the urinary tract, usually accompanied by white blood cells and inflammatory cells in the urine[8].Bacteriuria is a frequently used term that denotes the presence of bacteria in urine. The probability of the presence of bacteriuria can be ascertained by quantifying the number of bacteria in voided urine or in urine obtained via urethral catheterization. Significant bacteriuria is a term used to describe the number of bacteria in voided urine that usually exceeds the number caused by contamination from the anterior urethra (i.e., $\geq 10^5$ bacteria/ml). The implication being that in the presence of at least 10^5 bacteria/ml of urine, infection must be seriously considered[8].However studies of women with symptoms of cystitis have found that a colony count threshold of $\geq 10^2$ bacteria/mL is more sensitive (95%) and specific (85%) than a threshold of 10^5/mL for the diagnosis of acute cystitis in women. In men, the minimal level indicating infection appears to be 10^3/mL[8].

Urinary tract infections (UTIs) are one of the most common bacterial infections encountered in clinical practice both in community and hospital settings in all age groups[9]. It is the second most frequently occurring infection in general population after upper respiratory tract infection[10]. Urinary tract infections (UTIs) are the leading cause of Gram negative sepsis in hospitalized patients and are the origin for about half of all hospital acquired infections caused by urinary catheters[11] and are associated with considerable cost in terms of morbidity and economic and research expenditure[12].The hospital acquired urinary tract infections accounts to about 40% of the hospital acquired infections. Long term hospitalized patients with indwelling urinary catheters and patients undergoing urological treatment are prone to hospital acquired infections[13]. In ambulatory persons who undergo a single catheterization risk of UTI in only about 1% while as after a single catheterization of hospitalized patients, infection occurs in at least 10 %[5].Hospitalized patients are most likely to be infected by E.coli, Klebsiella spp., Proteus spp., Staphylococci, other Enterobacteriaceae, Pseudomonas aeruginosa, Enterococci, and Candida spp[11].Since the last two to three decades urinary tract infections (UTIs) due to multidrug resistant uropathogens have caused a growing concern worldwide[14].

MATERIAL AND METHODS:

This prospective cross sectional study was carried out in the Department of Microbiology of Government Medical College, Srinagar. A total of 800 patients were taken up for the study. The samples were selected randomly from the urine specimen received in the laboratory for urine culture and sensitivity. Hospitalized patients (IPD), Patients above the age of 2 years with suspected urinary tract infection, catheterized patients and patients who had under gone surgical instrumentation and patients on antibiotics were included in the study. Samples which were taken by following techniques: Suprapubic aspiration, Percutaneous nephrostomy (PCN aspirate),Cystoscopy and Ileal conduit were excluded from the study. Patients were advised to collect the midstream clean catch urine by voiding the first portion of urine. It is recommended that the midstream clean catch morning urine specimen be collected in a sterile, wide mouth, screw capped bottle after very thorough preliminary cleaning of external genitalia with soap and water. For Hospitalized patients with indwelling catheter Staff was advised to clamp off the catheter tubing above the port to allow the collection of freshly voided urine. The catheter port or wall of the tubing was then asked to be cleaned vigorously with 70% ethanol, and urine aspirated via a needle and syringe; it was advised to maintain the integrity of the closed drainage system to prevent the introduction of organisms into the bladder. If specimen was an intermittent catheter specimen it was advised that a red rubber catheter be introduced into the urethra periodically to drain urine from the bladder and collected directly into a specimen container. Urine was transported to the laboratory as soon as possible. It was cultured as early as possible after collection, preferably within 2 hours. In case of delay, it was advised to be refrigerated up to a maximum of 24 hours before plating as bacterial counts in refrigerated (4°C) urine remain constant for as long as 24 hours .If delay was expected to be for more than 24 hours then use of transport media (Urine transport tubes containing boric acid, sodium borate, and sodium formate) was advised.Direct Gram staining was performed and Smear was then examined under oil immersion (1000x).

The presence of 1 or 5 bacteria per oil immersion field (OIF) which is suggestive of significant bacteriuria.The specimen tubes were then placed in the refrigerator till plating and there after stored at 2 – 8°C until the final report was sent. For Culture the urine pot was turned over to mix it carefully and then the top of the container was removed. The end of a sterile calibrated loop designed to deliver a known volume, either 0.01 or 0.001 mL of urine was dipped into the urine and removed vertically making sure that there is no urine up the loop (as this would mean that a greater volume was cultured).The entire volume was spread over the surface of a 5% sheep blood agar plate and a MacConkey agar plate by making a single streak across the centre. The inoculum was evenly spread at right angles to the primary streak .Plates were incubated aerobically at 35-37°C for at 18-24 hours.The characteristic colony character and colony count were taken into consideration. The organism were later confirmed using conventional biochemical techniques after doing gram-staining.The number of bacteria were estimated by counting

the number of colonies on the surface of the media. One colony = 1,000 cfu/mL ($1x10^3$ cfu/ml) when we take .001 ml of urine and when a larger volume of urine i.e. .01ml is used one colony = 100 cfu/ml ($1x10^2$ cfu/ml).If there was a pure growth of 10-100 or over 100 colonies, the isolate was sub cultured for identification and antimicrobial susceptibility testing. For cultures that contained two organisms, one in low numbers (<100 colonies) and the other over 100 colonies, then only the predominant organism was sub cultured because the organism of lower numbers is unlikely to be causing the disease. If both are present at over 100 colonies, both organisms were sub cultured. If more than two organisms were isolated, then further processing was not done since this is highly likely to be a contaminated specimen.Antimicrobial susceptibility testing were performed using the Kirby-Bauer disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI). [15] The antibiotic sensitivity for Gram positive organisms were put on Vitek-2 compact identification system (Biomerieux, USA) following the manufactures instructions.

Table 7: Results Of Urine Culture

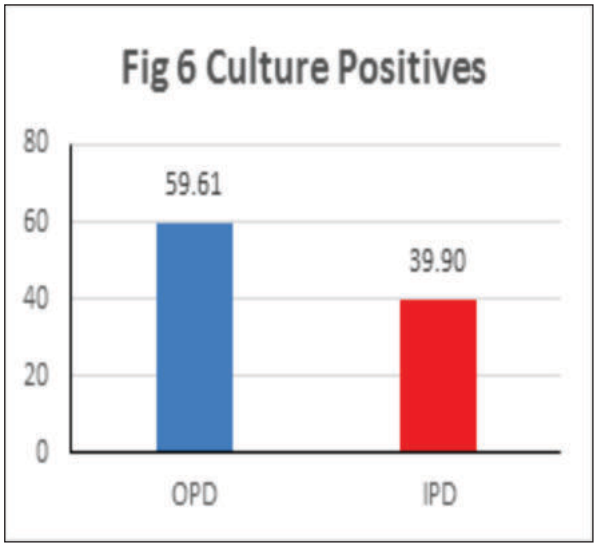
Culture	Frequency	Percent (%)
Positive	208	26 %
Negative	592	74 %
Total	800	100 %

Table 9: Gender Frequency Of Culture Positive Samples In Relation With Age.

Age	Frequency	%age	Culture Positive			
			Male		Female	
			Frequency	%age	Frequency	%age
<10	1	0.12%	1	0.48%	-	-
11-20	21	2.62%	5	2.40%	9	4.32%
21-40	304	38%	25	12.01%	53	25.48%
40-60	167	20.87%	13	6.25%	26	12.5%
>60	307	38.37%	39	18.75%	37	17.78%
Total	800	100%	83	39.89%	125	60.08%

Table 11: Gender Distribution Of Culture Positive Samples On The Basis Of Days Of Hospitalization

Duration of stay	Frequency	%age	Culture Positive			
			Male		Female	
			Frequency	%age	Frequency	%age
OPD/ short stay <48hrs	124	59.61 %	46	37.09 %	78	62.90 %
IPD>48 hrs	83	39.90 %	37	44.57 %	46	55.42 %



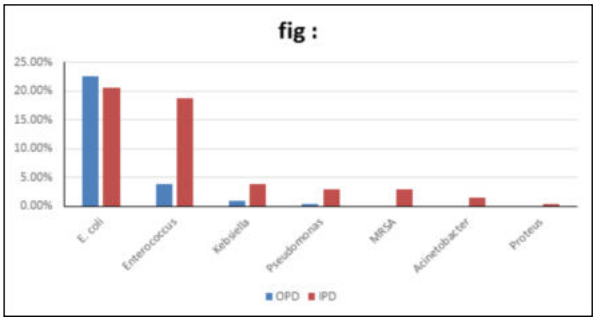


Table 16: Frequency Distribution Of Single Bacterial Isolates From Urine Culture

Organisms isolated	OPD	%age	IPD	%age
E. coli	47	22.59%	43	20.67%
Enterococcus	8	3.84%	39	18.75%
Kebsiella	2	0.96%	8	3.84%
Pseudomonas	1	0.48%	6	2.88%
MRSA	0	0%	6	2.88%
Acinetobacter	0	0%	3	1.44%
Proteus	0	0%	1	0.48%
Total	58	27.87%	106	50.94%

Table 17: Antibiotic Sensitivity Of E. Coli

Antibiotic	Sensitive	Resistant	Total
Amikacin	81	9	90
	90.0%	10.0%	100.0%
Cefoperazone/Salbactam	66	24	90
	73.3%	26.7%	100.0%
Ciprofloxacin	21	69	90
	23.3%	76.7%	100.0%
Cefepime	19	71	90
	21.1%	78.9%	100.0%
Trimethoprim-Sulfamethoxazole	41	49	90
	45.6%	54.4%	100.0%
Ceftriaxone	20	70	90
	22.2%	77.8%	100.0%
Gentamycin	68	22	90
	75.6%	24.4%	100.0%
Imepenem	84	6	90
	93.3%	6.7%	100.0%
Levofloxacin	16	74	90
	17.8%	82.2%	100.0%
Meropenem	66	24	90
	73.3%	26.7%	100.0%
Nitrofurantion	87	3	90
	96.7%	3.3%	100.0%
Piperacillin-tazobactam	62	28	90
	68.9%	31.1%	100.0%

Table 19: Antibiotic Sensitivity Of *Pseudomonas* Spp.

Antibiotic	Sensitive	Resistant	Total
Amikacin	5	2	7
	71.4%	28.6%	100.0%
Cefoperazone/salbactam	4	3	7
	57.1%	42.9%	100.0%
Ciprofloxacin	2	5	7
	28.6%	71.4%	100.0%
Cefepime	1	6	7
	14.3%	85.7%	100.0%
Gentamycin	2	5	7
	28.6%	71.4%	100.0%
Imepenem	5	2	7
	71.4%	28.6%	100.0%
Levofloxacin	1	6	7
	14.3%	85.7%	100.0%
Meropenem	3	4	7

	42.9%	57.1%	100.0%
Piperacillin-tazobactam	5	2	7
	71.43%	28.57%	100.0%
Tobramycin	2	5	7
	28.6%	71.4%	100.0%

Table 20: Antibiotic Sensitivity Of *Klebsiella* Spp.

Antibiotic	Sensitive	Resistant	Total
Amikacin	6	4	10
	60.0%	40.0%	100.0%
Cefoperazone/salbactam	4	6	10
	40.0%	60.0%	100.0%
Ciprofloxacin	4	6	10
	40.0%	60.0%	100.0%
Cefepime	4	6	10
	40.0%	60.0%	100.0%
Trimethoprim-sulfamethoxazole	6	4	10
	60.0%	40.0%	100.0%
Ceftriaxone	2	8	10
	20.0%	80.0%	100.0%
Gentamycin	7	3	10
	70.0%	30.0%	100.0%
Imepenem	8	2	10
	80.0%	20.0%	100.0%
Levofloxacin	2	8	10
	20.0%	80.0%	100.0%
Meropenem	6	4	10
	60.0%	40.0%	100.0%
Nitrofurantion	6	4	10
	60.0%	40.0%	100.0%
Piperacillin-tazobactam	7	3	10
	70.0%	30.0%	100.0%

DISCUSSION:

An estimated 150 to 250 million individuals worldwide develop urinary tract infection (UTI) every year.UTI is one of the most common infection affecting all age groups including men, women and children worldwide.UTI can affect both lower and upper urinary tract which may be acquired from community or hospital. Out of 800 samples taken up for the study 208 (26%) were culture positive and 592 (74%) were negative, Odoki M et al[16] reported almost the same frequency of urinary tract infections (UTIs), 86/267 (32.2%) in patients attending hospitals with suspected urinary tract infection. In our study among 208 positive samples 125(60.10%) were females and 83(39.90%) were males which is similar to the study conducted by Baral Ret al[1]where female predominance was observed with 71% whereas 29% males were affected by UTI. In our study incidence of UTI was predominantly in females of age group (21-40 yrs) 25.48% with respect males. Strom BL et al[17], Stamm WE et al[18], and Ako-Nai AK et al[19]who have reported the incidence of UTI in adult females much higher about 6 times higher than males of similar age.Our results indicate that the incidence in adult females was higher than males of similar age (2:1) whereas in older age groups of 60 years and above, incidence in male and female were almost same.In our study 15.86% patients had history of instrumentation which is in similarity with S. A. Ally et al[20] who reported instrumentation as an important risk factor for UTI. most common organism isolated on culture was Escherichia coli(43.26%) both in short stay patients (<48hrs hospital stay) /OPD 22.59% as well as in IPD (>48hrs hospital stay) 20.67%.

E.coli was isolated from patients of both uncomplicated and complicated UTI. In a similar study by Ahmad S[21]there was predominance of E.coli among the causative agents of urinary tract infection, supporting the view Pulverers G et al[22], Akbar DH[23], Rafay AM[24], Shamweel A et al[25]also reported E. coli as the most frequent cause of the infection. The reason of highest rate of isolation of E. coli as causative agent of UTI can be explained by the inherent virulence factors of uopathogenic E.coli which include Type 1 fimbriae, P-fimbriae that mediate urinary tract colonization and association with other microorganisms moving from the perianal area contaminated with fecal microbes .The second most common organism isolated in our study was Enterococcus faecalis(22.59%), the rate of isolation was much higher 18.75% in inpatients (>48hrs hospital stay) and only 3.84% in OPD/short stay patients (<48hrs hospital stay) this is in contrast with S. Ahmad[21]who reported Klebsiella pneumonia 22.4% as a second most common cause of urinary tract infection in Srinagar. In a study conducted by Shamweel and Mubaraki[25],Shamweel and Farooque[26], Ahmed and Ragaa[27], E. coli and Klebsiella pneumoniae accounted for approximately 70% of the isolates respectively. In our study Enterococcus spp ranked second amongst uropathogens, in IPD patients isolation rate was almost 5 times higher. In most of the patients there was a history of prolonged hospital stay, instrumentation, and catheterization. Prolonged hospital stay is associated with the colonization of the peri-urethral area with Enterococci further prolonged administration of antibiotics result in the overgrowth of the resistant Enterococci and other MDR GNB which than gain entrance to bladder by an ascending route[28].Urinary catheterization induces fibrinogen release into the bladder as part of the inflammatory response; this fibrinogen subsequently accumulates in the bladder and is deposited on the implanted catheter (Flores-Mireles AL et al[29]. Following fibrinogen deposition, the Ebp pilus adhesin — EbpA, which contains an N-terminal fibrinogen- binding domain — mediates catheter colonization and biofilm formation during UTIs caused by Enterococcus (Nielsen HV, et al[30]).Other less frequently isolated organisms in our study included Klebsiella spp 2 (0.96%) in OPD and 8 (3.84%) in IPD, Pseudomonas spp was 1 isolate in OPD (0.48%) and 6 (2.88%) in IPD, Acinetobacter 3 (1.44%), Proteus 1 (0.48%) found only in hospitalized patients (stay >48hrs).

Thus in our study gram negative bacteria were most predominant microorganisms resulting in more than 50% infections causing urinary tract infection.In our study we have seen that gram positive cocci especially Enterococcus result in UTI in a significant proportion of patients. E.coli showed following sensitivity pattern 96.7% to nitrofurantoin, 93.3% to imipenem, 90.0% to amikacin, 75.6% to gentamycin, 73.3% to cefoperazone-salbactam and meropenem both, 68.9% to pipercillin tazobactam.The sensitivity to TMP-SMX was 45.6%, and to ceftriaxone and cefipime was only 22.2% and 21.1% respectively. The organism also showed resistance to drugs like levofloxacin 82.2% and ciprofloxacin 76.7%. Similar study conducted by Thattil, et al[31]reported sensitivity of E. coli to imipenem as 98.2% followed by nitrofurantoin (82.3%), amikacin (81.1%), piperacillin tazobactum (75.2%) and cefotaxime 32.2% and E. coli was least sensitive to naldixic acid (15.5%). Biswas et al[32]found 100% sensitivity of E. coli to imipenem, meropenem, amikacin and nitrofurantoin followed by gentamycin 94.1%.Enterococcus faecalis isolated in our study was sensitive to Vancomycin 95.74% followed by Linezolid (93.6%), Nitrofurantoin (78.7%), HL-Amikacin (74.5%),HL-Gentamycin (70.2%). Enterococcus faecalis showed resistance to drugs commonly used to treat UTI i.e. 91.5% resistant to Ciprofloxacin and 89.4% resistant to Levofloxacin. Enterococcus spp. have intrinsic resistance to: Cephalosporins, Trimethoprim-sulfamethoxazole, Low or therapeutic concentrations of aminoglycosides[56]so antimicrobial sensitivity for these drugs was not tested whereas AST of high level aminoglycosides was detected by Vitek-2 automated system. In our study all isolates of S.aureus 2.88% were methicillin resistant and were primarily isolated from IPD patients, and were 100% sensitive to vancomycin and nitrofurantoin. These isolates also showed resistance to commonly used fluroquinolones like 83.3% isolates were resistant to ciprofloxacin and levofloxacin. A Study conducted by Reshmi Gopalakrishnan et al[33]reported that none of the Staphylococcus isolates and Enterococcus spp were vancomycin resistant.Other gram negative organisms

isolated in our study were highly resistant to antibiotics like Ciprofloxacin and Levofloxacin including Klebsiella species,(60% and 80%) P. aureginosa (71.4% and 85.7%).From the results of our study we suggest nitrofurantoin as the most effective drug for the treatment of UTI as well as for chemoprophylaxis of recurrent UTI caused by both GNB as well as GPC. Other drugs like aminoglycosides, carbepenems, fluroquinolones and linezolid (in GPC) should be reserved for patients with severe illness, keeping in mind other co-morbidities of the patient .Choosing judiciously whether to initiate antibiotic therapy and then selecting the most urinary-focused agent for the shortest appropriate duration are important factors in global efforts to stem the rise of antimicrobial-resistant organisms respectively. The implementation of antibiotic stewardship programs is crucial to minimize resistance. Appropriate antibiotics need to be prescribed based on the antibiotic susceptibility testing which will be narrow spectrum, effective and less expensive with least side effects.

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