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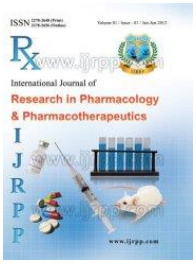

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# Changing trend of antimicrobial resistance pattern in UTI: one year retrospective study

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## ABSTRACT

### Background

The distribution of uropathogen and their susceptibility pattern to antibiotics vary regionally and even in same geographical region, and they change over time and during various season. Antimicrobial resistance pattern of locally occurring uropathogen is essential to serve as a basis for empirical treatment of urinary tract infection.

AIM: To study the most common uropathogen isolated, antimicrobial resistance pattern, and its seasonal trend if any from urine samples of patients suspected to be suffering from UTI.

### Study design

Retrospective study of one-year period from 1st Jan 2017 to 30 Dec 2017.

### Materials and methods

The culture and sensitivity data of the uropathogens from suspected cases of UTI were collected from the records of Microbiology Department, and the organisms were identified by standard methods. Antibiotic susceptibility was carried out. Percentage analysis was done.

### Results

A total of 5629 urine samples were analyzed, of which 1829 (32%) samples showed significant growth of uropathogens. Gram-negative rods accounted for more than 85% of the infections. Uropathogenic E.coli was the most predominant uropathogen (36%), followed by Enterococcus faecalis (27%) and Klebsiella (10.5%). We observed that resistance to Ampicillin is high ranging from 73.8%-95.2%, followed by amoxicillin–clavulanic acid 68.5%-90.4%, Cotrimoxazole 40.2%-83.3%, whereas nitrofurantoin 3.95%-9.50%, and carbapenem group

(imipenam, meropenam) 0.1%-4.45% showed least resistance over one year period. We also observed that the incidence of UTI due to E.coli rises in summer months but no seasonal variation to resistance could be inferred, rather there was a progressive increase in resistance to all antimicrobial over one year period.

**Conclusion**

Uropathogenic E Coli are most sensitive to nitrofurantoin and carbapenem group, so we recommend them for empirical treatment in UTI. Public health guidelines must stress on measures to prevent UTI in summers.

**Keywords:** Urinary tract infection; Antimicrobials; Resistance; Seasonal trends

## INTRODUCTION

Urinary tract infection (UTI) is the most common bacterial infection seen by primary care physician, affecting humans throughout their life, both in the community and in hospital. About 150 million per annum people were diagnosed with UTI each year worldwide, of which 10.5 million were in United States alone in 2007 [1]. UTI are caused by both gram negative and gram positive bacteria as well as by certain fungi. Uropathogenic Escherichia coli (UPEC) a gram negative bacilli is responsible more than 85% of UTI followed by Klebsiella, Enterococci, Pseudomonas, Proteus and Staphylococci [2]. UTI are a significant cause of morbidity in females of all age groups especially during pregnancy and in males at the two extremes of ages. The term UTI encompasses a variety of clinical entities which include asymptomatic bacteriuria (ASB), cystitis, prostatitis and pyelonephritis [1]. UTI is usually treated empirically with antibiotics which rely on the surveillance data obtained from epidemiological studies pertaining to resistance pattern of common uropathogen in that geographical area. Unnecessary and inappropriate use of antibiotics leads to development of multi drug resistant uropathogen. So it is advisable to monitor the resistance pattern to urinary pathogens and use antibiotic with a low resistance pattern [3]. The growing problem of antimicrobial resistance to the commonly prescribed antimicrobial results not only in treatment failure but adds to increased morbidity and pharmaco-economic burden to the society [4]. If treatment is delayed or is inadequate, complications like recurrent UTI occur which leads to pyelonephritis or permanent kidney damage [1]. Physician should have updated knowledge about the recent epidemiological data of UTI like most common organism isolated and antibiotic susceptibility pattern of uropathogen to determine appropriate empirical treatment [5]. Studies conducted in different geographical regions of the world to assess the trend of antimicrobial resistance pattern show significant increase in resistance to antimicrobials with seasonal pattern and vary according to geographical location [6]. Therefore reconsideration of antimicrobials for empirical treatment must be emphasized. Moreover antibiotic resistance pattern may change over time in the same geographical region so continuous monitoring is required. This study is undertaken to analyze most common uropathogen isolated, antimicrobial resistance pattern and temporal trends and seasonal variations, if any, of uropathogen in UTI over one year period in our region .

## MATERIAL AND METHODS

### Study design and setting

This retrospective observational study was conducted from 1st of January 2017 to 30 December 2017, at Pt. JNM Medical College Raipur Chhattisgarh India and associated BR Ambedkar Memorial Hospital. Patients of all age groups, suspected of UTI were included in the study. Data was collected from the department of microbiology records of result of urine samples collected for culture and sensitivity tests and were analyzed. Ethical approval was obtained from the Institutional ethics committee. 5629 urine samples of patients were screened for this study. Samples which showed significant growth were included in the analysis. Bacterial growth $>10^5$ colony-forming units (CFU)/ml in clean catch midstream urine culture is "significant bacteriuria", in a person with symptoms of the lower urinary tract infection like dysuria, frequency, supra-pubic pain and hematuria.

The isolates were identified by gram staining method and conventional biochemical methods. Antibiotic susceptibility patterns is done by using the

Kirby Bauer disc diffusion method and automated minimum inhibitory concentration (MIC) method using Vitek 2 as described in the clinical laboratory standard institutional (CLSI) guidelines 2011. The in vitro susceptibility pattern of antimicrobials to the isolated urinary pathogen was observed against ampicillin, amoxicillin-clavulanate, co-trimoxazole, nitrofurantoin, ciprofloxacin, norfloxacin, gentamycin, cefotaxime, cefoperazone-sulbactam, amikacin, imipenem, meropenem and Piperacillin–Tazobactam. Interpretation of result was done by measuring the zone of inhibition around the antibiotic discs in millimeters. Escherichia coli ATCC 25922, Staphylococcus aureus ATCC 29213, Pseudomonas aeruginosa ATCC 27853 and Enterococcus faecalis ATCC 29212 were used as quality control strains for antimicrobial susceptibility [7].

## STATISTICAL ANALYSIS

The microorganism was identified from the growth in the culture and its frequency was noted. Then their resistance pattern to tested antibiotics were noted and compared with other studies. Percentage analysis was used to analyze the data.

## RESULT

Of the 5629 urine samples, 1829 (32%) showed significant growth. 3800 (68%) samples had either contamination, or very low bacterial count /sterile so they were excluded. 1012 (55.3%) samples were from female and 817 (44.7%) were from males (figure 1).

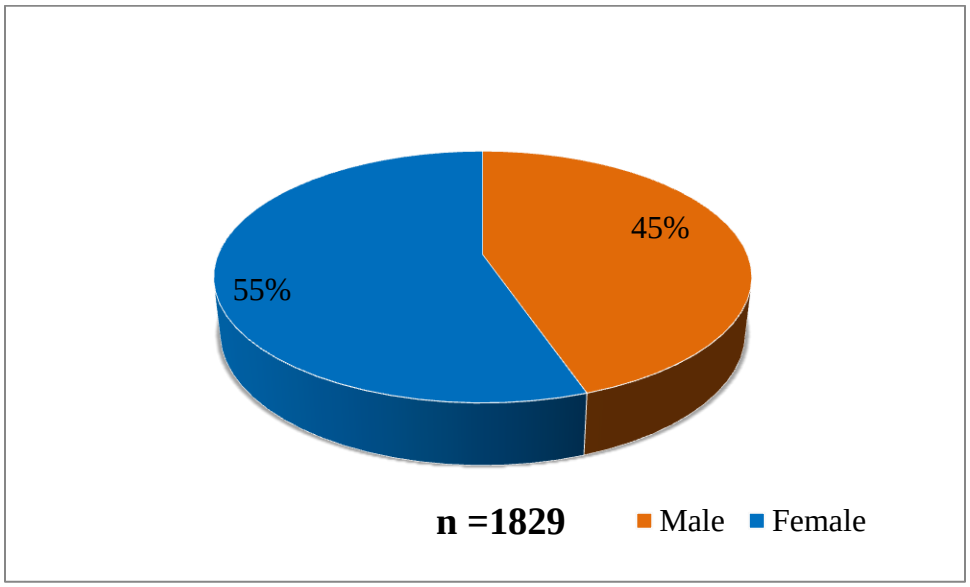


**Figure 1: Gender distribution of urinary tract infection (UTI).**

Approximately 85% isolates were gram negative rods and among them uropathogenic E.coli was predominant (36%), followed by Enterrococcus faecalis (27%) , Klebsiella (10.5 %), Pseudomonas areugenosa (5.2%) , Proteus (2.7%) CONS (5.3%), staph aureus (1.9%) ,others including Acinetobactor, Candida albicans and non albicans, Citrobacter were 11.27 % (figure 2).

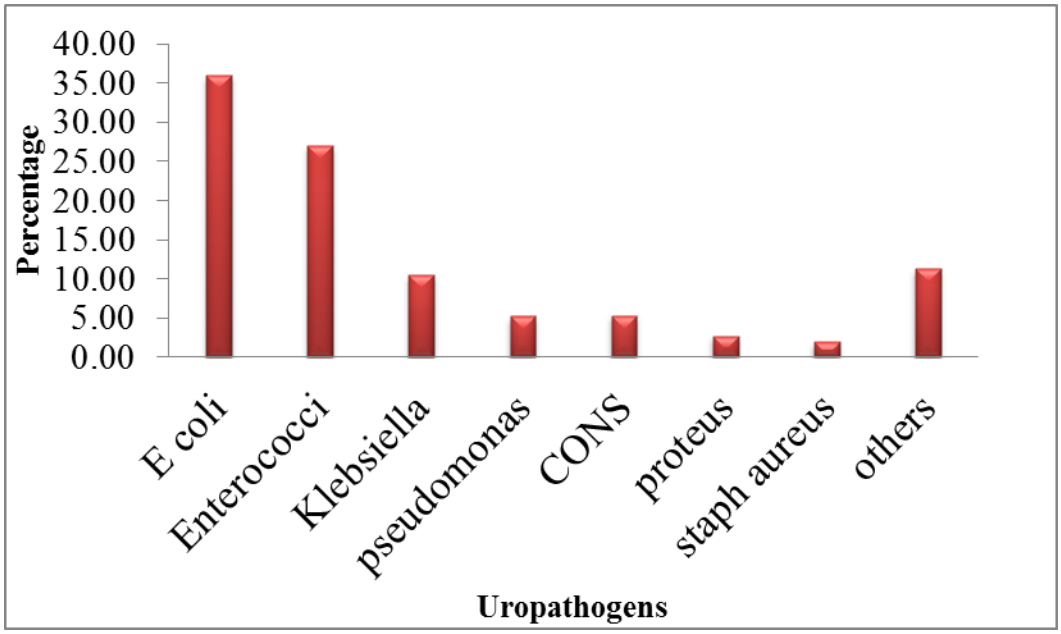


**Figure 2. Commonly isolated Uropathogen during one year.**

The specific antimicrobial resistance pattern was assessed in all the common isolated uropathogen and it revealed that overall 85% of the identified organism were resistance to ampicillin, followed by 75% to amoxicillin, 72 % to norfloxacillin, 59% to Ciprofloxacin, 68% to Cefazoline and only 4% to Nitrofurantoin(Figure3).

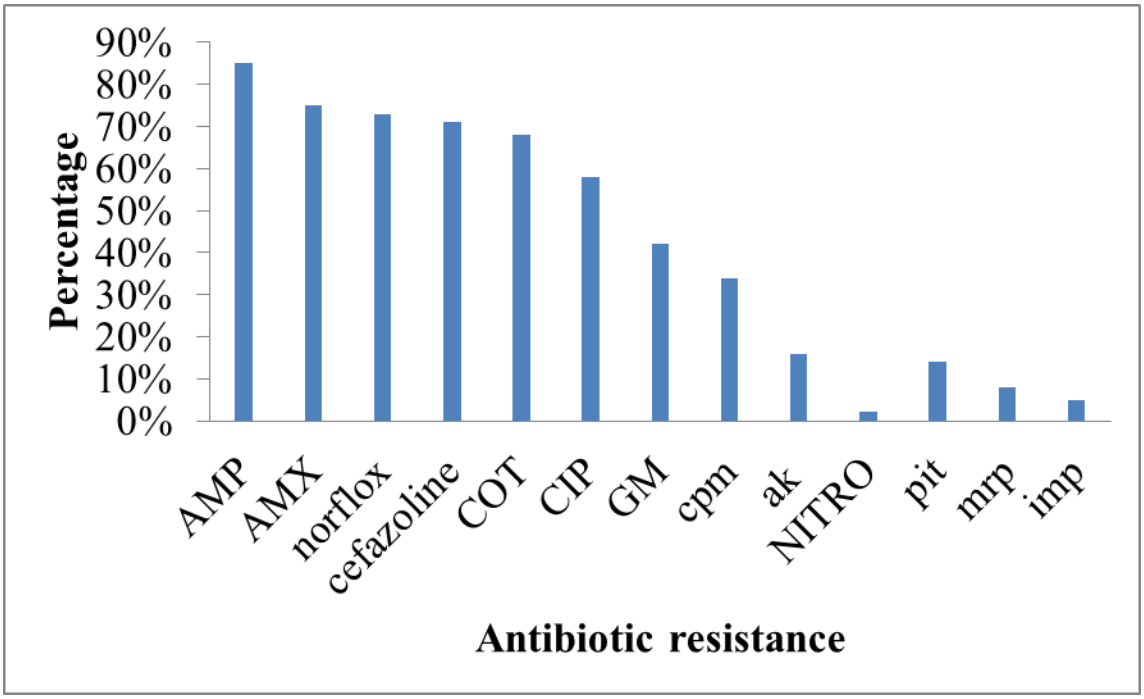


**Figure 3: Overall Antibiotic resistance pattern of Uropathogen.**

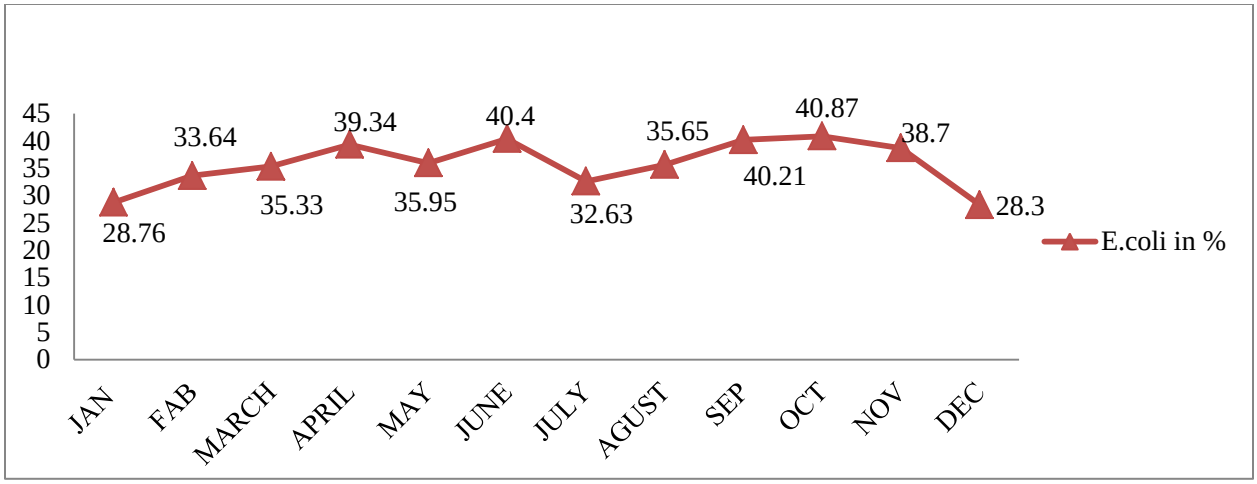


**Figure 4: Incidence of E. cloi growth over one year (since January to December 2017).**

E.coli isolates were tested against Ampicillin(AMP), Amoxyclav ,Cotrimoxazole(cot) ,Gentamycin (GM), Ciprofloxacin(cip), Norfloxacin(nx), Cefpotaxime (cft), cefazoline (cz30), Nitrofurantoin (NFT), carbapenem (imipenam ,meropenam), Amikacin (AK), Piperacillin - Tazobactam (PIT) etc . Imipenam showed least resistance (0.1-4.5%) followed by nitrofurantoin (2.7-9.5%), PIT (4.7-40%) as shown in table 1.

**Table 1: Monthly resistance pattern of E Coli for the tested antimicrobials**

| Antibiotic | JAN | FEB | MAR | APR | MAY | JUN | JUL | AUG | SEP | OCT | NOV | DEC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AMP | 73.8 | 77.7 | 65.90 | 73.50 | 57.8 | 82.2 | 76.5 | 84.4 | 86.4 | 96.4 | 96 | 95.2 |
| AMC | 68.5 | 70.35 | 62.2 | 67.55 | 74.8 | 71.3 | 68 | 68.8 | 70.2 | 89.2 | 81.65 | 90.4 |
| COT | 40.2 | 44.4 | 44.59 | 53.1 | 59.5 | 53.3 | 62.5 | 64.2 | 68.5 | 73.6 | 82.1 | 83.3 |
| GM | 10.6 | 16.7 | 26.1 | 13.89 | 34.37 | 40.7 | 31.9 | 42.2 | 29.7 | 57.1 | 36.6 | 45.2 |
| PIT | 4.70 | 3.38 | 5.80 | 6.38 | 7.1 | 8.50 | 11.50 | 14.2 | 16.50 | 30.26 | 38.30 | 39.50 |
| CFT | 15.6 | 19.40 | 40.40 | 38.80 | 43.70 | 77.50 | 80.30 | 71.20 | 66.60 | 92.20 | 85.00 | 78.50 |
| NX | 54.7 | 58.30 | 61.90 | 65.20 | 69.00 | 90.70 | 64.00 | 71.10 | 57.00 | 89.20 | 96.00 | 50.00 |
| CIP | 30.90 | 27.70 | 36.10 | 43.00 | 46.80 | 78.90 | 61.70 | 57.70 | 41.80 | 76.80 | 83.30 | 73.80 |
| NITRO | 5.35 | 3.95 | 4.70 | 5.50 | 6.25 | 6.38 | 8.50 | 4.44 | 6.50 | 5.35 | 8.35 | 9.50 |
| IMP | 0.1 | 1.23 | 0.45 | 1.50 | 1.80 | 2.34 | 2.45 | 3.50 | 3.45 | 2.35 | 3.45 | 4.45 |
| CZ-30 | 29.35 | 32.56 | 33.32 | 34.56 | 38.50 | 40.34 | 41.45 | 42.56 | 45.80 | 48.40 | 45.60 | 49.50 |

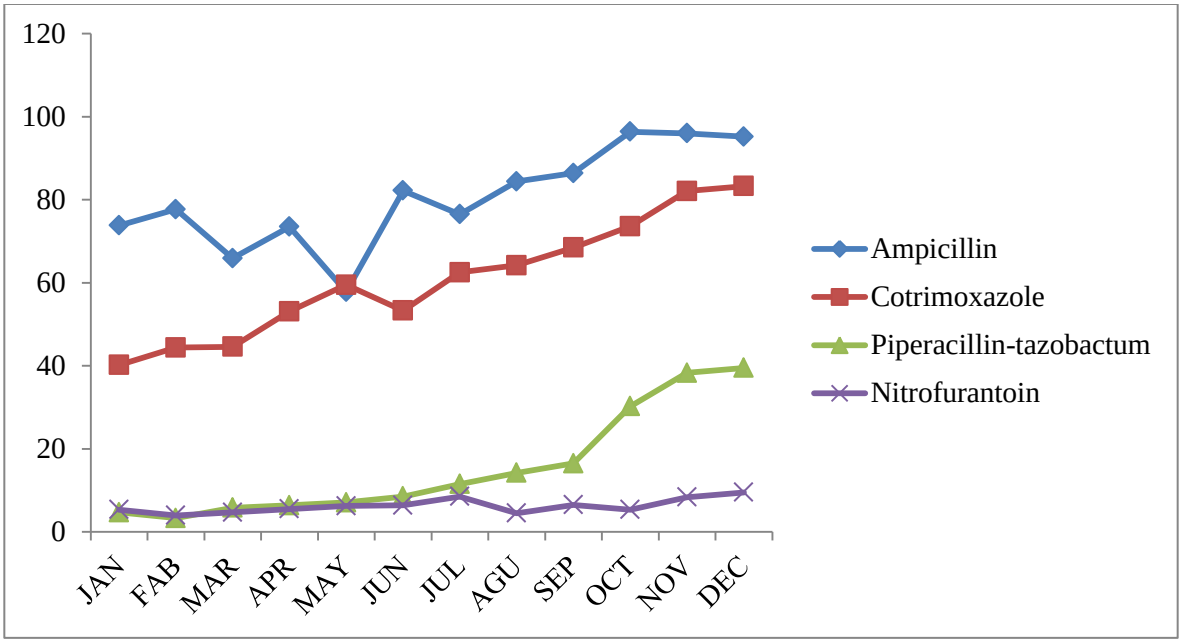


**Figure 5:** Resistance pattern to Ampicillin, Co-trimoxazole, Piperacillin-tazobactam, Nitrofurantoin over one year period.

## DISCUSSION

Antibiotic resistance pattern in local area helps to determine appropriate empirical treatment. The resistance pattern changes from time to time and from one geographical location to another. This study reveals the most common uropathogen isolated, antimicrobial resistance pattern, and its seasonal trend if any: from urine samples of patients suspected to be suffering from either community or hospital acquired UTI. We observed that only 32.49 % samples showed growth of microorganism, which is similar to study by which reported 29.3 % growth [8] however a higher incidence ranging from 52.52 % to 63.60% was reported from other parts of our country [4, 9] and our neighbor Bangladesh reported 74% a still higher [10]. Females show higher incidence of UTI than males, in the ratio 1.24 :1 which is due to the anatomy of female urethra which is shorter and close to anus and is consistent with other studies [1, 3, 11]. Gram negative rods are the most common organism causing UTI and they collectively account for around 80-85% of cases [4]. The most common uropathogen was E.coli (36%) in both sex , which vary from other study done in north India which showed E Coli accountability to 42.76% [4],whereas in south India it was 52.59% [12], north East India 53% [13]. In other countries also UTI due to E Coli constitutes 51.1% in Australia [6] and 92% in UK [3]. The second most common frequently occurring uropathogen was Enterococci (27%) followed by Klebsiella (10.5%). This finding is different from studies in other parts of our country where Klebsiella is the second leading pathogen [4, 12, 14]. In other countries also Klebsiella, proteus mirabilis, Enterococcus faecalis are the second leading uropathogen. This shows that there is a changing pattern in the uropathogen across our country as well as across the globe [15-17].

Over the past decade, the prevalence of drug resistance in E. coli has increased drastically, complicating management of these infections. The urinary isolates of E Coli had ampicillin resistance rates of 73-93%, followed by 75% resistance to amoxicillin –clavulanate, 73% to norfloxacin and 70% to cefazoline. Resistance to Nitrofurantoin ranged from 3.9 -9.5% and from 0.1-4.45% for Imipenam. Table 2 shows that resistance to Cotrimoxazole is very high in India whereas it is very less in developed countries. In India in 2008 no resistance to carbapenem (meropenam ) was reported [18], but we observe resistance to imipenam. We can see resistance rates to different antimicrobials in different country over a period between 2001-17 in table 2.

**Table 2. Resistance rates to different antimicrobials in different country**

| Drug | Our study 2017 | India 2008 [18] | India 2012[19] | Sweden 2002 [16] | United states 2001 [20] |
|---|---|---|---|---|---|
| Ampicillin | 73-93%, | | 88.4% | 29.8% | 37% |
| Amoxyclav | 62.2-90.4% | 58.4% | - | 3.4% | |
| Nitrofurantoin | 3.9 -9.5% | 34.3% | 17.2% | 1.2% | 0.7% |
| Carbapenem | 0.1-4.45% Imipenam | No resistance meropenam | - | - | - |
| Cotrimoxazole | 40.2-83.3% | 70% | 64.2% | 14.1% | 16.1% |

If we observe the trend from January to December over a period of one year, resistance has increased to almost all antimicrobials. Resistance to ampicillin was 73.8% in January which increased to 95.2% in December. Similarly nitrofurantoin resistance increased from 0.1% to 4.45% (Table 1).

Infectious disease society of America recommends short course of Nitrofurantoin monohydrate/macro crystals (100 mg twice daily for 5 days) as an appropriate choice for therapy due to minimal resistance and efficacy comparable to 3 days of Cotrimoxazole (160/800 mg [1 double-strength tablet] twice-daily for 3 days). Fosfomycin trometamol (3 g in a single dose) is an appropriate choice for therapy where it is available due to minimal resistance, but it appears to have inferior efficacy compared with standard short-course regimens. Amoxicillin or ampicillin should not be used for empirical treatment because of relatively poor efficacy and a very high prevalence of antimicrobial resistance to these agents. The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for empirical treatment of acute cystitis is based on expert opinion derived from clinical, in vitro, and mathematical modeling studies [21]. Indian National Treatment Guidelines for Antimicrobial Use in Infectious Diseases of Acute uncomplicated Cystitis recommends Nitrofurantoin 100 mg BD for 7 days or Cotrimoxazole 960mg BD for 3-5 days or Ciprofloxacin 500 mg BD for 3-5 days [22].

If we analyze the seasonal trend, a higher incidence of UTI is reported in summer months, gradually increasing from February with a peak in June up to November. Raipur Chattisgarh has long summer and a short winter of 2 months, there is a slight fall in July *i.e.* during the monsoon, where the temperature falls slightly. In a meta analysis a higher peaks were observed in summer months in countries like France, Germany, Italy, USA and China, which was assessed by the sales of drugs for UTI. The increase in summer ranged from 8% to 20% as compared to winter [23, 24]. Frank Schwab also observed that gram negative infection peaked in summer whereas S. pneumonia peaked in winter [25]. The possible explanation to the higher incidence in summer is: (1) Organism factor- Most UTI are caused by E Coli. Pathogenic E Coli infections outside the intestine are caused by strains carrying more virulent genes than typical strains. These gain access to human body through water and food chain , which are more contaminated during warm summer months, leading to increased incidence of UTI and blood stream infections; (2) Human factor- Seasonal change in human behavior: increased sexual activity, decreased water consumption and increased sweating leading to dehydration and decreased micturition lower urine output and reduced urine frequency, which delay flushing of urine tract, increase in recreational water sports and dietary changes [26]. The limitation of our study is our data is local and further studies at state level and national level are needed to study the trends.

## CONCLUSION

In our study we found that Nitrofurantoin and Carbapenem group of antibiotics are still sensitive (resistance <20%). In case of Piperacillin-Tazobactam there is rise in resistance pattern. There is a gradual persistent increase in resistance to all antimicrobials, and this may change and usually increases over time in the same geographical region. The increasing resistance to antimicrobials that are affordable like Amoxicillin–Clavulanic acid and Cotrimoxazole is important problem for physician. The increase in E Coli incidence during summer months can be reduced by appropriate measures. So

we recommend to use antibiotics with less resistance for empirical treatment like Nitrofurantoin and Carbapenem. Fosfomycin though not included in Indian guideline may be prescribed.

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