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A Concise Overview on Urinary Tract Infection (UTI) includes Microbial agents, Predisposing factors, Antibiotic Resistance and Antibiotic Stewardship.

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Abstract:

Introduction: Urinary tract infections (UTI) are the second most common infectious disease affecting more than 150 million people globally annually.Most predominant cause of UTI is Uropathogenic*E. coli* (UPEC) associated with antimicrobial resistance.

Aim and Objective: To provide an insight into the current scenario of the microorganisms causing UTI, and to evaluate various risk factors with its antibiotic profile

Materials and Methods: Urine sample were inoculated using a 0.001 ml calibrated loop onto sterile plate of Blood agar and Mac Conkey's agar. After an aerobic incubation at 37˚C, the plates showing significant growth as per the Kass count (single species count of more than 10^5 organisms per ml of urine) were processed further. The isolates obtained were identified at a species level as well as the antimicrobial susceptibility of the strain was determined by using fully automated bacterial identification system (VITEK 2 Compact; BioMérieux, Paris, France)

Result:*E. coli* was the major etiological agent, associated mainly with rural population (40/55), male gender, significantly associated with factors like catheterization and renal stone. 76% strains were resistant to Fosfomycin, 75% resistance to cefuroxime and 70% resistance to cefepime while 96% strains were sensitive to Tigecycline, 76% sensitive to nitrofurantoin. It was followed by *Klebsiella*primarily found in Rural males. 75% strains were resistant to Fosfomycin followed by cefoxitin, cefuroxime, cefotaxime and cefepime. Klebsiella was 100% sensitive to tigecycline and piperacillin+ tazobactam. Third pathogen was *Enterococcus faecalis*, predominant in females, associated with the presence of catheter, stone and prostate cancer. It was 100% resistant to Fosfomycin while it was 100% sensitive to tigecycline, Doxycycline, nitrofurantoin, and levofloxacin.

Conclusion: Most of the UTI were complicated associated with comorbidities. Emerging resistance amongst bacterial isolates was seen. A need to strengthen stewardship programs is urgently advocated.

Keywords: Antibiotic resistance,Antibiotic stewardship, Risk factors, Urinary tract infections(UTI)

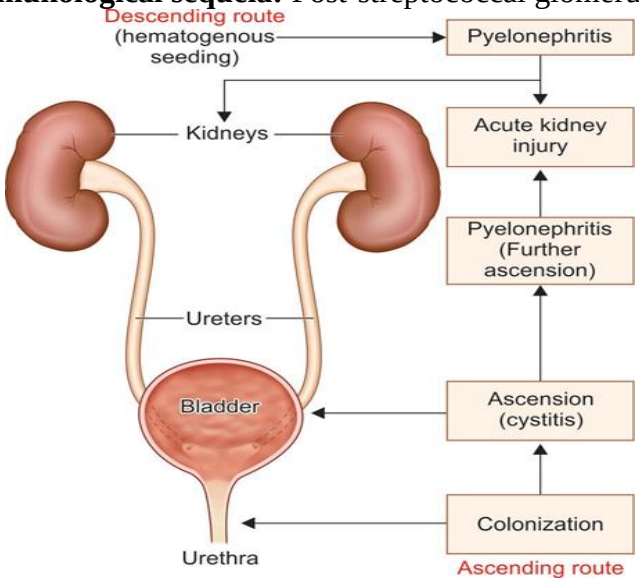
Introduction:

Urinary Tract infections are the Disease caused by microbial invasion of the urinary tract that extends from the renal cortex of the kidney to the urethral meatus. UTIs are among the most encountered infections, both in the community and in hospitals and represents the second most common microbial infection, after respiratory tract infections, encountered in medical practice today, [(1)] occurring from the neonates to the geriatric age group. [(1)] It presents a spectrum of clinical entities upon severity ranging from asymptomatic infection to acute pyelonephritis with sepsis. [(2)]

UTI can be present as either acute or chronic and can also be **Community-acquired or Hospital-acquired (CAUTI-Catheter Associated Urinary Tract Infection)**based on how it is acquired**. Based on type of infection,** UTI is classified into **Complicated UTI**: defined as UTI in male patients and females with certain comorbidities and Urinary tract abnormalities, also includes Health care associated infections. **Uncomplicated UTI:** Infections of bladder in non-pregnant women with no known functional or anatomical abnormalities or comorbidities. [(3)]

Several multifactorial predisposing factors for UTI are as follows- Gender: Higher prevalence in **females** due to short urethra and Close proximity of urethral meatus to anus**. Age**: Incidence increases with age, During first year of life prevalence same in both females and males - incidence in males until old age. In **Females:** incidence keeps increasing after first year of life, 5–17 years - incidence of bacteriuria - 1–3%, Adult life - incidence is around 10–20%. Reinfection is common in females (20–40 years of age)**. Pregnancy**: Anatomical and hormonal changes - asymptomatic bacteriuria common**. Structural and functional abnormality of urinary tract -** obstruction to the urine flow - urinary stasis – infection. **Structural obstruction** like urethral stricture, renal and ureteric stones, prostate enlargement, tumors, rénal transplants, etc. **Functional obstruction**: includes neurogenic bladder due to spinal cord injury or multiple sclerosis. **Bacterial virulence**: bacteria with pili leads to adhesion to uroepithelium. **Vesico-ureteric reflux**: allows urine from bladder up into ureters and sometimes into the renal pelvis and **Genetic factors**: Genetically determined receptors help in bacterial attachment. [(3)]

UTIs - classified into two types—lower UTI and upper UTI - depending upon the anatomical sites involved. Depending upon the source of infection: healthcare-associated (e.g. CAUTI) and community-acquired. In Lower UTI, Sites involves are Urethra and Bladder with local manifestations like Dysuria, Urgency and Frequency. while in Upper UTI sites involve are Kidney and Ureter with both local and systemic manifestation like fever, Vomiting, Abdominal pain etc. Upper UTI route of spread is both Ascending and Descending, while in Lower UTI the route is mainly Ascending (Apurba shastri). **Clinical Manifestations includes: In Lower UTI:** Asymptomatic bacteriuria, Cystitis, Urethritis, Acute urethral syndrome. **Upper UTI:** Pyelonephritis, Ureteritis, Perinephric abscess, Renal abscess, Renal tuberculosis, and **Immunological sequela:** Post-streptococcal glomerulonephritis (PSGN).



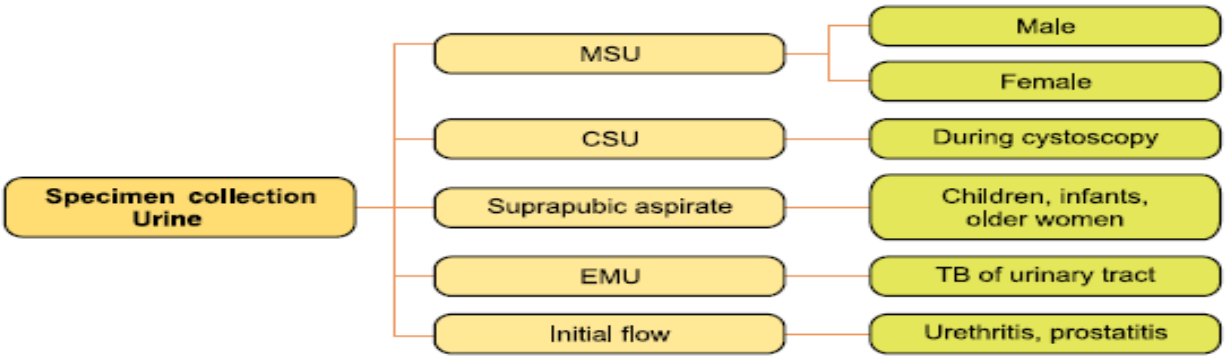
Source: Apurba Shastri[(3)]

Asymptomatic bacteriuria: It refers to the presence of ≥1 uropathogen isolated from urine culture at a count of $\geq 10^5$ CFU/ml in the absence of signs and symptoms, irrespective of the significant pyuria or catheterization. It is **Clinically significant in** - pregnant women, people undergoing prostatic surgery or any urologic procedure where bleeding is anticipated. Routine screening & treatment for asymptomatic UTI is highly recommended. Common in females and incidence increases with age. **Asymptomatic bacteriuria** is **Clinically not significant** - in non-pregnant, pre-menopausal women, old age, catheterized patient, or patients with spinal injury, neither screening nor treatment of asymptomatic UTI is needed.**Cystitis (Lower UTI)** is the infection of urinary bladder with the symptoms of Dysuria, frequency, urgency, and suprapubic tenderness. Urine becomes cloudy, with bad Odor, and in some cases haematuria. No associated systemic manifestation.**Acute Urethral Syndrome (Lower UTI):** Seen in **young sexually active females**. Classical symptoms of lower UTI as described for cystitis. In this case the Bacterial count is often low (10^2 to 10^5 CFU/mL). Pyuria is present. **Agents**: Mostly due to usual agents of UTI, few cases - caused by gonococcus, *Chlamydia*, *herpes* simplex virus, etc**Pyelonephritis (Upper UTI):**Inflammation of kidney parenchyma, calyces, and the renal pelvis. Associated with systemic manifestations - fever, flank pain, vomiting

ETIOLOGICAL AGENTS OF UTI[3]**:Escherichia coli (uropathogenic E. coli)** is the commonest cause (70%) of all forms of UTIs - community acquired & nosocomial UTI and upper & lower UTI. UPEC serotypes O1, O2, O4, O6, O7 and O75 are responsible for most UTIs **The virulence factors of UPEC include:** Cytotoxins (CNF 1–cytotoxic necrotizing factor 1 and SAT: Secreted autotransporter toxin), Hemolysins, Fimbriae (e.g. P fimbriae)–specific for strains causing lower UTI and Capsular K antigen–specific for strains causing upper UTI. Other endogenous flora - Gram-negative bacilli like *Klebsiella, Proteus, Acinetobacter* & Gram-positive cocci like *Staphylococcus saprophyticus, Enterococci* are also responsible for UTI. **Hospital acquired UTIs is mainly due to** Enterobacteriaceae Staphylococci and Pseudomonas

Bacteria invade urinary tract by two routes-Ascending Route: Most common route, Mainly the Enteric endogenous bacteria (*E. coli, other gram-negative bacilli, enterococci) cause via this route*. Facilitated by sexual intercourse, or instrumentation.**Descending Route**: Bacteraemia → Hematogenous seedling of pathogen (5% of UTIs).Organisms commonly associated with descending infection — *Staphylococcus aureus, Salmonella,* Mycobacterium tuberculosis, Leptospira and Candida.

Laboratory diagnosis of UTI mainly involved the culture of specimen like Urine and Blood



MSU: MID-STREAM URINE, **CSU:** CATHETERISED URINE, **EMU:** EARLY MORNING URINE

Urine collection: Done by noninvasive methods like Mid-stream Urine (MSU), Condom catheter, Indwelling Foley's catheter and Invasive methods includes-Suprapubic aspirate, straight in and out catheter, Cystoscopy and Nephrostomy.

For catheterized patient urine is collected in 2 ways.1-**If sample port is not present**: first the connecting tube of urobag is clamped- then the portion of tubing proximal to clamp is disinfected with alcohol swab. Finally, urine is aspirated by directly inserting the needle and syringe into tubing.2-**If the sample port is present** then urine is aspirated through the sampling port using sterile syringe after disinfecting the port with alcohol swab. Care should be taken that urine should never be collected from drainage bag and **Catheter tip** are **unsuitable** for culture as they colonize many organisms.**Transport**

of Urine: Urine specimen should be transported to the laboratory within 2 hrs. of collection, for delay > 2hrs it can be refrigerated at 2-8 ℃ for a maximum of 24 hrs. If refrigeration is not possible then preservatives like Boric acid glycerol can be used.**Screening of Urine** sample becomes a very important part of diagnosis as it prevents the unnecessary processing of all the specimens for Culture.

There are **Direct indicators** like presence of Pyuria (In urine wet mount if > 5 neutrophils/HPF in Uncentrifuged urine) and Bacteriuria (Gram's stain of urine). **Indirect indicators** methods reveal pyuria and Bacteriuria by detecting the presence of bacterial or neutrophil enzymes such as Leucocyte esterase test, Griess nitrite test, Catalase test etc. **Automated methods** are also available which includes image recognition analyzer (Beckman Coulter), Flow cytometry analysis etc.**Urine culture** is done on a plate of Blood agar, Mac Conkey's agar or CLED media. The recommended method of Urine culture is Semiquantitative method using a calibrated loop. Colony count of the pathogen is estimated by correlating it with number of colonies grown on culture media. If the volume of the MSU is 0.001ml and colonies are ≥ 10 colonies/Plate then the count is ≥ 10^4 CFU/ml. if the colonies are ≥100, then the count is ≥ 10^5 CFU/ml. **Antibody coated bacteria test:** Detection of antibody-coated bacteria differentiates upper UTI (involvement of the kidney) from lower UTI. Upper UTI results in antibody response, which allows the antibody to coat the microorganism Can be detected in the urine by immunofluorescence using antihuman immunoglobulin tagged to a fluorescent dye

Significant Bacteriuria

A count of ≥ 10^5 CFU/ml of urine is considered significant- indicates infection

A count between 10^4 to 10^5 CFU/ml. indicated doubtful significance and should be corelated clinically

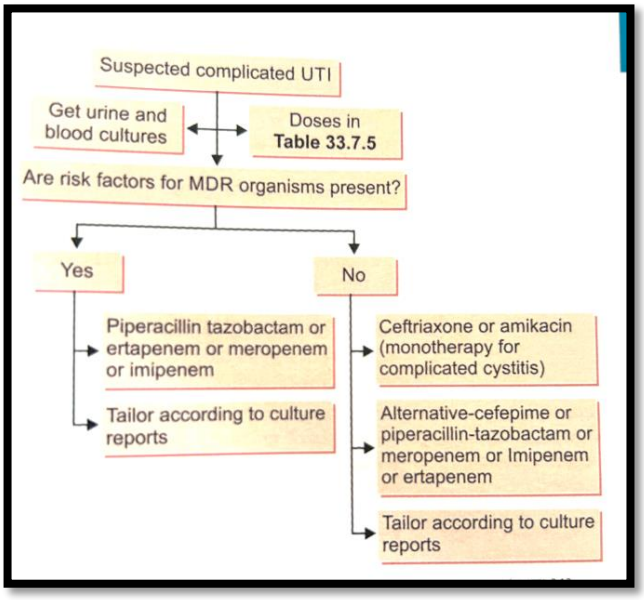
Low count of <10^4 CFU/ml is due to commensal flora(Contamination during the voiding) and its of no significance.

However low counts are considered significant in following condition:

Patient on antibiotics or diuretics, Acute urethral syndrome, Sample taken by suprapubic bladder aspiration and Catheterized patient: is patient is symptomatic then count of ≥ 10^3 CFU/ml is considered significant

Antimicrobial stewardship in UTI:

According to the CDC, Antimicrobial stewardship is defined as "the use of right antimicrobial, for the right patient, at the right time, with the right dose, route, and frequency, causing least harm to the patient and future patients. The 8 Ds of antimicrobial stewardship is **D**iagnosis (Clinical), **D**rug, **D**osage, **D**iagnostics (Microbiology), **D**e-escalation, **D**uration, **D**ebridement, **D**isease prevention. ASMP in health care facility is mainly required to overcome Multi Drug Resistance Organism (MDRO), so that to improve the patient's outcome, improve patients' safety and reduce the cost to health care. The choice of antimicrobial depends on factors like- Local spectrum and susceptibility of organisms, Risk of Multidrug Resistant organism (MDR), Type of UTI, Severity of infection, Risk of MDR in uncomplicated UTI like older age, Recurrent UTI etc. A high resistance of around 70% noted with drugs like amoxycillin, Amoxycillin-clavulanate and Fluoroquinolones, hence must be avoided as empirical therapy. Overall prevalence of Extended spectrum beta lactamase (ESBL) as per ICMR 2020 report is 74%. So empirical therapy must be tailored according to the local antibiogram



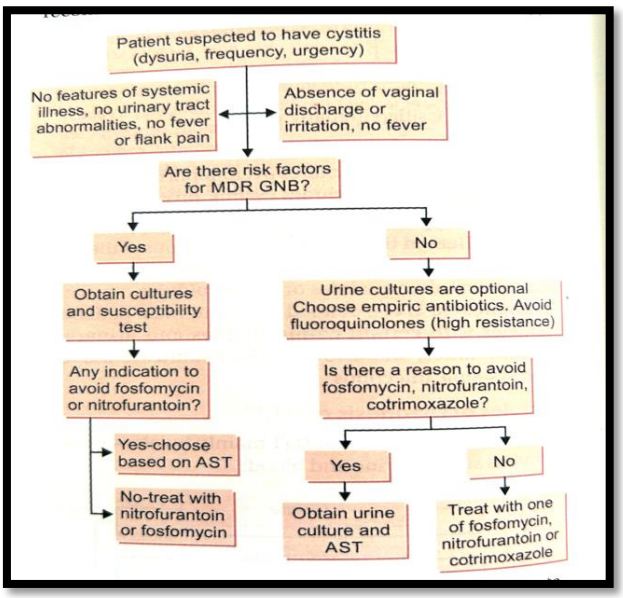


Table: **Algorithm for treatment of Complicated and Uncomplicated UTI**[3]

In case of uncomplicated Pyelonephritis (in non-pregnant, premenopausal women), Those patients who do not require hospitalization (Mild symptoms, fever < 39º C, no vomiting, no flank pain) can be treated with Oral antibiotics like Cotrimoxazole, Cefpodoxime, Ciprofloxacin and levofloxacin. Those required hospitalization must be treated with parenteral antibiotics. Never use Nitrofurantoin and oral Fosfomycin in the treatment of pyelonephritis. In case of complicated pyelonephritis (Severe symptoms, UTI in pregnant women, Hospital acquired UTI), cases are treated as inpatient. Ceftriaxone, Cefotaxime, Cefepime, Piperacillin-tazobactum can be used empirically when community acquired ESBL< 20%. Ciprofloxacin can be used if the Resistance is < 10%. Meropenem is used when the risk factors for MDR is present.

In most UTIs, treatment is often started empirically before culture reports are available. [2] Resistance developed in pathogens due to frequent misuse. [4] In the last few decades there have been significant changes in the antimicrobial resistance patterns of uropathogens and several reports on spread of bacterial resistance among uropathogens. [4] Recent reports show in vitro activity against Multi drug resistant (MDR) pathogens, including carbapenem-resistant Klebsiella pneumoniae (CR-Kp), Pseudomonas aeruginosa, extended-spectrum beta-lactamase (ESBL)-producing bacteria, and vancomycin-resistant enterococci (VRE). [4] The emergence of a plethora of multidrug-resistant (MDR) organisms has prompted re-evaluation of non-traditional antibiotics. [5] The introduction of antimicrobial agents that are not much used in clinical practice may show a ray of hope. **The current study was therefore undertaken with a special purpose, to provide an insight into the current scenario of the microorganisms causing UTI, and to evaluate various risk factors with its antibiotic profile**

MATERIALS AND METHODS:

The study was carried out in all the symptomatic patients (OPD/IPD) of urinary tract infection attending Dhiraj Hospital, Piparia, Vadodara.

Ethical Consideration: Approval of Sumandeep Vidyapeeth Institutional Ethical Committee (SVIEC) of SBKS Medical College, Piparia, Gujarat, was taken prior to the initiation of the work.

Study Design: Prospective Cross-Sectional study

Subjects: All the patients attending Dhiraj Hospital with symptoms of UTI

Sample Size: 110 urinary isolates

Inclusion Criteria: Any Patient irrespective of age, gender, or any underlying conditions, with the signs and symptoms of UTI, attending the OPD/IPD of Dhiraj Hospital was included in the study.

Exclusion Criteria: Those who are not willing to participate

Place of study: Microbiology Laboratory, Dhiraj Hospital, Piparia

Methodology: Urine samples received by the Microbiology Laboratory were inoculated using a 0.001 ml calibrated loop onto sterile plate of Blood agar and Mac Conkey's agar. After an aerobic incubation at 37˚C, the plates showing significant growth as per the Kass count (single species count of more than

10^5 organisms per ml of urine) were processed further and the isolates were identified up to the species level by using standard biochemical tests [6-9]. The isolates obtained were identified at a species level as well as the antimicrobial susceptibility of the strain will be determined by using fully automated bacterial identification system (VITEK 2 Compact; BioMérieux, Paris, France, and USA Phoenix TM 100; Becton Dickinson, MD, USA).

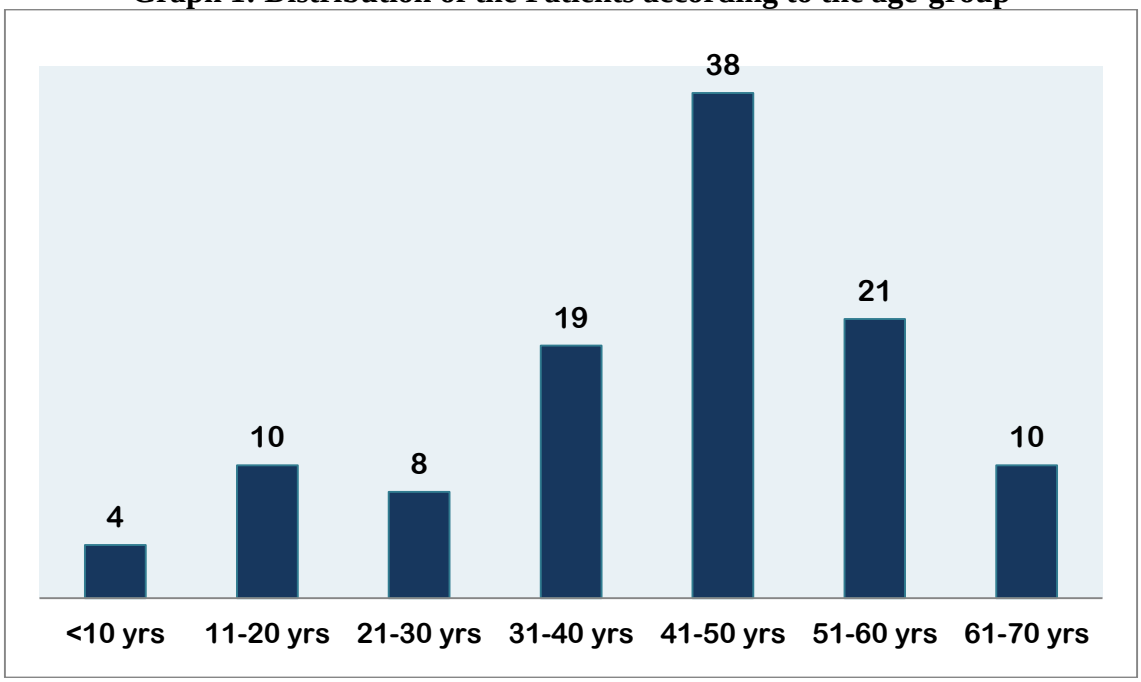
❖ **Antibiotics Susceptibility testing:**

✓ Checked for the following antibiotics: **by VITEK 2**

✓ Fosfomycin, Erythromycin(E), Penicillin(P), Linezolid(LZ), Levofloxacin(LE), Doxycycline(DO), Ticarcillin(TI), Piperacillin/tazobactum(PIT), Cefixime (CFX), Cefoxitin (CX), Ceftazidime (CAZ), Cefotaxim(CTX), Cefotaxim-sulbactum(CFS), Cefuroxime(CXM) Cefipime(CPM), Amikacin(AK), Gentamycin(GEN), Ciprofloxacin(CIP), Norfloxacin(NX), Nitrofurantoin(NIT), Aztreonam(AT), Piperacillin(PI),Tigecycline(TGC), Ticarcillin(TI), Amoxicillin-clavulanic acid(AMC), Co-trimoxazole(COT).

1. **Results:**

Graph 1: Distribution of the Patients according to the age-group



Age group affected 41-50 years and 51-60 years.

Chart 1: Distribution of patients according to gender

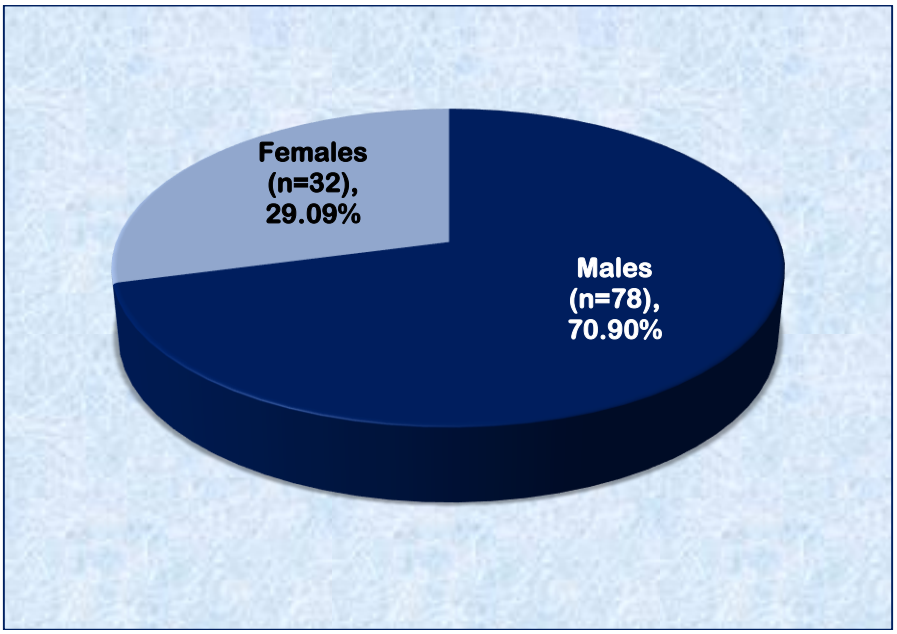


Table 1: Etiological agents causing Urinary Tract infection:

No.	Organisms	No.(%)
1	*Escherichia coli*	55(50)
2	*Klebsiella pneumonia*	12(10.9)
3	*Enterococcus faecium*	09(8.1)
4	*Pseudomonas aeruginosa*	08(7.2)
5	*Acinetobacter baumanni*	08(7.2)
6	*Staphylococcus hemolyticus(CONS)*	06(5.4)
7	*Proteus mirabilis*	03(2.7)
8	*Citrobacter freundii*	03(2.7)
9	*Enterobacter cloaca*	02(1.8)
10	*Providentia*	01(0.9)
11	*Morganella*	01(0.9)
12	*Aeromonas spp.*	01(0.9)
13	*Serratia marscecence*	01(0.9)
	Total	110

Table 2: Association of Uro-pathogens to clinical condition

ETIOLOGICAL AGENT	CLINICAL CONDITION
E.coli	87% found in the cases of urethritis, 10% in cases of cystitis.
Klebsiella pneumoniae	100% found in cases with urethritis
Enterococcus spp.	100% found in cases with urethritis

Acinetobacter baumanni	50% in cases of cystitis, rest 50% in cases with pyelonephritis
Pseudomonas aeruginosa	100% found in cases with urethritis
Proteus mirabilis	100% found in cases with pyelonephritis
CONS	67% in urethritis, 17% in cystitis and pyelonephritis
Aeromonas, Morganella, Serratia marscecence	Found in urethritis patient

Table 3: Distribution of Uropathogens from different Wards of Dhiraj Hospital

No. of the Pathogens	Organisms	Ward
76	**E.coli (41),** Acinetobacter (7), Klebsiella (6), Enterococci (6),CONS(5), Pseudomonas(4),Proteus(3), Morganella(1), Aeromonas (1), Enterobacter(1),Citrobacter(1)	Medicine ward
15	**E. coli (7),** Klebsiella (2), Enterococci (2), CONS(1), Pseudomonas(1),Providentia (1), Enterobacter(1)	Pediatric ward
08	**Klebsiella(3)**, E. coli(2), Pseudomonas(1), Acinetobacter(1), Citrobacter(1)	ICU
06	**E. coli(4),** Pseudomonas(1), Citrobacter(1)	Surgical ward
03	**E. coli(1)**, Pseudomonas(1), Serratia (1)	Orthopedic ward
02	Klebsiella(1), Enterococci(1)	Obstetric ward
Total-110		

Table 4: Evaluation of Risk factors for UTI:

Risk factors	pathogens
catheter	
Yes(n=23)	52% *E.coli*, 13% *acinetobacter*, 9% *Pseudomonas, proteus and Enterococcus*. **Isolation of single case of Serratia was a key feature.**
No(n=87)	49% *E.coli*, 13% *Klebsiella*, 8% *Enterococcus*, 7% *Pseudomonas*, 6% *Acinetobacter*.
Renal calculi	
Yes(n=11)	73% *E.coli*, 18% *acinetobacter* and *pseudomonas*, 9%CONS and *Enterococcus fecalis*
No(n=76)	48% *E.coli*, 14% *Klebsiella*, 8% *enterococcus*, 6% *pseudomonas aeruginosa*
Prostatic cancer/bladder cancer	
Yes(n=4)	Morgenella was isolated from 1 case, 50% E.coli

No(n=106)	34% E.coli, 10% Klebsiella, followed by others
Structural anomaly in urinary tract	
Yes(n=4)	100% E.coli was isolated
No(n=106)	31% E.coli and klebsiella

Table 5: Resistance pattern of uropathogens (n=110) to all the classes of antibiotics:

Antibiotics used	No. of strains resistant (%)
Fosfomycin	86(78%)
Erythromycin	40(36%)
Penicillin	41(37%)
Ticarcillin	41(37%)
Linezolid	53(48%)
Piperacillin+ tazobactum	41(37%)
Aztreonam	29(26%)
Cefoxitin (2nd Generation Cephalosporin)	50(45%)
Cefuroxime (2nd Generation Cephalosporin)	72(65%)
Cefotaxime (3rd Generation Cephalosporin)	47(42%)
Cefixime (3rd Generation Cephalosporin)	66(60%)
Ceftazidime (3rd Generation Cephalosporin)	47(42%)
Cefipime(4th Generation Cephalosporin)	68(62%)
Doxycycline	22(20%)
Tigecycline	4(3%)
Levofloxacin	22(20%)
Ciprofloxacin	54(49%)
Nitrofurantoin	22(20%)
Gentamycin	53(48%)
Co-trimoxazole	72(65%)

Table 6: Antibiotic Resistance Pattern of Uropathogens

	E.	*Klebsie*	*Entero-*	*Pseu*	*Proteu*	*Acine*	*CO*

	coli	*lla*	*coccus*	*do-monas*	*s*	*to bacter*	*NS*
Fosfomycin	76%	75%	100%	88%	33%	100%	83 %
Erythromycin	45%	17%	22%	50%	33%	13%	33 %
Penicillin	47%	17%	22%	50%	33%	13%	33 %
Ticarcillin	47%	17%	22%	50%	33%	13%	33 %
Linezolid	56%	50%	44%	38%	0%	25%	67 %
Piperacillin+ tazobactum	53%	0%	44%	50%	0%	75%	33 %
Aztreonam	38%	17%	22%	13%	33%	0%	33 %
Cefoxitin	38%	67%	56%	38%	0%	25%	83 %
Cefuroxime	75%	58%	44%	50%	67%	63%	67 %
Cefotaxime	53%	58%	0%	38%	33%	38%	17 %
Cefixime	69%	50%	44%	50%	67%	50%	67 %
Ceftazidime	53%	58%	0%	38%	33%	38%	17 %
Cefipime	70%	58%	56%	38%	67%	50%	67 %
Doxycycline	24%	50%	0%	0%	33%	25%	17 %
Tigecycline	4%	0%	0%	25%	67%	0%	0%
Levofloxacin	24%	50%	0%	0%	0%	25%	17 %
Ciprofloxacin	69%	33%	0%	50%	33%	38%	33 %
Nitrofurantoin	24%	50%	0%	0%	0%	25%	17 %

Conclusions-

UTI is more prevalent in males compare to female and middle age group of 41-50 yrs are mainly affected.Most common presenting symptom was polyuria and dysuria, followed by anuria with fever and abdominal pain.Most common clinical condition was urethritis followed by cystitis and pyelonephritis.E. coli was the major etiological agent, associated mainly with rural population (40/55), male gender, significantly associated with factors like catheterization and renal stone. 76% strains were resistant to Fosfomycin, 75% resistance to cefuroxime and 70% resistance to cefepime while 96% strains were sensitive to Tigecycline, 76% sensitive to nitrofurantoin.Klebsiella was the second isolated uropathogen mainly found in males of rural area, none of the patients were on catheter or having renal stone. 75% strains were resistant to Fosfomycin followed by cefoxitin, cefuroxime, cefotaxime and cefepime. Klebsiella was 100% sensitive to tigecycline and piperacillin+tazobactum.Third pathogen was

Enterococcus faecalis, predominant in females, associated with the presence of catheter, stone and prostate cancer. It was 100% resistant to Fosfomycin while it was 100% sensitive to tigecycline, Doxycycline, nitrofurantoin, and levofloxacin.Fourth pathogen was *Pseudomonas*, predominant in males and was associated with catheter and stones. 88% resistant to Fosfomycin, while 100% sensitive to doxycycline and nitrofurantoin.Fifth was *Acinetobacter baumanni*, more in males of rural area and was associated with catheter and calculi. 100% resistant to Fosfomycin, while 100% sensitive to Aztreonam and tigecycline.CONS were found in males of urban area, not associated with catheter and calculi. 83% strains were resistant to Fosfomycin.Serratiamarscecence was isolated from one case from orthopedic ward; patient was on catheter, with urethritis, resistant to fosfomycin.

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