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NITROFURANTOIN SENSITIVITY PATTERN PAN INDIA

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ABSTRACT

The prevalence of urinary tract infections (UTIs) varies from 21.8% to 31.3% in various parts of the country. The most common pathogens causing UTIs in the descending order of their prevalence include *Escherichia coli* (45.12%), *Klebsiella* spp. (18.17%) and *Enterococcus* spp. (9.23%). Nitrofurantoin was categorized as an A-I antibiotic for treating UTIs as per the IDSA guidelines, while nitrofurantoin 100 mg tablet dosage form was added to the WHO model list of essential medicines since 2013. The major strength of nitrofurantoin is its action at multiple sites and levels which helped the drug to maintain an excellent level of sensitivity over six decades of clinical practice besides being well tolerated for treating acute uncomplicated cystitis. In this review, we tried to analyse, from all the recent accessible and available clinical studies, nitrofurantoin sensitivity pattern across various parts of India, while also comparing it with the sensitivity of other commonly used antimicrobials. We have found that not only has nitrofurantoin retained excellent sensitivity to the most common uropathogens across India, but also stands out to be the antimicrobial of choice when considering other parameters like oral route of administration, safety profile and cost-effectiveness in the management of UTIs.

KEYWORDS: *Escherichia coli* (45.12%), *Klebsiella* spp. (18.17%) and *Enterococcus* spp. (9.23%).

URINARY TRACT INFECTIONS (UTIs) – DEFINITIONS AND STATISTICS

The American National Institute for Health and Clinical Excellence (NICE) defines UTI as a combination of clinical features (urinary tract symptoms) and the presence of bacteria in urine.[1] These infections can occur in any part of the urinary tract, although infection of the

bladder (cystitis) and the urethra (urethritis) are more common relative to the upper portion involving the kidneys (pyelonephritis).[1-3] Urinary tract infections are classified into complicated or uncomplicated and acute or recurrent.[2,3] Recurrent UTIs can be problematic for many people, occurring in 3% to 5% of women and 80% of children who previously experienced an uncomplicated infection.[2] Infections of the urinary tract are among the most common bacterial infections and have become very common occurring in people of all ages as well as in all ethnic groups affecting approximately 150 million people every year throughout the world.[3,4] Women and older adults comprise the majority of cases, with UTIs affecting more than 11.3 million women per annum, or up to 5% of all females.[2,5] Among the UTI cases, approximately, 35% are nosocomial infections in origin.[4] These infections also affect children, involving approximately 7% of girls and 2% of boys by the age of 6 years.[2] On the other hand, UTIs were more common among males compared to females in the 0-1 year age group.[6]

In India, the prevalence of UTIs varies from 21.8% to 31.3% in various parts of the country.[5] According to one estimate, 7 million visits to emergency units and 100 thousand hospitalizations may present with symptomatic UTIs every year.[7] With as many as 35% of hospital-acquired infections, UTI has also become the most common nosocomial infection, besides being the second most common cause of bacteraemia in hospitalized patients.[7] In case of females, UTIs usually occur after 2 years of life. The most common pathogens causing UTIs in the descending order of their prevalence include *Escherichia coli* (45.12%), *Klebsiella* spp. (18.17%) and *Enterococcus* spp. (9.23%) (Fig. 1).[6]

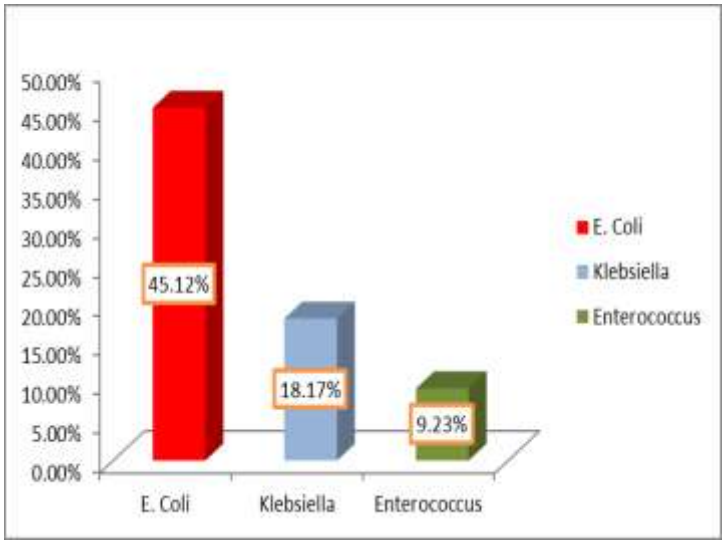


Fig.1. Common isolated pathogen seen in females above 2 years of life in UTI indication

NITROFURANTOIN DISCOVERY AND USE

Nitrofurantoin [chemical name: 1-(5-Nitrofurfurylideneamino) hydantoin, $C_8H_6N_4O_5$] is a synthetic antibacterial agent available since World War II.[8] An antimicrobial compound and nitrofuran derivative, nitrofurantoin was first used in clinical practice in 1952.[9] It is synthesized by adding a nitro group and a hydantoin side chain to furan.[9] Nitrofurantoin is categorized as a grade A-I antibiotic in the treatment of UTIs as per the IDSA guidelines[10], while nitrofurantoin 100 mg tablets dosage form is included in the WHO model list of essential medicines since 2013.[11]

Indications & Dosage

Nitrofurantoin was indicated for uncomplicated UTIs in adults at a dosage of 50 to 100 mg PO four times per day for 7 days or until 3 days after sterile urine. Nitrofurantoin is to be taken along with food or milk to suppress the GI irritation which is usually known to occur with its consumption. Modified release (MR) nitrofurantoin formulations are preferred over the conventional formulations because the former maintain urinary concentration over duration of 12 hours, decrease dosage frequency to twice a day, better gastrointestinal tolerability and enhanced patient compliance. When nitrofurantoin MR formulation is given, a part of the drug is released immediately and gets rapidly accumulated in urine for immediate action within first hour while the remaining drug is released steadily and continuously for the whole day to maintain adequate urinary concentration.[12,13] Nitrofurantoin MR formulation for uncomplicated UTIs consist of 100 mg PO two times per day for 7 days. Long-term suppressive therapy consists of 50 to 100 mg PO at bedtime. In children with uncomplicated UTIs, nitrofurantoin is given in the dosage, 5 to 7 mg/kg/day PO divided four times daily for 1 week or until 3 days after sterile urine. It was also indicated for long-term suppressive therapy in paediatrics by reducing the doses to as low as 1 mg/kg/day PO divided one to two times per day. In children older than 12 years of age, nitrofurantoin MR formulation is also available for uncomplicated UTIs, given at a dose of 100 mg PO two times per day for 7 days. For treating uncomplicated cystitis in women, IDSA recommends 100 mg nitrofurantoin dual-release formulation PO two times per day for 5 days (to be avoided if early pyelonephritis suspected).

Nitrofurantoin is also used in the management of complicated UTIs. In an article sponsored by the British Society for Antimicrobial Chemotherapy (BSAC) in 2010, nitrofurantoin is suggested for treating complicated and uncomplicated lower UTIs at a dose of 100 mg q6h

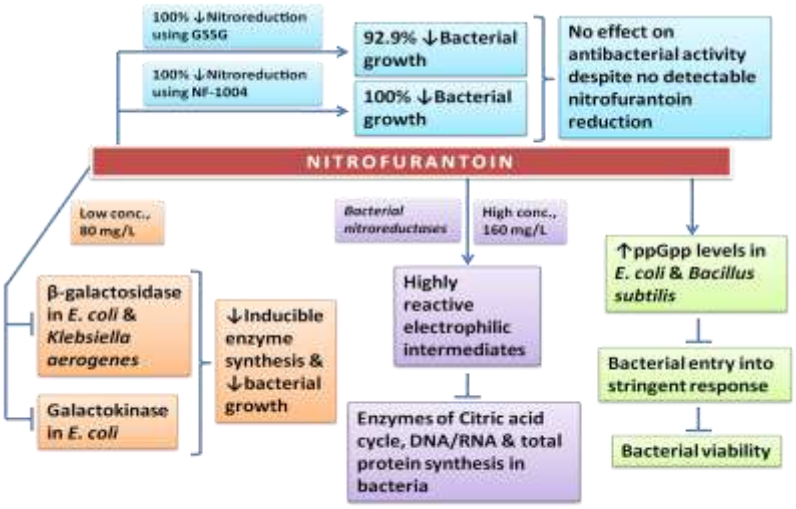
for a minimum of 7 days.[11] The National Health Services Area Prescribing Committee (NHS APC) review in its latest version recommended nitrofurantoin MR for the first line treatment of complicated UTIs (may be complicated by previous urogenital surgery; urinary tract abnormality or impaired host defences) in women >65 years, at a dosage of 100 mg BID for 7 days.[14]

Note

Contraindications to the use of nitrofurantoin include reduced creatinine clearance (<60 mL/min), pregnancy 38 weeks or longer and in infants aged <1 month.[15,16] Haemolytic anaemia in G6PD deficiency (including susceptible infants exposed through breast milk), hepatotoxicity (monitor LFTs periodically) and peripheral neuropathy are some of the rarely occurring known adverse effects.[15,16] Nitrofurantoin is not effective for use in complicated or upper UTIs.[9,16,17]

Mechanism of Action

Though the mechanism of its action is complex and not fully understood[16], nitrofurantoin's antibacterial effects appear to depend on its ability to induce suicide in sensitive strains. Depending on the drug's concentration, susceptible bacteria reduce nitrofurantoin to its electrophilic intermediates which are highly reactive thereby disrupting the complete synthesis of proteins leading to the bacterial growth arrest or cell death.[16-20] At low concentrations (80 mg/L equivalent to minimum inhibitory concentration), nitrofurantoin has been found to inhibit inducible enzyme synthesis of β-galactosidase and galactokinase in *E. coli* or β-galactosidase alone in *Klebsiella aerogenes* and arrest bacterial growth.[19] At higher concentrations (160 mg/L), bacterial reductases have been found to convert nitrofurantoin to highly reactive electrophilic intermediates which in turn non-specifically attack and inhibit enzymes of citric acid cycle, nucleoid and total protein synthesis thus bringing about bacterial cell death.[20] Another mechanism of action, shown to exist for nitrofurantoin, does not necessitate the production of reactive intermediates by bacterial reductases.[19] This was proved by using potential competitive inhibitors of bacterial reductase system, GSSG or NF-1004, independently[19], increasing their concentration till there was 100% inhibition in nitrofurantoin reduction and having found no significant change in the antibacterial activity of the molecule. The absence of significant bacterial resistance to nitrofurantoin is possibly owing to the combination of nitrofurantoin's manifold targets and multiple mechanisms of action as shown in Fig. 2.



GSSG, oxidized glutathione; NF-1004, a poorly active nitrofuran antibacterial; conc., concentration; ppGpp, guanosine tetraphosphate.

Fig. 2. Nitrofurantoin Multi-modal Action: Nitrofurantoin acts by multiple mechanisms attacking multiple sites as elucidated above. At low concentrations, nitrofurantoin has been found to inhibit inducible enzyme synthesis and arresting bacterial cell growth. At higher concentrations, bacterial reductases have been found to convert nitrofurantoin to highly reactive electrophilic intermediates which in turn cause bacterial cell death. Furthermore, it has been observed that, in bacteria which enter into stringent response, nitrofurantoin was able to virtually increase ppGpp levels and inhibit the regulation of events which help bacterial viability. In addition, nitrofurantoin was found to act independent of being reduced by bacterial reductases. This had been proved by using potential competitive inhibitors of bacterial reductase system, GSSG or NF-1004 and finding that no significant change has been observed in the antibacterial activity of the molecule.

Nitrofurantoin following oral administration showed rapid and complete absorption from the GI tract and maximum excretion in its unchanged form in the urine (~40%). The usual dose of the drug gives a concentration of an estimated 200 µg/ml in urine, making it bactericidal. Nitrofurantoin has maintained an excellent level of sensitivity over 4 decades and is well tolerated in the management of acute uncomplicated cystitis.[21] The success of nitrofurantoin may be attributed to several factors, some of which are – narrow tissue distribution, negligible serum concentration, having one major indication i.e. cystitis, bactericidal against predominant uropathogens, viz. *E. coli* and *Klebsiella* spp. and limited contact with bacteria outside the urinary tract.

CURRENT TREATMENT GUIDELINES RECOMMENDING NITROFURANTOIN IN UTIs

UTI cases are usually treated empirically, wherein the antimicrobial agent is chosen based on the experience of the treating physician coupled with his/her knowledge of the infection epidemiology in general and resistance pattern observed in his/her institution or community.[22] Empirical treatment with antimicrobial agents is not a choice, rather, physicians follow under compelling situations like patient's insistence for immediate relief, risk of complications during severe infections, bacteria causing community-acquired acute UTIs being narrow spectrum, lack of antibiogram facilities, etc.[23] There is a notion that the gap between empirical and definitive treatments can be narrowed by periodically checking the resistance pattern of uropathogens.

The empiric treatment for acute uncomplicated cystitis in the US used to be trimethoprim-sulphamethoxazole (TMP-SMX) double strength as a 3-day course provided the TMP/ SMX-resistant pathogens <10% in the area. As the resistant pathogens exceeded 10-20%, non-resistant therapies like nitrofurantoin started becoming the empirical treatment of choice.[24] The Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases, in their 2010 updated guidelines, recommended nitrofurantoin monohydrate/macrocrystals at a dose of 100 mg BID for 5 days for treating acute uncomplicated cystitis in women as a suitable choice of therapy owing to the drug's minimal resistance record besides low tendency for collateral harm as compared to 3-day TMP/SMX regimen. Going by the clinical trial data of nitrofurantoin against a comparator, there were four randomized trials published in the recent past, all of which revealed an 88% - 93% clinical cure rate and an 81% - 92% bacterial cure rate with nitrofurantoin. Notably, nitrofurantoin retained its high sensitivity besides being effective in the 5-day regimen.[10]

E. coli has been recurrently vulnerable to nitrofurantoin, fosfomycin and mecillinam despite these drugs being used over many years which may be a proof of their inconsequential effects on normal faecal microflora and negligible collateral damage.[10] The American College of Obstetricians and Gynecologists (ACOG) recommends a 7-day, QID regimen of nitrofurantoin macrocrystals 50 to 100 mg or a 7-day, BID regimen of nitrofurantoin monohydrate crystals 100 mg for treating nonpregnant women with uncomplicated acute bacterial cystitis.[25] Nitrofurantoin was rated "B, I" for treating UTIs in pregnancy as per the 1999 IDSA guidelines.[26]

Existing Antimicrobial Agents and their Sensitivity against Uropathogens

One of the major barriers to medical management of UTIs is the increasing rate at which multidrug resistance is developing. Therefore, empirical antibiotics are selected based on the knowledge of the prevailing local resistance pattern from time to time in the given region.[27]

Trimethoprim is a synthetic antimicrobial agent which acts by selective inhibition of dihydrofolic acid synthesis in bacterial cells. It is indicated in acute uncomplicated infections at a dose of 100 mg orally every 12 hours or twice the strength every 24 hours for 10 days. It is a broad-spectrum antibiotic *in vitro*. However, it is prone to resistance, which is caused by reduced cell permeability or changes in the quantity or constitution of dihydrofolate reductase. The IDSA guidelines recommend a 3-day, BID trimethoprim-sulfamethoxazole (TMP-SMX) double-strength tablet (160 mg-800 mg) for treating acute uncomplicated cystitis where the uropathogens' local resistance rates ≤20% or if sensitivity testing is done.[10] However, the same guidelines dissuaded the empirical usage of TMP-SMX if it has been received by the patients earlier at some stage in the preceding 3 months.[10] Another important drawback to the use of TMP-SMX is its vulnerability to cross-resistance from other antibiotics. In fact, in considering the value of retaining the usefulness of TMP-SMX for the handling of other serious infections, countries like Germany have discouraged this drug combination as first-line approach for uncomplicated cystitis.[28]

Fosfomycin is another bactericidal agent for treating uncomplicated cystitis in vulnerable strains of *E. coli* and *Enterococcus faecalis*. Slight cross-resistance exists between fosfomycin and other antimicrobials.[10] An important concern with fluoroquinolones is the growing resistance among pathogens and other microorganisms. Therefore, these drugs should be set aside as optional therapies for acute cystitis.[29] Ampicillin is normally used along with an aminoglycoside (gentamicin) for empirical or focussed action against *E. faecalis* in complicated cystitis patients in whom resistant organisms are suspected to be the cause of infection.

Nitrofurantoin, unlike many other antimicrobials, has the benefit of withstanding growing antimicrobial resistance. There are not only many studies to elucidate this observation in the next section comprising a collection of clinical studies across India, this finding is in concurrence with the observations of nitrofurantoin usage across many parts of the world. For example, in one antibiogram by Olson et al. in 2009, out of 176 urinary isolates infected with *E. coli*, 29.6% were resistant to TMP-SMX while none were found resistant to nitrofurantoin.

In the same study, resistance to ciprofloxacin was 1.8% in first-time UTIs versus 11.8% in recurring UTIs. Accordingly, the authors recommended nitrofurantoin as the first-line treatment for uncomplicated lower UTIs.[30] In another study, by McKinnell et al., which did an overall analysis of the cost-effectiveness cum antimicrobial resistance, nitrofurantoin once again proved to be a better option over fluoroquinolone or TMP-SMX.[31]

Table 1. Regional resistance patterns of the most common uropathogen, *Escherichia coli* to Different Antimicrobials in various studies across India

Author, year and place of study	Percentage of *Escherichia coli* isolates resistant to antimicrobials									
	Ampicillin	Augmentin	Co-trimoxazole	Nitrofurantoin	Ciprofloxacin	Cefpodoxime	Cefaclor	Ofloxacin	Gentamicin	Amikacin
Mohammed Akram, et al., 2007, Aligarh (32)	-	-	76	80	69	85	-	-	64	51
Selvakumar et al., 2007, Southern India (33)	96	72	71	62	92	-	-	62	73	21
Kothari et al., 2008, Delhi (34)	-	59.2	74	24.4	72	-	-	-	-	33
Sood et al., 2012, Jaipur (35)	81.2	80.7	67.8	5.8	74.7	-	-	-	28	8.2
Sabharwal et al., 2012, Rajasthan (36)	90	78	75	10	80	-	-	-	15	00
Shaifali et al., 2012, Lucknow (37)	52.2	-	39.2	13.1	60.9	-	65.2	-	54.4	95.7
Dash et al., 2013, Odisha (38)	94.7	63.7	51.9	9.8	53.4	58.2	66.7	44.6	38.3	5.3

NITROFURANTOIN SENSITIVITY PATTERN ACROSS DIFFERENT REGIONS OF INDIA

Nitrofurantoin, a bactericidal at therapeutic concentrations, not only offers good efficacy with no or manageable side effect profile, but is found over the years to suffer minimal resistance. The drug has been rated A-I in the 2010 update of IDSA practice guidelines for treating cystitis.[10]

We tried to analyse, from all the recent accessible and available clinical studies, nitrofurantoin sensitivity pattern across various parts of India, while also comparing the sensitivities of other antimicrobials tested.

Northern, North Central and North Eastern Regions

E. coli is the most common uropathogen with changing resistance patterns demanding careful selection of empirical therapy with appropriate safety and efficacy. Nitrofurantoin has proved to be an effective antimicrobial in managing UTIs caused by *E. coli* as well as ESBL-producing *E. coli*. In a large retrospective study conducted in Shimla by Ganju et al. in 2015, a total of 1,498 pathogenic cultures were identified of which 747 were *E. coli* isolates. The percent sensitivity of *E. coli* to nitrofurantoin, gentamicin and norfloxacin is given in Fig. 3. Of note, resistance to co-trimoxazole in inpatients and outpatients was 43% and 55% respectively.[39]

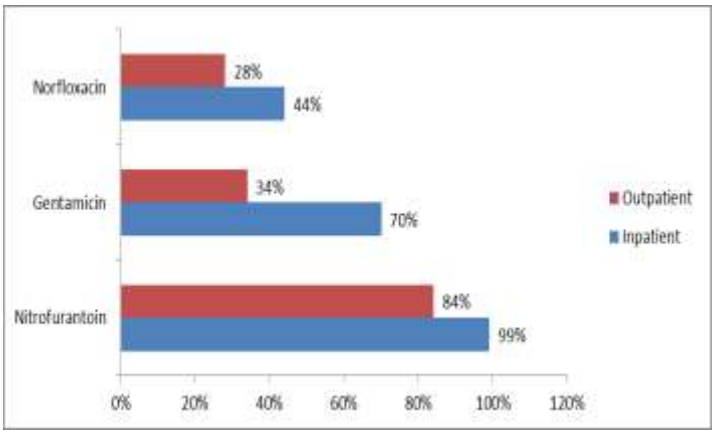


Fig. 3. Sensitivity of Urinary Isolates of *E. coli* in inpatient and outpatient.

In community practice, UTIs are the second most common menace to public health. In a large retrospective study conducted in Delhi NCR by Ahmed et al. in 2015, to find out the resistance profile of community-acquired UTIs (CA-UTI) versus hospital-acquired UTIs (HA-UTI), uropathogens were identified in the samples of 214 (20.82%) of 1,028 suspected

CA-UTI patients and 98 (24.38%) of 402 HA-UTI patients. *Escherichia coli* was found to be the predominant uropathogen both in CAUTI and HAUTI followed by *Klebsiella* spp. and *Enterococcus* spp. High level of resistance to fluoroquinolones and third generation cephalosporins was noted. None of the *Enterococcus* spp. in CAUTI was resistant to nitrofurantoin while only a minor fraction (28%) of HAUTI isolates were resistant to nitrofurantoin.[4] These results were consistent with those of a larger retrospective study conducted in Khanpur, Haryana by Sandhu et al. in 2014 in 4,533 urine samples in which *E. coli* isolates showed maximum sensitivity to nitrofurantoin (87.12%) followed by amikacin (86.53%) and gentamicin (68.19%). Antimicrobials that failed to show therapeutic sensitivity include cefazolin (13.18%), norfloxacin (15.47%), cotrimoxazole (17.77%), amoxyclav (17.77%) and ciprofloxacin (23.78%). The authors opined that nitrofurantoin may become the most preferred alternative to co-trimoxazole since the latter's resistance remains high in uncomplicated cystitis.[40]

The effectiveness of nitrofurantoin in multidrug resistant (MDR) *E. coli* isolates in an earlier study in 2011 from Rohtak, Haryana, wherein 29.62% of 135 *E. coli* isolates with clinically suspected UTIs were identified as multidrug resistant[41], the sensitivity to MDR uropathogens was as given in Fig. 4.

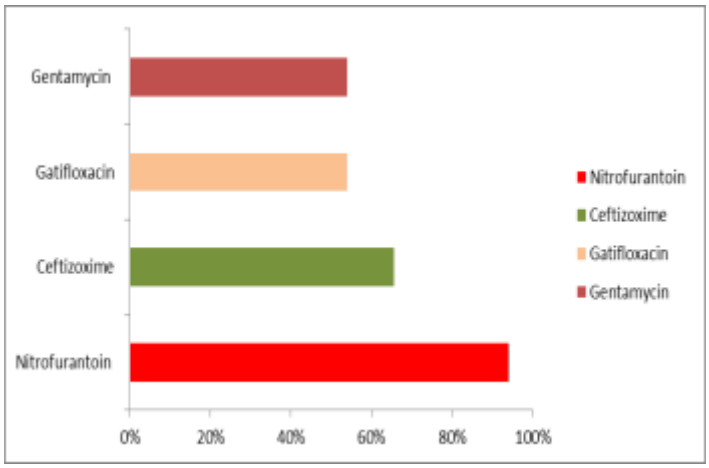


Fig. 4. Sensitivity of Antibiotics to Multidrug Resistant (MDR) *E. coli*.

The US based IDSA recognized some microbes and called them "ESKAPE pathogens" (*Enterococcus faecium, S. aureus, Klebsiella* spp., *Acinetobacter* spp., *Pseudomonas* spp., and *Enterobacter* spp.) for novel effectual therapies.[42] However, the disposition of drug vulnerability of UTI-causing microorganisms changes with time and place. For example, in the urban community of Meerut, Uttar Pradesh, Prakash and Saxena conducted a study

collecting urine samples from 288 patients. The UTI prevalence was 53.82% with sex distribution as in Fig. 5 and Gram type distribution as in Fig. 6. *Escherichia coli* was the most prevalent gram negative isolate.[43]

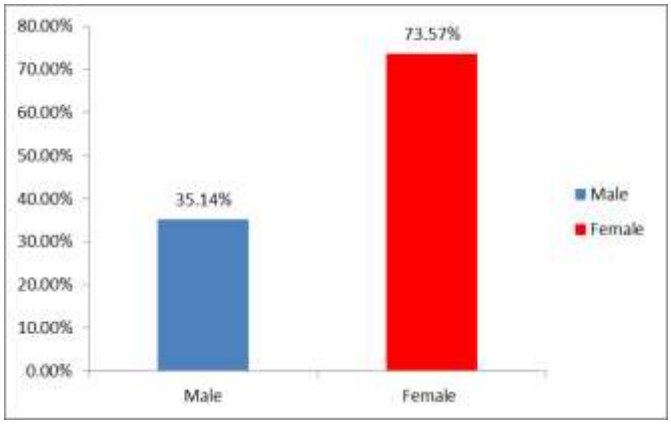


Fig. 5. Sex wise Prevalance of UTI

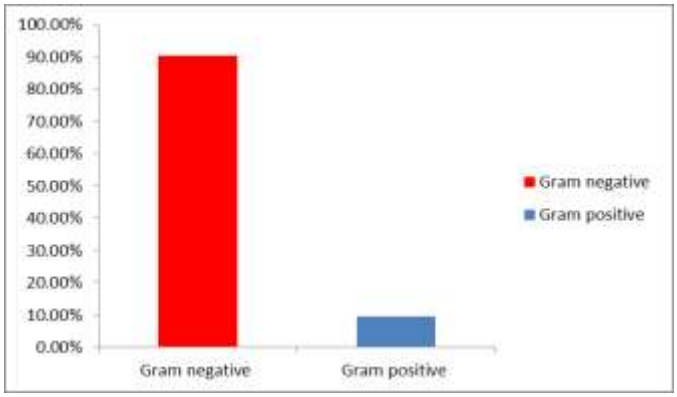


Fig. 6. Prevalence of Gram negative and gram positive in UTI

Alam et al., in a different setting from the same state, U.P, examined hospital wastewater in the city of Aligarh. A total of 69 isolates of enteric bacteria were isolated of which 73.9% strains were found to be resistant to ampicillin followed by nalidixic acid (72.5%), penicillin (63.8%), co-trimoxazole (55.1%), norfloxacin (53.6%), methicillin (52.7%), cefuroxime (39.1%), cefotaxime (23.2%) and cefixime (20.3%). Resistance to nitrofurantoin was recorded in less than 13% strains.[44]

In the recent years, empirical treatment preference for UTIs has changed from co-trimoxazole to quinolones owing to the rate of resistance and high level of therapeutic failure cases being reported from the overt use of co-trimoxazole. But results from many studies show that nitrofurantoin has an advantage over commonly used quinolones like ciprofloxacin and ceftazidime when it comes to combating bacterial resistance. Evidence of this finding can be

observed from studies conducted in the Northern states of Uttar Pradesh and Rajasthan (Fig. 7).

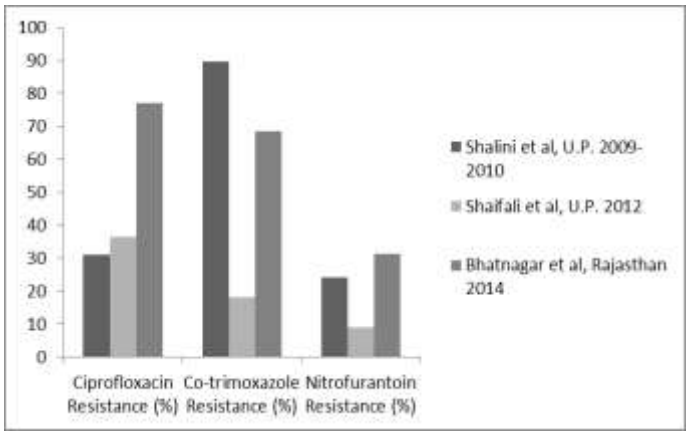


Fig. 7. Comparison of resistance patterns of uropathogenic *Klebsiella* spp. to the three commonly used empirical antimicrobials

Bhatnagar et al. performed a study in 2014 in Udaipur, Rajasthan in which a total 498 samples were tested and 251 cases of bacterial pathogens were isolated. The most common organisms isolated were *Escherichia coli* followed by *Klebsiella* spp. *Enterococcus* spp., *Pseudomonas* spp. and Coagulase-negative *Staphylococcus* spp. Only 29 (11.5%) were resistant to nitrofurantoin among oral antibiotics, making nitrofurantoin a choice of treatment when requiring oral administration for patient convenience.[18] These results were in concordance with those of a much larger study carried out in the capital city of Jaipur, consisting of 6,348 urine specimens. 41.8% (2,653) of the urine samples were culture positive, with the most common bacterial isolate being *E. coli*, followed by Coagulase-negative *Staphylococci* and *Klebsiella* species. While the bacteria causing UTIs exhibited extremely high resistance to fluroquinolones and cephalosporins, resistance to nitrofurantoin was low.[45]

Pathogens causing UTIs in community and hospital set up show different percentages of prevalence. This was also shown by Gupta et al. in their study in which 1,410 cultures of proven urine isolates were collected in Chandigarh. The various uropathogens identified were *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, Acinetobacter baumanii* and *Enterococcus faecalis*. Antibiotic sensitivity order of these strains showed that nitrofurantoin was an effective antibiotic for outpatients besides first generation cephalosporins, norfloxacin/ciprofloxacin for treatment of UTIs.[46] In a smaller but wider study by Kumar et al., 55 *E. coli* strains isolated from urine cultures received from

different parts of the country were analysed. 90.9% of the isolates were found to be sensitive to nitrofurantoin.[47]

Urinary tract infections are more frequent in females of which cystitis represents the widely occurring infection. While appropriate antibiotic treatment gives superior microbial alleviation rates and avoidance of reinfection in females with uncomplicated cystitis, such management requires selective drug resistance in pathogenic and commensal bacteria. In a prospective study conducted in Garhwal region of Uttaranchal to identify the most appropriate empirical antibiotic for acute cystitis, 354 (67.5%) nonpregnant women sample specimens yielded *E. coli*. Resistance was not only found to be least against nitrofurantoin (9.3%), but also, >80% of the fluoroquinolone-resistant strains were found to be sensitive to nitrofurantoin. Besides, the difference in sensitivity rates of *E. coli* isolates to nitrofurantoin and each of the commonly prescribed empirical antibiotics was found to be statistically significant ($p< 0.01$ for ciprofloxacin, norfloxacin, TMP/SMX and $p<0.05$ for gentamicin). Nitrofurantoin was the most effective, not only for *E. coli* (90.7%), but also for all the isolates combined (85.1%). Moreover, 83.5% and 87% of the strains resistant to norfloxacin and ciprofloxacin respectively, were sensitive to nitrofurantoin.[23] In a similar prospective, observational study conducted in Lucknow in outpatient females aged ≥15 years, the overall prevalence of UTIs was found to be 45.32%. *Escherichia coli* followed by *Klebsiella pneumoniae* were the most common isolates. The most effective antibiotic for *E. coli* isolates was found to be nitrofurantoin (86.95%) followed by amoxicillin (69.56%), nalidixic acid (65.21%) and co-trimoxazole (60.86%) (Fig. 8). For *Klebsiella* isolates too, highest efficacy was noted with nitrofurantoin (90.90%) followed by co-trimoxazole and tetracycline (81.81%).[37]

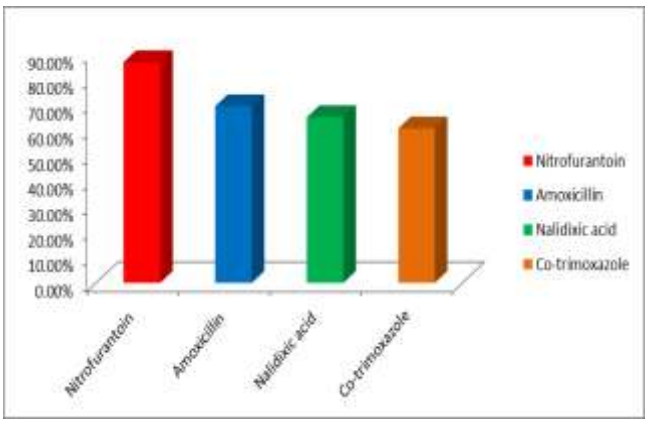


Fig. 8. Effectiveness of antibiotics for *E. coli* isolates from OPD patients

The most suited antibiotic for empirical therapy should have low resistance rates against the potential pathogens, be free of adverse effects, achieve significant urinary concentrations, satisfy patient compliance and be cost-effective.[23] The first four factors are particularly important when considering treatment for special populations like obstetrics and paediatrics. A prospective study conducted in obstetric patients in Rajasthan, identified 60 out of 250 samples (24%) screened from pregnant females to be positive on culture. *Enterobacteriaceae* accounted for nearly two-thirds of the isolates of which *E. coli* accounted for 63% of the isolates followed by *Klebsiella pneumoniae* (8%). Despite significantly high resistance noted to β-lactam antimicrobials, fluoroquinolones and cotrimoxazole, both by the Gram-negative bacilli as well as Gram-positive cocci, resistance was quite low against nitrofurantoin.[36]

Paediatric UTIs generally occur with a male preponderance in the first year of infancy which reverses in the latter years of life. There are studies showing that nitrofurantoin promises to be one of the best choices for treatment of UTIs in paediatrics too. For example, in a study conducted in New Delhi between 2011 and 2013 in which 1,108 infants < 1year were enrolled, the male: female ratio was found to be 3:2. The percentage of common uropathogens was as given in Fig. 9. Maximum gram negative isolates (50%) showed high resistance to gentamicin, amikacin, cefotaxime and norfloxacin while most of the isolates were found susceptible to nitrofurantoin.[48]

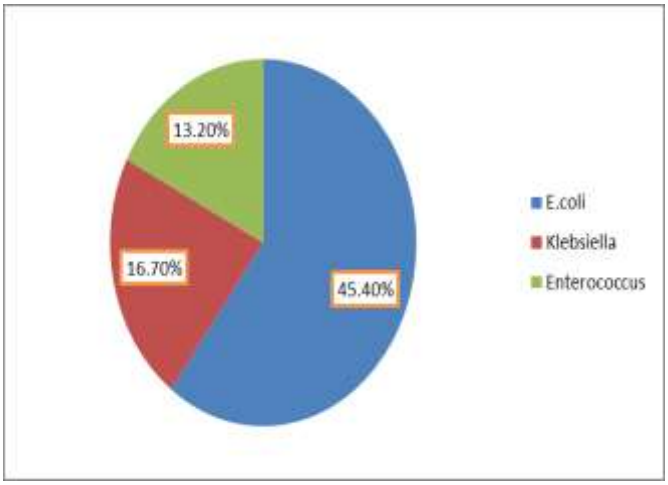


Fig. 9. Common bacterial isolate in children below 1 years.

In a larger paediatric study conducted by Taneja et al. in 1,974 children aged < 12 years over a period of 6 months in North India; significant bacteriuria was found in 558 children (28.3%). Common uropathogens isolated are given in Fig. 10. Against lactose-fermenting

Enterobacteriaceae, *in vitro* resistance was found to be least against nitrofurantoin (26.7%) and imipenem (3.7%).[49]

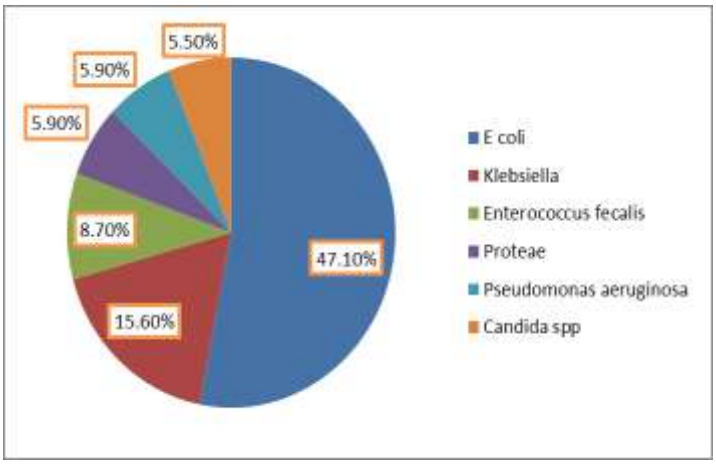


Fig. 10. Common Uropathogen in children below 12 years (Tertiary care centre)

A bacterium resistant to one antibiotic is often likely to be resistant to other antibiotics, thereby predisposing the patient to treatment failure with other antibiotics as well. Appropriate choice of therapy with the most sensitive antibiotic to the most commonly identified uropathogens is an important prerequisite for selecting empirical treatment. A retrospective study carried out by Sharma et al. in Patiala, Punjab, in inpatients for three years from 2012 to 2014, analysed the type of organisms most common in urine sample and the drugs still effective for the particular organism. Consistent with other studies, *E. coli* was identified the most frequent isolate throughout the three years (67.66%). Year wise percentage of resistance against nitrofurantoin dropped over the three consecutive years from 36.1% (2012) to 18.15% (2014) while resistance to ceftriaxone increased from 53.39% (2012) to 73.33% (2014). *E. coli* showed absolute resistance (100%) to cotrimoxazole and tetracycline. Among fluoroquinolones (75%) and aminoglycosides (67%) too, *E. coli* showed high amount of resistance over the three years on an average.[50]

While nitrofurantoin offers good resistance to the most common uropathogen, *E. coli*, most gram negative and few gram positive species, there are variations where other commonly used antimicrobials were identified as better alternatives, particularly in UTIs caused by gram positive spp. which form a small fraction of all the UTIs. For instance, in a study carried out between 2008 and 2009, in Amritsar, Punjab, to study the susceptibility pattern of CNS (coagulase-negative *Staphylococci*) to various antimicrobial agents, a total of 300 strains of CNS isolated from various clinical specimens were subjected to antimicrobial sensitivity

testing. All the isolates were susceptible to vancomycin, linezolid and teicoplanin in while maximum resistance was noted against penicillin (100%) followed by ciprofloxacin (36.3%), norfloxacin (34.3%), gentamicin (34%), nitrofurantoin (29.9%), erythromycin (27.9%) and amikacin (22.7%).[51]

Eastern Region

Malnutrition, poor hygiene and low socio-economic status are associated with UTIs and these factors are usually found in rural settings. The resistance pattern of community-acquired uropathogens has been little documented in Eastern India. In a study conducted by Dash et al. to determine the prevalence of CAUTI in rural Odisha, urine samples were collected from 1,670 adult patients. Prevalence was significantly higher in females than in males (45.2%, versus 18.4%, $P \leq 0.0001$). *Escherichia coli* was the most prevalent isolate followed by *Enterococcus* spp. (9.7%). Of the ten commonly used antibiotics and antibiotic combinations tested, nitrofurantoin was one of the two antimicrobial agents which showed a low resistance rate of 9.8%.[38]

Likewise, studies comparing the incidence and antimicrobial resistance patterns in uropathogens obtained from paediatric samples of the Eastern states too concurred with the results of other parts of the country. Sharan et al. conducted a study in which 64 children <5yrs with CAUTI were found urine culture positive cases in Jamshedpur. *E. coli* was the most frequently identified uropathogen though *Klebsiella, Proteus* and *Pseudomonas* were also present. *E. coli* was most susceptible to nitrofurantoin, followed by levofloxacin, ofloxacin and azithromycin. Increased level of resistance was observed for penicillin and cephalosporin analogues.[52] In an alternate study from West Bengal conducted over a 33 month period and published in the same year, 2013, the overall prevalence of UTI was 196/300 (65.3%). Prevalence of UTI in girls (59.6%) was higher than that in boys (40.3%) and *Escherichia coli* was responsible for majority of the UTIs, followed by *Proteus* spp. and *Klebsiella* spp. *E. coli* exhibited highest percentage of resistance against tetracycline (85.6%), followed by ampicillin (67.5%) and co-trimoxazole (66.2%). *Klebsiella* spp. showed highest percentage of resistance against tetracycline (80.8%), followed by ciprofloxacin (76.0%). Nitrofurantoin was found highly effective against *E. coli, Klebsiella sp.* as well as *S. Aureus*.[53]

Western Region

Affordability with respect to personal/community hygiene was a major hurdle to economically backward populations which comprise a large part of urban and semi-urban communities of developing countries like India. Jadhav et al. studied the virulence spectrum and antimicrobial resistance by extensive genotyping and phenotyping of 150 UPEC (uropathogenic *E. coli*) isolates from Pune from 2009 to 2010. These isolates were analyzed in comparison with 50 commensal *E. coli* isolates from India as well as 50 ExPEC (extraintestinal pathogenic *E. coli*) strains from Germany. *E. coli* from UTI cases expressed greater fraction of type I (45%) and P fimbriae (40%) when compared to faecal isolates (25% and 8% respectively). Haemolytic group comprised 60% of UPEC and only 2% of *E. coli* from faeces. Clinical isolates exhibited highest sensitivity to nitrofurantoin (42.7%) and least sensitivity to amoxicillin (32.7%). Furthermore, isolates from India and Germany (as well as worldwide sources) were found to be genetically different with no proof to support spreading out of *E. coli* from India to the west or vice-versa.[54]

Among paediatrics too, ampicillin and co-trimoxazole which were commonly used for empirical therapy are now showing resistance. In a large retrospective, observational study from Pune, India, 1,575 urine samples of children aged 0 – 12 years were collected for suspected UTIs. The most commonly isolated uropathogen was *Escherichia coli* followed by *Klebsiella* spp. and *Enterococcus* spp. Isolated pathogens were highly resistant to ampicillin, co-trimoxazole, and norfloxacin (82%–98%) while nitrofurantoin had a low resistance of 28.5% maintaining its high sensitivity.[6]

There are few studies, however, whose findings showed nitrofurantoin to be less effective compared to other antimicrobials used in those studies. In one study from Jamnagar from 2005 to 2006, prevalence of UTIs was evaluated taking samples of 3,046 patients of which 1,416 (46.48%) tested culture positive, the most common uropathogens being *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, in addition to *Proteus mirabilis*. Antimicrobial susceptibility tests *in vitro* revealed that the gram negative bacteria were susceptible to quinolone derivatives (gatifloxacin, levofloxacin) and meropenem. Gram positive isolates, on the other hand, were sensitive to linazolid, erythromycin & quinolone derivatives (gatifloxacin, levofloxacin). Nitrofurantoin on the other hand, was found to be ineffective on many of the microbes isolated in this particular study.[7] However, this study did not give more details of the disease setting, whether complicated or upper UTIs included,

in which case nitrofurantoin is known to be less effective by mechanism of its action, but not a result of the uropathogens developing resistance to the drug.

Southern Region

There are no region specific guidelines for treating UTIs as the local resistance pattern is ever changing in the light of rising resistance to commonly used antimicrobials like amoxicillin, sulfa drugs, cotrimoxazole and fluoroquinolones. Nitrofurantoin for the most part remained an exception to this rationale not only worldwide but also nationwide in the management of uncomplicated lower UTIs which comprise majority of the UTIs. A study conducted by George et al. in a tertiary hospital in Bangalore analysed urine culture samples of 196 patients. *Escherichia coli* was identified as the most common uropathogen. Gram negative bacteria constituted the largest group (84.1% or 53/63) and showed high level of sensitivity to nitrofurantoin (77.4%). Most of the gram‑positive organisms were also found to be susceptible to nitrofurantoin (70%). In the same study, uropathogens demonstrated high resistance to cotrimoxazole, fluoroquinolones, and beta‑lactam antibiotics.[5]

Alternatively, in a study conducted by Niranjan et al. in a tertiary care hospital in Puducherry for analysing the antimicrobial resistance among *Escherichia coli*, 76.51% were found to be multi drug resistant (MDR). Least sensitivity was noted to ampicillin (11.6%), amoxicillin-clavulanic acid (25.6%), norfloxacin (25.8%), cefuroxime (27.8%), ceftriaxone (28.6%) and co-trimoxazole (35.8%), while nitrofurantoin showed good sensitivity (82.1%).[55] Furthermore, another observational, retrospective study from Puducherry by Saravanan et al. showed that antimicrobials in frequent use for a long time, viz. co-trimoxazole; ampicillin/amoxicillin, fluoroquinolones and third generation cephalosporins were the major antimicrobials to which most common uropathogens developed resistance. It was a relatively large one, designed to find out the bacterial strains to which drug sensitivity has decreased and resistance has emerged, conducted for a period of one year from 2011 to 2012. A small fraction of 125 out of 999 samples, i.e. 12.5%, showed significant growth of bacteria which developed resistance to either single or multiple drugs. *Escherichia* (32.8%) was the most common organism isolated followed by Methicillin-sensitive *Staphylococcus aureus* (20.8%), *Klebsiella* (20%), Methicillin-resistant *Staphylococcus aureus* (13.6%), *Pseudomonas* (8%), *Proteus* (1.6%) and (0.8%) each of *Citrobacter* and *Enterococci*. Least sensitivity was noted to first line antimicrobials commonly prescribed such as co-trimoxazole, ampicillin, amoxicillin, amoxicillin/clavulanic acid, fluoroquinolone derivatives, third-generation

cephalosporins and nalidixic acid. Nitrofurantoin exhibited high sensitivity among gram negative as well as gram positive bacteria while amikacin, doxycycline, macrolides, clindamycin and vancomycin were sensitive against either gram negative or gram positive bacteria.[56]

Mathai et al. in a gender-specific study included only women, assessed the differences in antimicrobial resistance between urban and rural areas of Tamil Nadu in which 1,095 commensal *E. coli* and 29 infecting *E. coli* were tested. 510 of the commensal *E. coli* were from rural women while 585 remaining were from urban women. 463 (42%) of the commensal isolates showed resistance to one or more drugs; 92 (8.4%) were resistant to all three drugs commonly used, namely ampicillin, co-trimoxazole and nalidixic acid. There was no significant difference between resistance rates in commensal *E. coli* collected in rural and urban areas. In the same study, only 16 (1.5%) of the isolates were found resistant to nitrofurantoin.[57] Similar results were obtained in a prospective study by Lavanya et al. in which 500 women in their first/second trimesters were screened from the Obstetric department of KGH, Visakhapatnam. Primigravida had the highest culture positivity (66.6%), incidence was higher in <20 years age group (71.42%) and *Escherichia coli* was once again the most common organism isolated in the test and control groups. The organisms were found to be resistant to norfloxacin, amoxicillin and nitrofurantoin in the decreasing order.[58]

The profile of paediatric UTIs, bacterial pathogens involved, and also vesicoureteric reflux (VUR) and renal scarring were observed in a cross-sectional study conducted in 2013 in Puducherry, enrolling 524 paediatric patients aged ≤13 years. 186 (35.4%) children had UTIs with 105 (56.4%) being infants, 80 (43.52%) between 1-13 yr and 129 (69.35%) males. Bladder obstruction due to posterior urethral valve (PUV) was observed in 3 patients, hydronephrosis in 1 patient, VUR in 18 patients and renal scarring in 33 patients. *Escherichia coli* was the most common uropathogen isolated, found sensitive to nitrofurantoin, cefoperazone-sulbactam, aminoglycosides and meropenem in the decreasing order.[59]

Table 2. Nitrofurantoin Sensitivity Pattern to the three most identified uropathogens, *Escherichia coli, Klebsiella* and *Enterococcus* species, from Studies conducted across India

Region	Place	Population	Nitrofurantoin Sensitivity (%)			Reference
			Escherichia coli	*Klebsiella* spp.	*Enterococcus* spp.	
Northern, North Central & North Eastern	Shimla	Inpatients (inp) and outpatients (outp)	99 (inp), 84 (outp)			Ganju, Sunite A, et al., 2016 (39)
	Delhi	Outpatients	75.6	-	-	Kothari and Sagar 2008 (34)
	Delhi	CAUTI, HAUTI	-	-	100 (CAUTI), 72 (HAUTI)	Ahmed, N, et al., 2015 (4)
	New Delhi	Infants	95	83	83	Kaur et al., 2014 (48)
	Rohtak	Clinically suspected UTI patients	94	-	-	Mittal, S, et al., 2014 (60)
	Khanpur	Inpatients and outpatients	90.61 (females), 83.09 (males), 94.59 (Gynae/Obstetrics), 82.35 (Paediatrics)	-	-	Sandhu, R, et al., 2014 (40)
	Lucknow	Female outpatients	87	91	-	Shaifali et al., 2012 (37)
	Aligarh	Hospital wastewater	100	25	-	Alam, M. Z, 2013 (44)
	Dehradun	Acute uncomplicated cystitis	90.7	78	-	Biswas et al., 2006 (23)
	Chandigarh	Inpatients and outpatients	85 – 88	57	-	Gupta, V, et al., 2002 (46)
	Jamshedpur	Children < 5yrs	100	80	-	Sharan, R, et al., 2013 (52)
	Meerut	Outpatients from 15 to ≥48 years	74.24	37.93	-	Prakash, D, et al., 2013 (43)
	Udaipur	Inpatients and outpatients	95.21	68.58	90.48	Bhatnagar, R, et al., 2015 (18)
	Jaipur	Inpatients (inp) and outpatients (outp)	86 (inp), 91 (outp)	67 (inp), 67 (outp)	78 (inp), 100 (outp)	Sharma, R, et al., 2014 (45)
Eastern	West Bengal	Paediatric outpatients	100	100	-	Choudhury, P, et al., 2013 (53)
	Odisha	CAUTI patients	90.2	-	-	Dash, M, et al., 2013 (38)
Western	Pune	Semiurban industrialized area	57.3	-	-	Jadhav, S, et al., 2011 (54)
	Pune	Children 0 – 12 years	-	-	63.77	Nale, S. S, et al., 2014 (6)

Southern	Bangalore	Outpatients	71.4 (males), 86.5 (females)	40	100	George, C, et al., 2015 (5)
	Puducherry	Inpatients	82.1	-	-	Niranjan & Malini 2014 (55)
	Puducherry	Paediatric patients	100	86.6	96.8	Gupta, P, et al., 2015 (59)
	Vellore	Inpatients and outpatients	80	-	6	Veeraraghavan, B & Shakti, L, 2013 (17)

Studies of Extended-Spectrum β-Lactamase (ESBL) producing strains

β-lactamases known to hydrolyze gram-negative targeting extended-spectrum cephalosporins were first reported in 1983[61] and can be inhibited by β-lactamase inhibitors. These new β-lactamases coined extended-spectrum β-lactamases (ESBLs) pose a major problem for clinical therapeutics with several community-acquired pathogens that commonly cause UTIs and diarrhea also being found to be ESBL producers.[62] Nitrofurantoin has shown promising results in managing ESBL producing *E. coli* while being moderately effective against ESBL producing *Klebsiella* spp.

Table 3. Susceptibility of ESBL spp. to nitrofurantoin among drug resistant isolates outside India

Reference	Country	Susceptible rate (%) for Extended-Spectrum β-Lactamase producing spp.	
		E. coli	***Klebsiella***
Liu et al., 2011 (63)	Taiwan	79.1	13.6
Maina et al., 2013 (64)	Kenya	88.9	50
Auer et al., 2010 (65)	Austria	94	-
Puerto et al., 2006 (66)	Spain	71.3	-

In a recent study conducted at a Faridabad hospital in Haryana by Singh et al., ESBL producing *Klebsiella pneumoniae* (51.1%) from 223 nonduplicate isolates of *K. pneumoniae* were analysed for antimicrobial susceptibility profile. Susceptibility to various antimicrobials was found as given in table 4. Notably nitrofurantoin showed susceptibility pattern better than drugs like piperacillin and third generation cephalosporins.[67]

TABLE 4. Antibiotic susceptibility against ESBL producing *Klebsiella*.

Antibiotics	Susceptibility against ESBL producing *Klebsiella pneumoniae*
β-lactamase inhibitor combinations	67–81%
Aminoglycosides	62–76%
3rd generation cephalosporins	14–24%
Piperacillin	19–23%

fluoroquinolones	29–57%
Aztreonam	15–24%
Nitrofurantoin	57%

The percentage of ESBL producers in an earlier multicentric, retrospective study conducted nearby the same region comprising 5 hospitals from Delhi (34) was found to be a small fraction of 26.9% (137/508) of the gram negative isolates. Of this, 29.1% were *E. coli*, 25.6% were *Klebsiella* spp., 28.6% were *Enterobacter* spp. and 3.4% were *Proteus* spp. It included outpatient adult non-pregnant females with the main objective of establishing local guidelines on empirical treatment of CAUTI. As usual, antibiotic sensitivity of the gram-negative isolates, which include one-fourth of ESBL producers, was high for β-lactamase antibiotics like amikacin (75.6%), piperacillin-tazobactam (90.2%) and meropenem (100%) while it was alarmingly low for TMP-SXT (30%), ciprofloxacin (35.8%), amoxicillin (17.7%) and even amoxicillin/clavulanate (41.6%). Nitrofurantoin (65.7%) was the only non β-lactamase inhibitor that showed moderately high sensitivity on the isolates.

A similarly large retrospective study was done a few years back in patients visiting a hospital in Jaipur[35] between 2007 and 2009. Consecutively, 2,012 urine specimens from symptomatic UTI cases of outpatient clinics were analysed for antimicrobial sensitivity. Pathogens were isolated from 346 (17.16%) patients and *Escherichia coli* was found to be the most frequently isolated uropathogen. ESBL production was observed in 23.83% of *E. coli* strains and 8.69% of *Klebsiella* strains. A high proportion of *E. coli* strains were found to have been resistant to ampicillin, amoxicillin/clavulanic acid, co-trimoxazole, nalidixic acid, norfloxacin and ciprofloxacin. Table 5. Nitrofurantoin was found to maintain least resistance (5‑6%) to *E. coli* throughout the 2½ years of study period. In this study, it was found that except for nitrofurantoin, resistance to agents commonly used as empirical oral treatments for UTIs caused by ESBL producing strains was quite high.

Table 5. Resistance pattern of ESBL producing *E. coli*

Antibiotics	**Resistance against ESBL producing *E. coli***
Ampicillin	>80%
Amoxicillin/clavulanic acid	>80%
Co-trimoxazole	>67%
Nalidixic acid	>95%
Norfloxacin	>77%
Ciprofloxacin	>74%
Nitrofurantoin	5-6%

In the South too, a large study was carried out in 2002 in which 2,261 urine samples were tested for significant bacteriuria, identifying 715 samples contaminated with various bacterial isolates. *E. coli* (353) and *K. pneumoniae*[65] constitute significant numbers with ESBL production observed in 41% of *E. coli* and 40% of *K. pneumoniae*. The susceptibility of ESBL producers to various non-β-lactam antibiotics was as shown in Fig. 11. Nitrofurantoin and amikacin were suggested for treating these patients upon observing co-resistance to non-β-lactam antibiotics like norfloxacin, co-trimoxazole and gentamicin.[68]

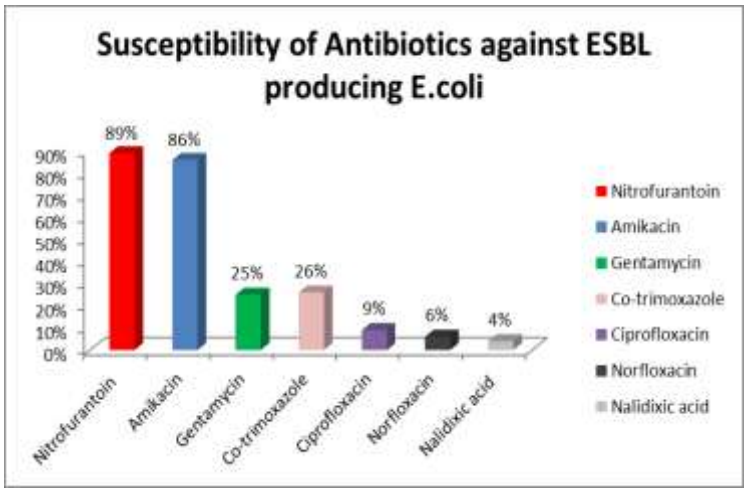


Fig. 11. Antibiotic Susceptibility against ESBL producing *E. coli*

CONCLUSION

The most common hospital-acquired and second most common community-acquired infections are UTIs. Knowledge on antimicrobial sensitivity pattern which is essential for appropriate therapy of these infections is ever changing due to the ability of bacteria to undergo mutations and develop resistant strains. Add to the predicament, reduced patient compliance coupled with unfinished course of therapy results in the growth of resistance to many of these antimicrobials.

Nitrofurantoin is an age-old molecule, but has withstood the emergence of antibiotic resistance in the treatment of bacterial UTIs. This may be due to the non-specific attack on bacterial ribosomal proteins by highly reactive nitrofurantoin intermediates along with manifold sites of attack including disruption of nuclear material unlike antimicrobials that target one site as with ampicillin or two sites as with co-trimoxazole.

Many times empirical treatment is prescribed from sparse knowledge of the antibiotic sensitivity patterns of uropathogens in the local area or by resorting to prescribing broad-

spectrum antibiotics. The use of co-trimoxazole and penicillin analogues to treat UTIs is restricted by high rates of resistance. Ciprofloxacin despite being favoured for its broad-spectrum of action earlier, however, decreasing sensitivity to this drug, pregnancy time contraindication (category C) and its undesirable impact on gut flora has made it inappropriate for empirical therapy of UTIs. Fosfomycin has good activity against *E. coli* but resistance rate is high among *Klebsiella* spp. On the other hand, nitrofurantoin's sensitivity against the most common uropathogens like *E. coli* and *Klebsiella* spp. remained virtually unchanged since its introduction into clinical practice in 1952 till date as ascertained in our analysis of many recent studies conducted throughout the length and breadth of India. Taking this into consideration, along with its manageable adverse event profile, nitrofurantoin can be safely regarded as the first line antimicrobial of choice in the empirical treatment and prophylaxis of lower UTIs.

Conflicts of Interest

The authors of this review article has no financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of this paper.

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REFERENCES

1. NICE Quality Standards Advisory Committee. Urinary tract infections in adults, 2015 Jun; https://www.nice.org.uk/guidance/qs90.
2. Goodman CC, Fuller KS. Pathology: Implications for the Physical Therapist, 4 ed. Missouri: Elsevier Saunders; 2015.
3. American Urological Association. Adult UTI, (accessed 21st Mar, 2016); https://www.auanet.org/education/adult-uti.cfm.
4. Ahmed N, Raghuraman K, Baruah F, Grover R. Antibiotic resistance pattern of uropathogens: An experience from north Indian cancer patient. J Global Infect Dis. 2015; 7(3): 113.

5. George C, Norman G, Ramana G, Mukherjee D, Rao T. Treatment of uncomplicated symptomatic urinary tract infections: Resistance patterns and misuse of antibiotics. J Family Med Prim Care. 2015; 4(3): 416.
6. Nale SS. Study of Aetiology and Anti-biogram of Uropathogens in Children-A Retrospective Analysis. Jcdr. 2014.
7. Patel SK, Taviad PKP, Sinha M, Javadekar TB, Chaudhari VP. Urinary Tract Infections (UTI) among patients at G.G. Hospital & Medical College, Jamnagar, Natl J Community Med. 2012; 3(1): 138-41.
8. Foye WO, Lemke TL, Williams DA. Foye's principles of medicinal chemistry. Philadelphia: Lippincott Williams & Wilkins; 2013.
9. Munoz-Davila M. Role of Old Antibiotics in the Era of Antibiotic Resistance. Highlighted Nitrofurantoin for the Treatment of Lower Urinary Tract Infections. Antibiotics. 2014 Oct; 3(1): 39–48.
10. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical Infectious Diseases. 2011 Feb; 52(5).
11. Pallett A, Hand K. Complicated urinary tract infections: practical solutions for the treatment of multiresistant Gram-negative bacteria. Journal of Antimicrobial Chemotherapy. 2010; 65(Supplement 3): iii25–iii33.
12. Spencer RC, Moseley DJ, Greensmith MJ. Nitrofurantoin modified release versus trimethoprim or co-trimoxazole in the treatment of uncomplicated urinary tract infection in general practice. J Antimicrob Chemother. 1994 May; 33 Suppl A: 121-9.
13. Antimicrobial Prescribing Guidelines in General Practice; National Health Service; 2012; v1.0: 14-19.
14. Antimicrobial Guide and Management of Common Infections in Primary Care: Strategies to Optimise Prescribing of Antimicrobials in Primary Care. v6.2. National Health Service; 2015. Based upon advice contained in the Public Health England publication, Management of Infection Guidance for Primary Care, October 2014.
15. Hamilton RJ, Tarascon Pocket Pharmacopoeia, 15 ed. United States of America: Jones & Bartlett Learning; 2014.
16. Katzung BG, Trevor AJ. Basic & Clinical Pharmacology, 13 ed. United States of America: McGraw-Hill Education; 2015.

17. Veeraraghavan B, Shakti L. Advantage and limitations of nitrofurantoin in multi-drug resistant Indian scenario. Indian J Med Microbiol. 2015; 33(4): 477.
18. Bhatnagar R, Soni P, SK, Mehra SK, Solanki A, Tomar J. Study of nitrofurantoin susceptibility among uropathogenic bacterial isolates at a tertiary care hospital, Udaipur, Rajasthan. World Journal of Pharmaceutical Research. 2015; 4(5): 2124–32.
19. McOsker CC, Fitzpatrick PM. Nitrofurantoin: Mechanism of action and implications for resistance development in common uropathogens. Journal of Antimicrobial Chemotherapy. 1994 Jan; 33(suppl A): 23–30.
20. Brown O, Seither R. Oxygen and redox-active drugs: Shared toxicity sites. Fundamental and Applied Toxicology. 1983; 3(4): 209–14.
21. Wein AJ, Kavoussi LR, Partin AW, Peters CA. Campbell-Walsh Urology, 11 ed. Philadelphia: Elsevier Inc.; 2016.
22. Gupta K, Sahm DF, Mayfield D, Stamm WE. Antimicrobial Resistance Among Uropathogens that Cause Community-Acquired Urinary Tract Infections in Women: A Nationwide Analysis. CLIN INFECT DIS. 2001; 33(1): 89–94.
23. Biswas D, Gupta P, Prasad R, Singh V, Arya M, Kumar A. Choice of antibiotic for empirical therapy of acute cystitis in a setting of high antimicrobial resistance. Indian J Med Sci. 2006; 60(2): 53.
24. Karlowsky JA, Thornsberry C, Jones ME, Sahm DF. Susceptibility of Antimicrobial-Resistant Urinary Escherichia coli Isolates to Fluoroquinolones and Nitrofurantoin. CLIN INFECT DIS. 2003; 36(2): 183–7.
25. ACOG Practice Bulletin No. 91: Treatment of Urinary Tract Infections in Nonpregnant Women. Obstetrics & Gynecology. 2008; 111(3): 785–94.
26. Johnson EK, Wolf JS, Kim ED. Urinary Tract Infections in Pregnancy Medication [Internet]. Urinary Tract Infections in Pregnancy Medication: Antibiotics. Medscape; [accessed 2016Feb22]. Retrieved from: http://emedicine.medscape.com/article/452604-medication.
27. Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010; 7(12): 653–60.
28. Wagenlehner FME, Hoyme U, Kaase M, Funfstuck R, Naber KG, Schmiemann G. Uncomplicated Urinary Tract Infections. Dtsch Arztebl Int, 2011; 108(24): 415–23.
29. Schaeffer EM. Re: Risk Factors for Fluoroquinolone-Resistant Escherichia Coli in Adults With Community-Onset Febrile Urinary Tract Infection. The Journal of Urology. 2012; 187(1): 153.

30. Olson RP, Harrell LJ, Kaye KS. Antibiotic Resistance in Urinary Isolates of Escherichia coli from College Women with Urinary Tract Infections. Antimicrobial Agents and Chemotherapy. 2008; 53(3): 1285–6.
31. Mckinnell JA, Stollenwerk NS, Jung CW, Miller LG. Nitrofurantoin Compares Favorably to Recommended Agents as Empirical Treatment of Uncomplicated Urinary Tract Infections in a Decision and Cost Analysis. Mayo Clinic Proceedings. 2011; 86(6): 480–8.
32. Mohammed A, Mohammed S, Asad UK. Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in J N M C Hospital Aligarh, India. Ann Clin Microbiol Antimicrob. 2007 Mar; 6(4).
33. Selvakumar BN, Jasmine R. Antibiotic Susceptibility of ESBL-Producing Urinary Isolates at a Tertiary Care Hospital in Tiruchirappalli, South India. J of Medical Sciences. 2007 Jan; 7(3): 443–6.
34. Kothari A, Sagar V. Antibiotic resistance in pathogens causing community-acquired urinary tract infections in India: a multicenter study. J Infect Dev Ctries. 2008 Jan; 2(05).
35. Sood S, Gupta R. Antibiotic resistance pattern of community acquired uropathogens at a tertiary care hospital in Jaipur, Rajasthan. Indian J Community Med. 2012; 37(1): 39.
36. Sabharwal E. Antibiotic susceptibility patterns of uropathogens in obstetric patients. North Am J Med Sci. 2012; 4(7): 316.
37. Mahmood S, Shaifali I, Ahmed J, Gupta U. Antibiotic susceptibility patterns of urinary pathogens in female outpatients. North Am J Med Sci. 2012; 4(4): 163.
38. Dash M, Padhi S, Mohanty I, Panda P, Parida B. Antimicrobial resistance in pathogens causing urinary tract infections in a rural community of Odisha, India. J Fam Community Med. 2013; 20(1): 20.
39. Ganju SA, AK, Mokta K, Kanga AK. Nitrofurantoin Revisited: Susceptibility Pattern of Uropathogenic Escherichia Coli in a Tertiary Care Hospital, Shimla, India. Wjpps. 2016; 5(3): 1466-473.
40. Sandhu R, Singh K, Sharma, G. Study of Nitrofurantoin Susceptibility in Urinary Isolates of E.coli – A Need to Revert Back to Older Drugs. Am. J. Pharm Tech Res, 2014; 4(4): 414-23.
41. Mittal S, Sharma M, Chaudhary U. Study of virulence factors of uropathogenic Escherichia coli and its antibiotic susceptibility pattern. Indian J Pathol Microbiol. 2014; 57(1): 61.

42. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. CLIN INFECT DIS. 2009; 48(1): 1–12.
43. Prakash D, Saxena RS. Distribution and Antimicrobial Susceptibility Pattern of Bacterial Pathogens Causing Urinary Tract Infection in Urban Community of Meerut City, India. ISRN Microbiology. 2013; 2013: 1–13.
44. Alam MZ, Aqil F, Ahmad I, Ahmad S. Incidence and transferability of antibiotic resistance in the enteric bacteria isolated from hospital wastewater. Braz J Microbiol. 2013; 44(3): 799–806.
45. Sharma R, Jain M, Vyas L, Singhal A. Hospital and community isolates of uropathogens and their antibiotic sensitivity pattern from a tertiary care hospital in North West India. Ann Med Health Sci Res. 2014; 4(1): 51.
46. Gupta V, Yadav A, Joshi RM. Antibiotic resistance pattern in uropathogens. Indian J Med Microbiol. 2002; 20: 96-98.
47. Kumar Y, Sood S, Sharma A, Mani KR. Antibiogram and characterization of resistance markers among Escherichia coli Isolates from urinary tract infections. J Infect Dev Ctries. 2013; 7(07).
48. Kaur N, Sharma S, Malhotra S, Madan P, Hans C. Urinary Tract Infection: Aetiology and Antimicrobial Resistance Pattern in Infants from A Tertiary Care Hospital in Northern India. Jcdr. 2014; 8(10): 1-3.
49. Taneja N, Chatterjee SS, Singh M, Singh S, Sharma M. Pediatric urinary tract infections in a tertiary care centre from North India. Indian J Med Res, 2010; 131: 101-105.
50. Sharma N, Gupta A, Walia G, Bakhshi R. Pattern of Antimicrobial Resistance Of Escherichia Coli Isolates From Urinary Tract Infection Patients: A Three Year Retrospective Study. J App Pharm Sci. 2016; 062–5.
51. Sharma V, Jindal N, Devi P. Prevalence of methicillin resistant coagulase negative staphylococci in a tertiary care hospital. Iran J Microbiol. 2010; 2(4): 185-8.
52. Sharan R, Kumar D, Mukherjee B. Bacteriology and antibiotic resistance pattern in community acquired urinary tract infection. Indian Pediatr. 2013; 50(7): 707.
53. Choudhury P, Chaudhuri SN, Chattopadhyay C. Frequency of Urinary Tract Infections in Children and Antibacterial Resistance Pattern of Urinary Isolates in India. IJPHC, 2013; 2(3): 37-41.

54. Jadhav S, Hussain A, Devi S, Kumar A, Parveen S, Gandham N, et al. Virulence Characteristics and Genetic Affinities of Multiple Drug Resistant Uropathogenic Escherichia coli from a Semi Urban Locality in India. PLoS ONE. 2011; 6(3).
55. Niranjan V, Malini A. Antimicrobial resistance pattern in Escherichia coli causing urinary tract infection among inpatients. Indian J Med Res. 2014; 139: 945-8.
56. Saravanan R, Raveendaran V. Antimicrobial resistance pattern in a tertiary care hospital: An observational study. J Basic Clin Pharma. 2013; 4(3): 56.
57. Mathai E, Chandy S, Thomas K, Antoniswamy B, Joseph I, Mathai M, et al. Antimicrobial resistance surveillance among commensal Escherichia coli in rural and urban areas in Southern India. Tropical Medicine & International Health. 2008; 13(1): 41–5.
58. Lavanya SV, Jogalakshmi D. Asymptomatic bacteriuria in antenatal women. Indian J Med Microbiol, 2002; 20: 105-6.
59. Mandal J, Krishnamurthy S, Barathi D, Pandit N, Gupta P. Profile of urinary tract infections in paediatric patients. Indian J Med Res. 2015; 141(4): 473.
60. Mittal S, Sharma M, Chaudhary U. Study of virulence factors of uropathogenic Escherichia coli and its antibiotic susceptibility pattern. Indian J Pathol Microbiol. 2014; 57(1): 61.
61. Paterson DL, Bonomo RA. Extended-Spectrum -Lactamases: a Clinical Update. Clinical Microbiology Reviews. 2005 Jan; 18(4): 657–86.
62. Rawat D, Nair D. Extended-spectrum ß-lactamases in gram negative bacteria. J Global Infect Dis. 2010; 2(3): 263.
63. Liu H-Y, Lin H-C, Lin Y-C, Yu S-H, Wu W-H, Lee Y-J. Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan. Journal of Microbiology, Immunology and Infection. 2011; 44(5): 364–8.
64. Maina D, Makau P, Nyerere A, Revathi G. Antimicrobial resistance patterns in extended-spectrum β-lactamase producing Escherichia coli and Klebsiella pneumoniae isolates in a private tertiary hospital, Kenya. Microbiol Discov. 2013; 1(1): 5.
65. Auer S, Wojna A, Hell M. Oral Treatment Options for Ambulatory Patients with Urinary Tract Infections Caused by Extended-Spectrum-β-Lactamase-Producing Escherichia coli. Antimicrobial Agents and Chemotherapy. 2010; 54(9): 4006–8.
66. Puerto AS, Fernández JG, Juan De Dios Luna Del Castillo, Pino MJS, Angulo GP. In vitro activity of β-lactam and non–β-lactam antibiotics in extended-spectrum β-

lactamase–producing clinical isolates of Escherichia coli. Diagnostic Microbiology and Infectious Disease. 2006; 54(2): 135–9.

67. Singh A, Jain S, Kumar D, Singh R, Bhatt H. Antimicrobial susceptibility pattern of extended-spectrum beta- lactamase producing Klebsiella pneumoniae clinical isolates in an Indian tertiary hospital. J Res Pharm Pract. 2015; 4(3): 153.
68. Babypadmini S, Appalaraju B. Extended spectrum β-lactamases in urinary isolates of Escherichia coli and Klebsiella pneumoniae - prevalence and susceptibility pattern in a tertiary care hospital. Indian Journal of Medical Microbiology. 2004; 22(3): 172-4.