

Emergence of Quinolone Resistance in UTI In Gynaecological Patients

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Abstract: Urinary tract infections (UTIs) are amongst the most common infections encountered in clinical practice⁽¹⁾. Urinary tract infection is one of the most common bacterial infections in women, and 50% to 60% of adult women experience a UTI during their lifetime.

Aim Of The Study To study the emergence of quinolone resistance in UTI in gynaecological patients.

Objectives To isolate and identify the uropathogens from the urine samples. And To detect the antimicrobial resistance of uropathogens to fluoroquinolones. A total of 300 urine culture sensitivity reports were analyzed of patients who were suspected to be having urinary tract infection, In the present study, a total of 300 subjects were studied *Escherichia coli* (33%) was the most common uropathogen, *Klebsiella*(28%) being the second commonest. Maximum resistance was seen in nalidixic acid, ciprofloxacin, followed by norfloxacin. The drug most sensitive to the uropathogens studied was amikacin, followed by P/T and imipenem .

Conclusion As we face a serious global resistance problem we need to adopt a series of measures to address the problem

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I. Introduction

Urinary tract infections (UTIs) are amongst the most common infections encountered in clinical practice⁽¹⁾. Urinary tract infection is one of the most common bacterial infections in women, and 50% to 60% of adult women experience a UTI during their lifetime^(2,3).

Women are more inclined to develop UTI due to their anatomical features like short urethra, and other factors like pregnancy, use of diaphragms and sexual activity⁽⁴⁻⁶⁾. The use of quinolone antibiotics for the treatment of complicated and uncomplicated urinary tract infections globally has led to the emergence and spread of resistance among enteric pathogens, especially *Escherichia coli*⁽⁷⁾.

Ciprofloxacin and Levofloxacin are the most commonly prescribed quinolones for UTI treatment⁽⁸⁾, while Norfloxacin is suggested for long term prophylaxis⁽⁹⁾.

High norfloxacin resistance among Gram-negative bacteria has also been reported in India, as it is routinely prescribed for UTIs⁽¹⁰⁾. A detailed study in South India has revealed high resistance pattern to ciprofloxacin among the different members of Enterobacteriaceae other than *E. Coli*, such as *Klebsiella* and *Citrobacter* species.

Quinolone resistance was reported to be higher for elderly patients, especially those with complications⁽¹¹⁾.

Recently, several studies have revealed increasing trends of resistance to many antimicrobials including the fluoroquinolones⁽¹²⁾ The increase in bacterial resistance to fluoroquinolone is multifactorial⁽¹³⁾

The present study was undertaken to assess the current antibiotic resistance pattern in the common uropathogens isolated at Gandhi hospital. Further, risk assessment was also performed to determine the factors responsible for the emergence of quinolone resistance.

Aim Of The Study

To study the emergence of quinolone resistance in UTI in gynaecological patients.

OBJECTIVES

1. To isolate and identify the uropathogens from the urine samples.
2. To detect the antimicrobial resistance of uropathogens to fluoroquinolones.

II. Materials & Methods

Place of study: Gandhi Hospital, Secunderabad

Study design: Observational study

Sample size: 300 urine culture sensitivity reports.

Study duration: October 2015 to september 2017.

Methodology

Clean-catch midstream urine specimens from patients diagnosed clinically to be having UTI on the basis of symptoms (fever, dysuria & increased frequency of urination) were inoculated on Blood Agar and McConkey Agar plates, which were incubated aerobically at 37°C overnight. Plates showing growth suggestive of significant bacteruria, with colony counts exceeding 10⁵ CFU/ml were subjected to standard biochemical tests for identification and antimicrobial sensitivity testing by Kirby- Bauer disc diffusion method. Interpretation as 'Sensitive' or 'Resistant' was done on the basis of the diameters of zones of inhibition of bacterial growth as recommended by the disc manufacturer. Antibiotics against which sensitivity was tested in the present study included Amoxycillin, Amoxiclav, Ciprofloxacin, Norfloxacin, Levofloxacin, Co-trimoxazole, Tetracycline, Imipenem, cefuroxime, Vancomycin, Nalidixic acid, Amikacin and Nitrofurantoin.

All the women gave informed verbal consent to participate in the study, which was approved by the institutional ethics committee.

Inclusion Criteria

All women of reproductive age group with symptoms of urinary tract infections.

Exclusion Criteria:

Pregnant women

Women with STD's

Statistical Analysis

The data was registered in the computer by creating spread sheet. The data was analysed and percentages for individual variable calculated.

III. Results Of The Study

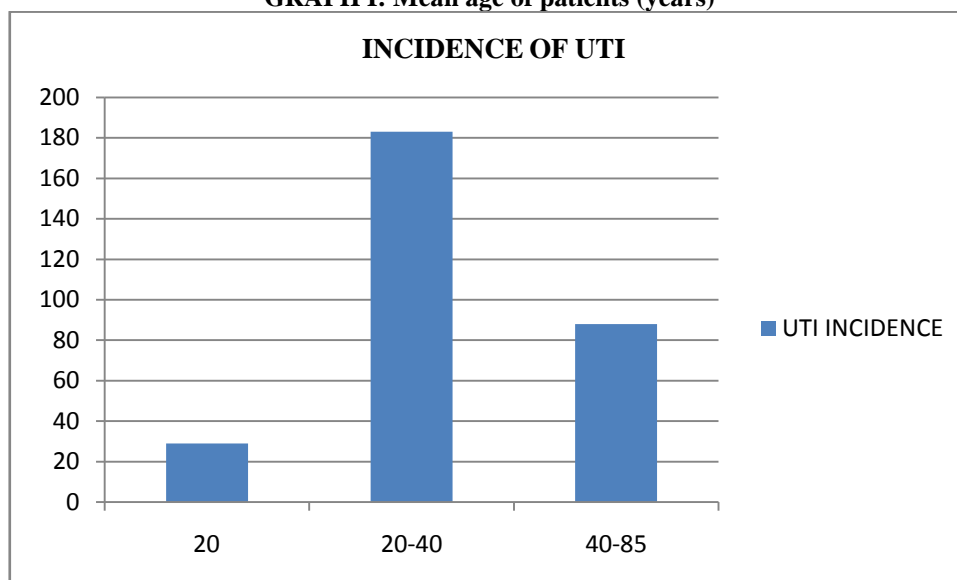
1. Mean Age Of Patients

TABLE I:

ORGANISMS ISOLATED	<20YRS	20-40YRS	40-80YRS	TOTAL
<i>Escherichia coli</i>	12	58	29	99
<i>Klebsiella spp</i>	11	45	30	86
<i>Enterococcus spp</i>	2	22	9	33
<i>Coagulase negative Staphylococcus</i>	2	13	1	16
<i>Staphylococcus aureus</i>	2	10	3	15
<i>Citrobacter spp</i>	0	7	6	13
<i>Candida spp</i>	0	8	5	13
<i>Polymicrobial</i>	0	8	4	12
<i>Enterobacter spp</i>	0	5	0	5
<i>Pseudomonas spp</i>	0	3	1	4
<i>Proteus spp</i>	4	3	0	3
<i>Streptococcus</i>	0	1	0	1
TOTAL	29	183	88	300

Age group between 21-40 showed highest incidence of UTI followed by 40-80yrs and then below 20yrs. This showed that more incidence of UTI among sexually active population.

GRAPH I: Mean age of patients (years)



2. MICRO-ORGANISMS ISOLATED FROM THE URINE SAMPLES

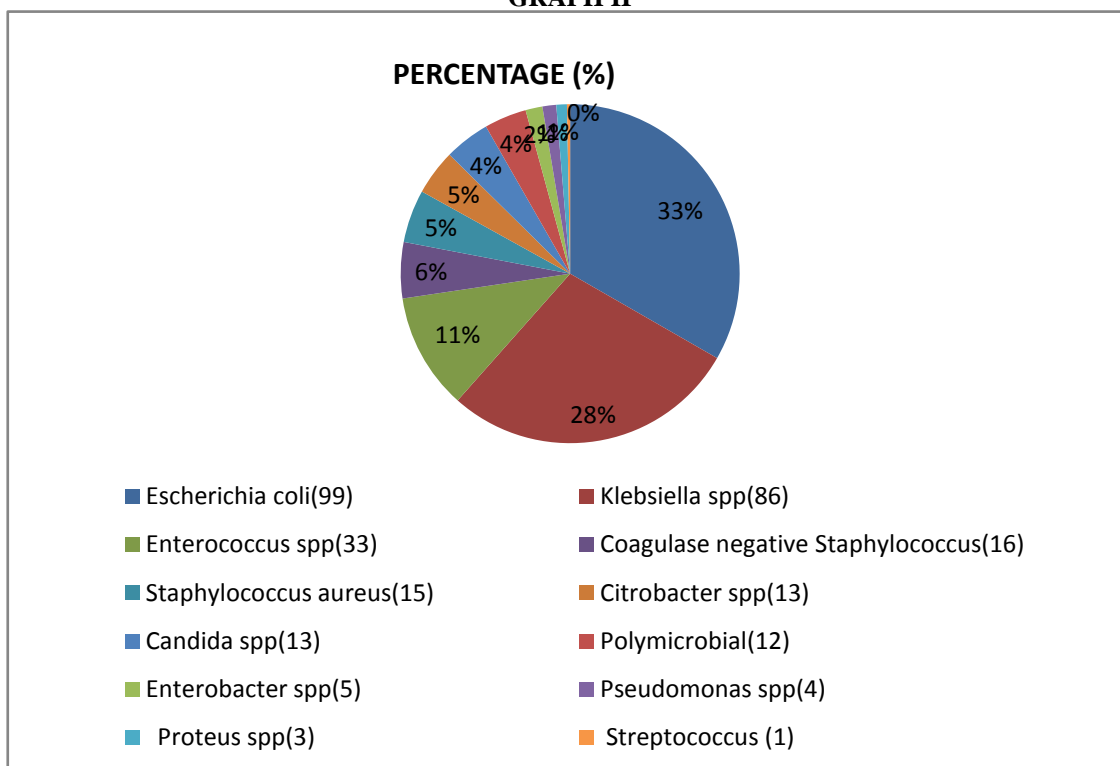
A total of 300 isolates of uropathogens were isolated

The distribution of the different species among these isolates were as follows

TABLE 2:

ORGANISMS ISOLATED	NUMBER	PERCENTAGE (%)
<i>Escherichia coli</i>	99	33
<i>Klebsiella spp</i>	86	28
<i>Enterococcus spp</i>	33	11
<i>Coagulasenegative Staphylococcus</i>	16	5.3
<i>Staphylococcus aureus</i>	15	5
<i>Citrobacter spp</i>	13	4.3
<i>Candida spp</i>	13	4.3
<i>Polymicrobial</i>	12	4
<i>Enterobacter spp</i>	5	1.6
<i>Pseudomonas spp</i>	4	1.3
<i>Proteus spp</i>	3	1
<i>Streptococcus</i>	1	0.3
TOTAL	300	100

GRAPH II



Frequency of uropathogens in UTI

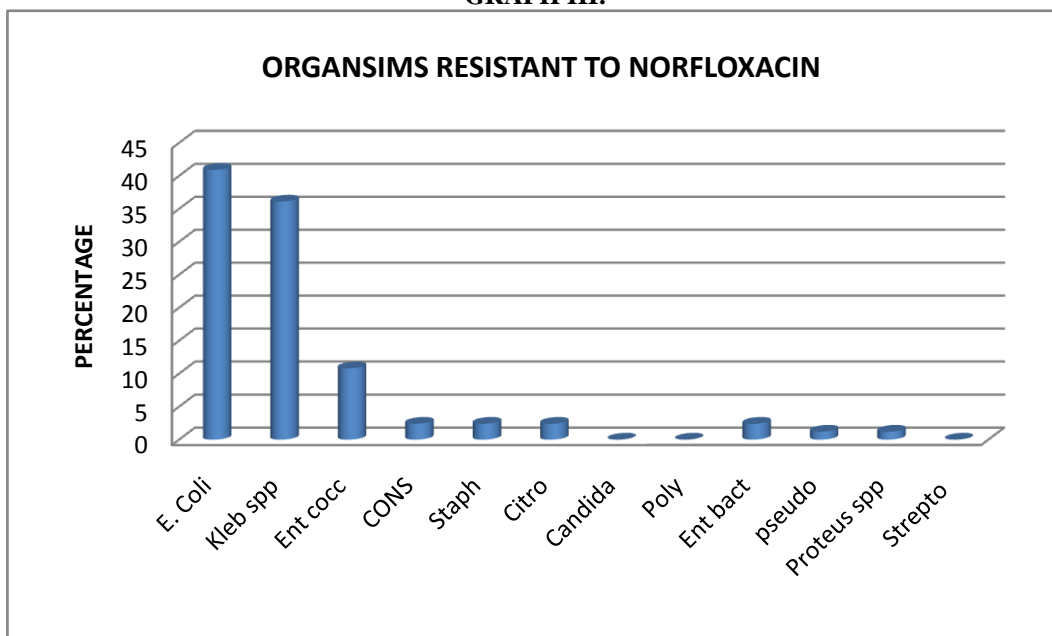
Among 300 isolates major bacterial isolate from UTI was *E.coli* (33%) and the second most common organism was *Klebsiellae spp* (28%) followed by *Enterococcus spp*, *CONS*, *Staphylococcus aureus*, *Citrobacter*, *Candida spp*, *Pseudomonas spp*, and *Enterobacter*.

3. RESISTANCE OF ISOLATED STRAINS TO NORFLOXACIN

TABLE 3:

ORGANISMS RESISTANT TO NORFLOXACIN	PERCENTAGE (%)	NO OF CASES
<i>E. Coli</i>	40.9	34
<i>Kleb spp</i>	36.1	30
<i>Ent cocc</i>	10.8	9
<i>CONS</i>	2.4	12
<i>Staph</i>	2.4	2
<i>Citro</i>	2.4	2
<i>Candida</i>	0	0
<i>Poly</i>	0	0
<i>Ent bact</i>	2.4	2
<i>Pseudo</i>	1.2	1
<i>Proteus spp</i>	1.2	1
<i>Strepto</i>	0	0
TOTAL	100	82

GRAPH III:



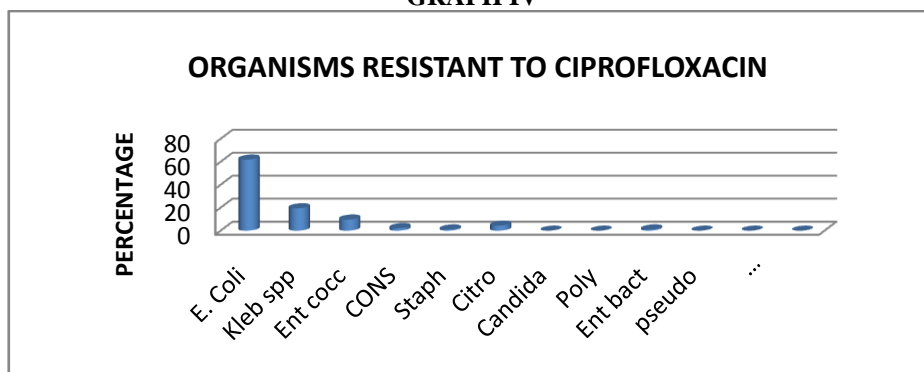
In the present study E.coli was resistant to norfloxacin-40.9% and klebsiella was resistant- 36.1%.

4. RESISTANCE OF ISOLATED STRAINS TO CIPROFLOXACIN

TABLE 4:

ORGANISMS RESISTANT TO CIPROFLOXACIN	PERCENTAGE (%)	NO OF CASES
<i>E. Coli</i>	61.9	57
<i>Kleb spp</i>	19.5	18
<i>Ent cocc</i>	9.7	9
<i>CONS</i>	2.17	2
<i>Staph</i>	1.08	1
<i>Citro</i>	4.3	4
<i>Candida</i>	0	0
<i>Poly</i>	0	0
<i>Ent bact</i>	1.08	1
<i>Pseudo</i>	0	0
<i>Proteus spp</i>	0	0
<i>Strepto</i>	0	0
TOTAL	100	82

GRAPH IV



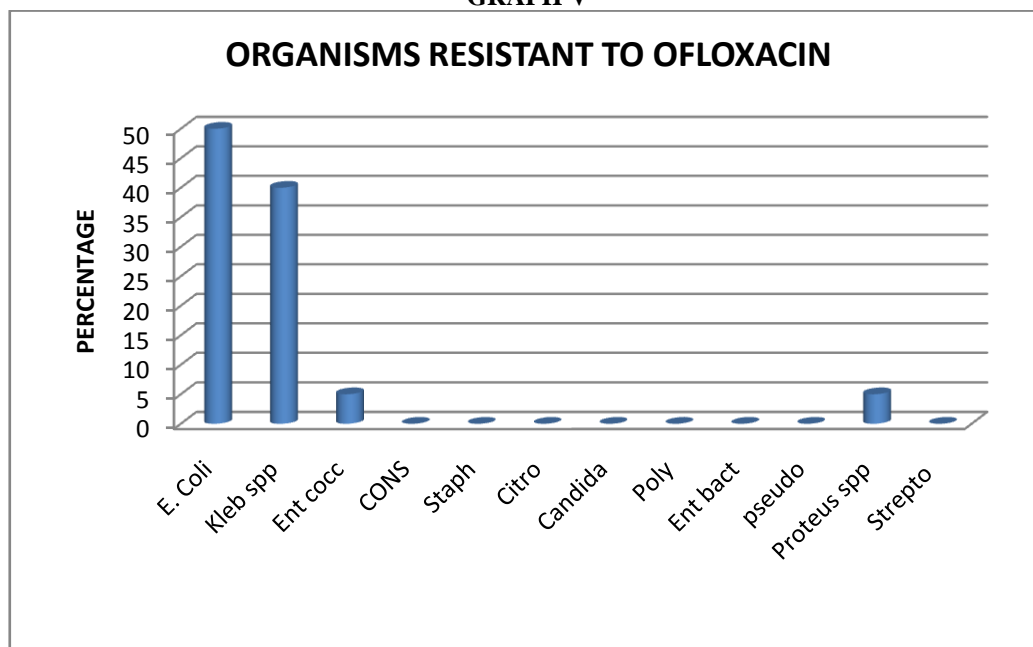
High resistance was observed in our study to ciprofloxacin to both E.coli and Klebsiella. Resistance to E.coli was- 61.9% and to Klebsiella was 19.5%.

5. RESISTANCE OF ISOLATED STRAINS TO OFLOXACIN

TABLE 5

ORGANISMS RESISTANT TO OFLOXACIN	PERCENTAGE (%)	NO OF CASES
<i>E. Coli</i>	50	10
<i>Kleb spp</i>	40	8
<i>Ent cocc</i>	5	1
<i>CONS</i>	0	0
<i>Staph</i>	0	0
<i>Citro</i>	0	0
<i>Candida</i>	0	0
<i>Poly</i>	0	0
<i>Ent bact</i>	0	0
<i>Pseudo</i>	0	0
<i>Proteus spp</i>	5	1
<i>Strepto</i>	0	0
TOTAL	100	20

GRAPH V



50% resistance was observed to E.coli and 40% to Klebsiella in our study

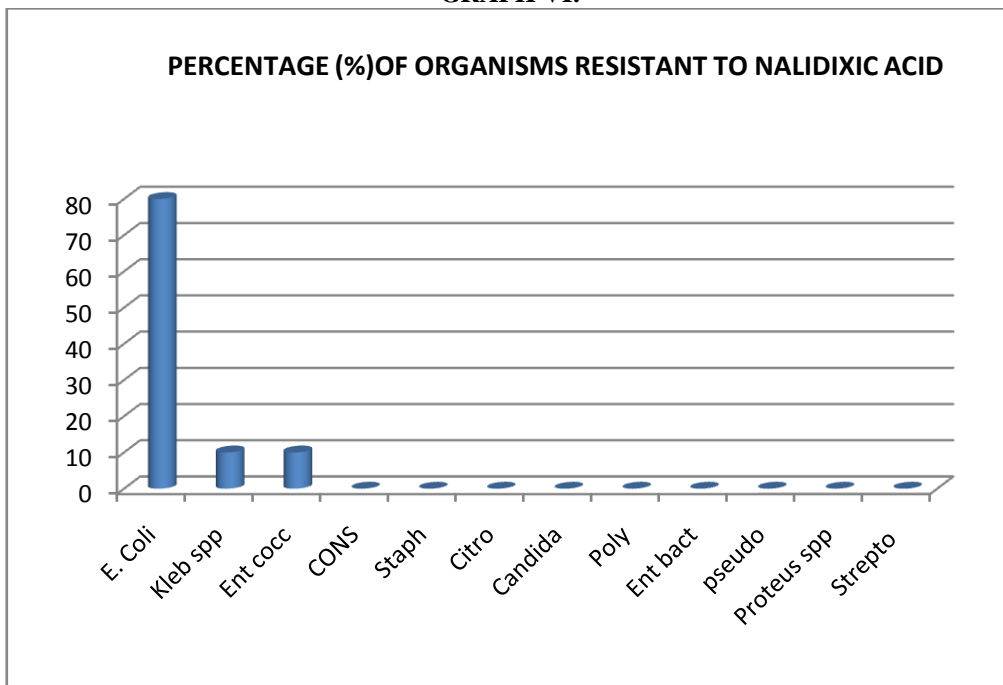
6. RESISTANCE OF ISOLATED STRAINS TO NALIDIXIC ACID

TABLE 6:

ORGANISMS RESISTANT TO NALIDIXIC ACID	PERCENTAGE (%)	NO OF CASES
<i>E. Coli</i>	80	8
<i>Kleb spp</i>	10	1
<i>Ent cocc</i>	10	1
<i>CONS</i>	0	0
<i>Staph</i>	0	0

<i>Citro</i>	0	0
<i>Candida</i>	0	0
<i>Poly</i>	0	0
<i>Ent bact</i>	0	0
<i>Pseudo</i>	0	1
<i>Proteus spp</i>	0	0
<i>Strepto</i>	0	0
TOTAL	100	10

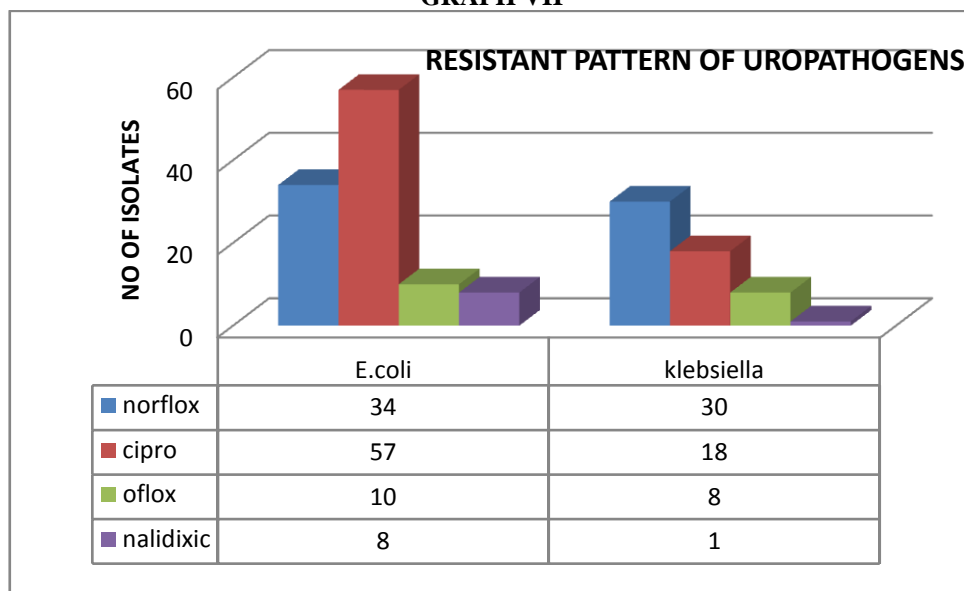
GRAPH VI:



High resistance was noted to nalidixic acid, for E.coli 80% and for Klebsiella 10%, Enterococcus was also resistant to nalidixic acid 10%.

7. RESISTANCE PATTERN OF UROPATHOGENS TO QUINOLONE

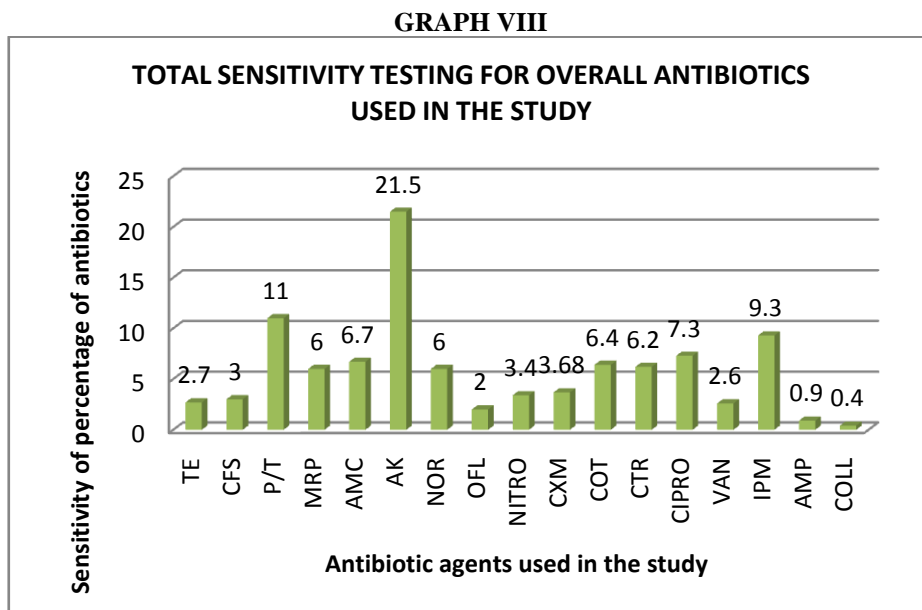
GRAPH VII



This figure shows the resistant pattern of E.coli and Klebsiella to the fluoroquinolones, highest resistance is seen to ciprofloxacin followed by norfloxacin.

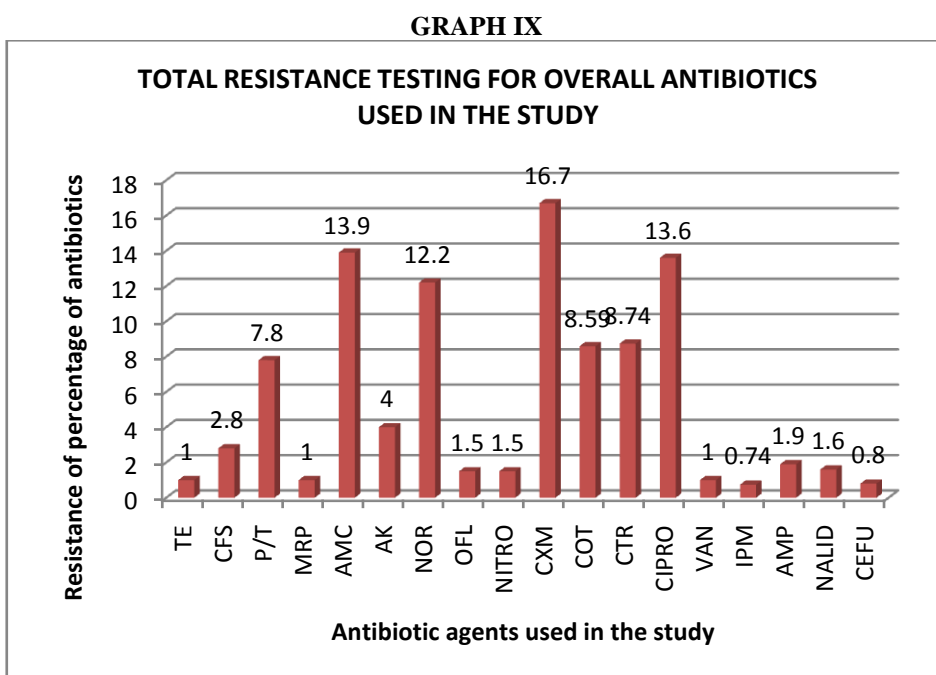
8. TOTAL SENSITIVITY TESTING FOR OVERALL ANTIBIOTICS USED IN THE STUDY

In this study the most sensitive drug was Amikacin, followed by P/T and imipenem.



9. TOTAL RESISTANCE TESTING FOR OVERALL ANTIBIOTICS USED IN THE STUDY

In this study the drug with maximum resistance was cotrimoxazole. Amoxicillin and quinolones followed the list.



IV. Discussion

There is an increased emergence of antibiotic resistance in the uropathogens, reasons for this are many like irrational, inappropriate use of antibiotics before the availability of the urine culture results, lack of knowledge of local antimicrobial susceptibility patterns and over the counter medications.

In the present study, a total of 300 subjects were studied Escherichia coli (33%) was the most common uropathogen, Klebsiella(28%) being the second commonest. Other common organisms in our study was coagulase negative Staphylococcus (5.3%), Pseudomonas spp (1.3%), Enterococcus spp (11%) , Staphylococcus aureus (5%), Enterobacter spp(1.6%) which also correlate well with the studies.

Antibiotic resistance is a major clinical problem in treating infections caused by these microorganisms. The resistance to antimicrobials has increased over years. Resistance pattern varies from region to region.

In our study high level of resistance was seen to ciprofloxacin for E.coli it is 61.9% ,for Klebsiella spp it is 19.5%.

In this study most of the UTIs caused by gram negative bacteria were resistant to beta lactams and fluoroquinolones. Higher resistance rates to all antibiotics tested in our study may be explained by high and uncontrolled consumption of these antibiotics during the past decade in our institute. All antimicrobials are available as over-the-counter drugs without requiring the physicians prescriptions in our country.

However Imipenem showed lowest resistance rates with only 4% resistance in Escherichia coli, 2% in Klebsiella spp.

Piperacillin/tazobactam combination also showed less resistance followed by carbapenems with the resistance rate of 18% in Escherichia coli, 20% in Klebsiella spp.

Resistance rate of cotrimoxazole which is commonly used in urinary tract infections was also high with 25% of Escherichia coli, 21% of Klebsiella spp, being resistant to it. whereas the conventional urinary antiseptic nitrofurantoin showed 9% resistance in Escherichia coli, and 1% in Klebsiella spp making this drug an effective drug in 2/3rds of the cases.

Vancomycin remained the best drug against these isolates with 100% sensitivity.

Similar resistance pattern was noted by various workers from different parts of India^[9-12] In somasekara et al¹⁷ study highest resistance of E.coli was seen towards ciprofloxacin and ceftazidme (72% and 58% respectively). Cotrimoxazole resistance was also 68.8% whereas only 8% were imipenem resistant.

In mandal et al¹¹ study 73% of E.coli were resistant to ciprofloxacin. Meropenem resistance in E.coli and Klebsiella was 9.8% and 18% respectively which is similar to our study. Vancomycin was the best drug with highest sensitivity which is similar to our study.

Alarming resistance to such agents requires periodic monitoring in order to take appropriate decisions when prescribing such antibiotics. A good infection control and antibiotic policy will certainly help in delaying the era of unabated microorganisms for which no antibiotic is going to be effective.

As seen in the table below the maximum resistance in this study was to cotrimoxazole(59%) and ciprofloxacin (52%) in E.coli. In Klebsiella maximum resistance was seen to cotrimoxazole (50%) and to norfloxacin(33.2%). This is showing that resistance to fluoroquinolones is on the rise. The most sensitive drugs being amikacin and imipenem with sensitivity of 70% and 28% respectively.

TABLE: 7

ANTIBIOTIC	Escherichia coli (N-99)		Klebsiella spp (N-86)	
	Resistant (%)	Sensitive(%)	Resistant (%)	Sensitive(%)
Tetracycline	4%	5%	0	1%
CFS	4%	5%	10.7%	8.13%
P/T	18%	24%	23.8%	16.2%
MRP	4%	11%	3.4%	17.4%
AMC	39%	12%	27.9%	3.4%
AK	8%	70%	9.3%	67.8%
NOR	35%	20%	33.7%	18.6%
OFL	10%	5%	9.3%	8.1%
NITRO	4%	10%	5.8%	9.3%
CXM	59%	13%	50%	8.1%
COT	25%	17%	24.4%	19.7%
CTR	18%	14%	30.2%	20.9%
CIPRO	52%	19%	20.9%	26.7%
VAN	1%	3%	0%	0%
IPM	4%	28%	2.3%	26.7%
AMP	6%	1%	2.3%	0%

COLL	0%	2%	0%	0%
NALID	9%	0%	1%	0%
CEFUROXIME	1%	0%	2.3%	0%

AGE DISTRIBUTION OF PATIENTS

Age group between 21-40 showed highest incidence of UTI followed by 40-80yrs and then below 20yrs.. This showed that more incidence of UTI among sexually active population

TABLE : 8

Study/ Age group(years)	15-20	21-40	>40
Present Study	29	183	88
Anusha SU et.al 2014 ¹⁴	10	26	18
Sonali Waske et al 2017 ¹⁵	10	350	155

This study was consistent with the study done by Anusha et al and Sonali Waske et al.

SOCIOECONOMIC STATUS AND UTI

According to the present study 87.6% of the patients belong to low socioeconomic group, as most of the patients attending Gandhi Hospital , being a government institute belong to low income group.

According to studies done by **Wesley WE et al 2002²¹**, **Kiningham R et al 1993**, (92.6%)incidence is high in low socioeconomic groups due to poor sanitation, lack of general hygienic practice.

This is consistent with the present study

But in the present study comparison with high socioeconomic class could not be made out as the patients attending Gandhi Hospital mostly belong to low socioeconomic status.

DIABETES AND UTI

Study conducted by **C.A. Czaja et al 2009²** on Women enrolled in the Epidemiology of Diabetes Interventions and Complications study were surveyed at year 10 as part of the Uro-EDIC study to assess the prevalence of cystitis and pyelonephritis in the preceding 12 months, which was 15% and 3%, respectively.

In this study 21 patients with diabetes reported which is 7%.

Geerlings SE et al 2000¹⁹, conducted a study on patients with either type 1 or type 2 diabetes who were between 18 and 75 years of age.

A total of 34 women (14%) with type 1 diabetes developed a UTI.

A total of 81 (23%) women with type 2 diabetes developed a UTI.

Recurrence Of Uti

In this study 29% (89) reported with history of previous UTI, as consistent with the study done by **B Foxman. 1990¹⁸**

Contraception And Uti

In this study only 3.33% gave the history of contraception, which is not significant

Sexual Activity And Uti

In the present study sexual activity was associated with UTI IN 20.3% as seen in studies done by Kunnin C M, which stated a close relation with sexual activity and UTI

Catheterization And Uti

In the present study only 5% of the patients were catheterized and was consistent with **Smith P.W. et al ²²and Saint S. et al 2008**, conducted a study about long-term indwelling urinary catheter with associated bacteriuria which was found in 5% - 10% of patients in long-term care facilities (28.29). Having a catheter in situ for ≥ 7 days was significantly associated with post-operative UTI.

PROLAPSE AND UTI

In the present study only 5% of the patients were admitted for prolapse and also had UTI, which was not significant. **Emrah Toz et al 2015¹⁶** conducted a study in turkey to investigate the existence of a relationship between pelvic organ prolapse (POP) and recurrent urinary tract infection (UTI). The mean age of

the 210 participants was 54.64±5.15 years. No association between POP and recurrent UTI was seen. In the prolapse group, 22 women (21%) had recurrent UTI compared with 19 women (18%) in the control group (P=0.316). Post-void residual (PVR) volumes .50 mL were associated with increased prevalence of recurrent UTI.

FOSFOMYCIN

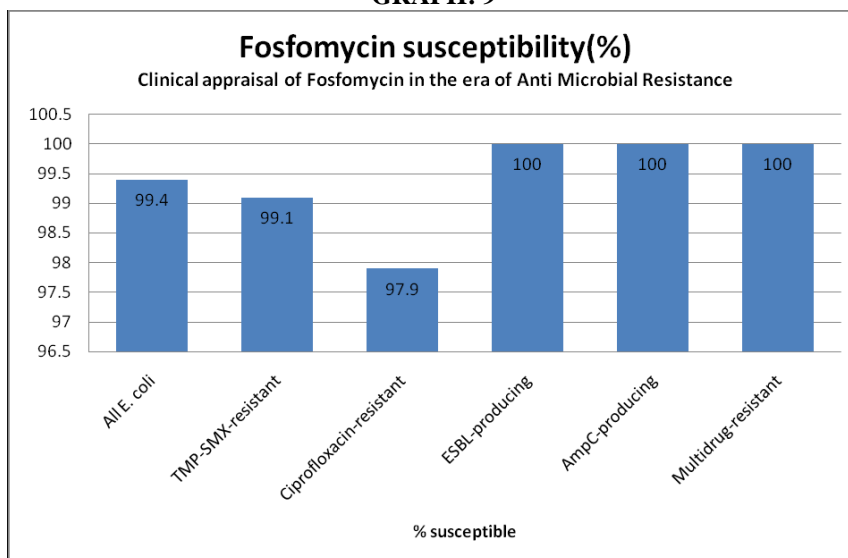
The present upcoming drug is Fosfomycin. Fosfomycin trometamol exhibits considerably high antimicrobial activity against urinary clinical isolates with relatively high levels of antimicrobial resistance. Fosfomycin trometamol is a bactericidal antibiotic agent, discovered in 1969. Resistance to fosfomycin remains rare in regions where it is widely used. It decreases bacterial adhesion and this effect could also reduce resistance development(106).

Fosfomycin Susceptibility

TABLE :9

E. coli isolate phenotype	% susceptible
All E. coli	99.4
TMP-SMX-resistant	99.1
Ciprofloxacin-resistant	97.9
ESBL-producing	100
AmpC-producing	100
Multidrug-resistant	100

GRAPH: 9



SUMMARY

The study entitled “EMERGENCE OF QUINOLONE RESISTANCE IN UTI IN GYNAECOLOGICAL PATIENTS” was conducted in the Department of Obstetrics and Gynaecology, Gandhi Medical College, Musheerabad from October 2015 to September 2018.

- The most common uropathogen isolated in the present study was E.coli (33%), followed by Klebsiella(28%).
- Next common organism isolated was Enterococcus(11%).
- In the present study the commonest age incidence for UTI was between 20-40yrs.
- In the present study resistance observed for the quinolones in E.coli and Klebsiella

TABLE: 10

ANTIBIOTIC RESISTANCE	E.coli	Klebsiella
NORFLOXACIN	40.9%	36.1%
CIPROFLOXACIN	61.9%	19.5%
OFLOXACIN	50%	40%

NALIDIXIC ACID	80%	10%
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- Maximum resistance was seen in ciprofloxacin, followed by norfloxacin
- The drug most sensitive to the uropathogens studied was amikacin, followed by P/T and imipenem
- The most resistant drug was cotrimoxazole, followed by ciprofloxacin.
- There is increasing resistance to quinolone noted in this hospital

V. Conclusion

As we face a serious global resistance problem we need to adopt a series of measures to address the problem. These include (i) decreasing antibiotic use to reduce selection pressure for resistance (ii) improving our knowledge of how bacteria become resistant and how they ameliorate the resulting fitness costs (iii) improving dosing regimens with the aim of reducing the emergence of resistance and preventing the selection of resistant mutants

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