Original Research Article

Nitrofurantoin Proving Old is Gold? - In the Era of Antibiotic Resistance: A Study in a Tertiary Care Hospital

Vijaya[1], Sweetha Nayak Nagar[2*], Maureen Edwards[3], Pallavi Uday Naik[4]

[1]Associate Professor, Department of Microbiology, Srinivas Institute of Medical Sciences & Research Centre, Mukka, Surathkal, Mangalore, Karnataka, India

[2] Associate Professor, Department of Microbiology, Srinivas Institute of Medical Sciences & Research Centre, Mukka, Surathkal, Mangalore, Karnataka, India

[3] Tutor, Department of Microbiology, Srinivas Institute of Medical Sciences & Research Centre, Mukka, Surathkal, Mangalore, Karnataka, India

[4]Intern, Father Muller Medical College, Kankanady, Mangalore, Karnataka, India

Received: 26-05-2021 / Revised: 12-06-2021 / Accepted: 29-07-2021

Abstract

Background: Urinary tract infection represents one of the most common diseases encountered in medical practice today. Due to increasing multidrug resistance in major uropathogens, the therapeutic choices are becoming less. Most uropathogens still relatively susceptible to Nitrofurantoin which makes this drug a good alternative for treatment. This study was undertaken to assess the effect of Nitrofurantoin against the uropathogens. **Materials and Methods:** This is a prospective study between Jan 2020 to June 2021, undertaken in Srinivas Institute of Medical Sciences and Research Centre, Mukka, Mangalore. Standard culture techniques for urine samples were followed. Antibiotic sensitivity test was done by Kirby-Bauer disc diffusion method and interpretation was done following Clinical and Laboratory Standards Institute (CLSI) guidelines. ESBL detection was done by NCCLS phenotypic confirmatory combination disc diffusion method using ceftazidime (30 µg) alone and ceftazidime + clavulanic acid (30 µg/ 10 µg). **Results:** In our study the most common organism was E.coli 62.5%, followed by Klebsiella spp.13%. The other isolates were Enterococcus 8.6%, Pseudomonas 6.8%, Proteus-2.4%, Acinetobacter 2.0%, Citrobacter1.8%, Coagulase negative staphylococci 1.7% and Candida1.2%. The antibiotic sensitivity pattern of the isolates to nitrofurantoin among GNB was E.coli 90.3%, Klebsiella spp. 62.2%, Citrobacter 87.7% and among GPCs, Coagulase negative Staphylococci(CONS) 98.4% and Enterococcus 94.2%. Among E.coli 91.6% of Non ESBL E.coli and 88.6% of ESBL E.coli were sensitive to Nitrofuantoin. Among Klebsiella spp.63.5% of non ESBL Klebsiella and 59.8% of ESBL Klebsiella were sensitive to Nitrofurantoin.

Key words: Nitrofurantoin, UTI, E.coli.

Background

Urinary tract infection (UTI) represents one of the most common diseases encountered in medical practice today and occurring from the neonate to the geriatric age[1]. Due to increasing multidrug resistance in major uropathogens, the therapeutic choices are becoming less. Bacteria isolated from UTIs are often resistant to Ampicillin, Trimethoprim, Co-trimoxazole and Fluoroquinolones. Most uropathogens are still relatively susceptible to Nitrofurantoin which makes this drug a good choice for treatment[2]. Nitrofurantoin was approved by the FDA in 1953 for treatment of acute uncomplicated UTIs and was prescribed widely for the next two decades, until its popularity decreased in 1970s with the advent of other oral antibiotics like Co-trimoxazole and β-lactams. However, recently the increasing resistance to Co-trimoxazole and fluoroquinolones has led to renewed interest in this old drug.

*Correspondence
Dr. Sweetha Nayak Nagar
Associate Professor, Department of Microbiology, Srinivas Institute of Medical Sciences & Research Centre, Mukka, Surathkal, Mangalore, Karnataka, India.
E-mail: sweetsnayak@yahoo.com

With rise in ESBL producing and carbapenem resistant bacteria, several guidelines were revised to reposition Nitrofurantoin as first line therapy for uncomplicated lower UTI[3]. Nitrofurantoin is a cost effective, well tolerated oral broad-spectrum bactericidal antibiotic. It acts at multiple sites, various steps in carbohydrate synthesis, interferes with the synthesis of cell wall, bacterial proteins and DNA of both Gram positive and Gram-negative pathogens[4]. It is metabolized in renal tissue and rapidly excreted in the urine. Due to this rapid excretion, the urinary concentration of Nitrofurantoin is more than 100 µg/mL (up to 250 µg/mL). This higher concentration in urine makes it an ideal choice for treatment of urinary tract infection[5]. Nitrofurantoin remains an excellent empirical choice when no prior culture results are available to guide therapy[6]. This drug is active against most common uropathogens including *E.coli, Citrobacter spp., Staphylococcus saprophyticus, and Enterococcus spp.* whereas, *Enterobacter spp.* and *Klebsiella spp.* are moderately inhibited. *Proteus spp., Providencia spp., Morganella morgannii, Serratia spp., Pseudomonas spp., and Acinetobacter spp.* are mostly resistant to this drug[7]. Nitrofurantoin has been used successfully for a long time for the prophylaxis and treatment of acute lower urinary tract infections in adults, children and pregnant women except in the last three months of pregnancy and in patients suffering from renal disease. In the International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women published by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Nitrofurantoin has been recommended as one first-line antibiotic of

empiric antibacterial treatment of uncomplicated cystitis in otherwise healthy women[8]. Many of the current guidelines for treating UTI has also recommended the same.

Nitrofurantoin could also be a further option for oral antimicrobial treatment of acute uncomplicated cystitis produced by ESBL-producing bacteria[9]. Studies have shown the effectiveness of this drug does not differ between ESBL-producing *E. coli* and Non-ESBL-producing *E. coli* strains[10]. Nitrofurantoin is also recommended for the treatment of catheter-associated bacteriuria, which is the most common cause of urinary tract infection. In this sense, it is used prophylactically during or following urinary tract instrumentation. At present Nitrofurantoin is being used increasingly to treat nosocomial vancomycin-resistant enterococcal (VRE) urinary tract infections also[11].Since Nitrofurantoin is useful against microorganisms which are the most frequent causes of nosocomial lower UTIs, ie, catheter-associated bacteriuria, this study was undertaken to assess the effect of Nitrofurantoin against the Gram-positive and Gram-negative uropathogens.

Materials and methods

This is a one and half year prospective study done between Jan 2020 to June 2021 in Srinivas Institute of Medical Sciences and Research Centre, Mukka, Mangalore. A total of 11,020 urine specimens obtained from outpatients and inpatients were analysed. Urine culture was done by standard loop method, a semi-quantitative method. The organisms isolated from urine culture were identified by conventional biochemical tests. Antimicrobial susceptibility test was done by Kirby-Bauer disc diffusion method on Mueller-Hinton agar and the interpretations were carried out according to the Clinical and Laboratory Standards Institute guidelines. Antibiotics against which sensitivity was tested included Ampicillin (10 µg), Amoxyclav (20 µg/10 µg), Ceftazidime (30 µg), Ceftriaxone (30 µg), Aztreonam (30 µg), Gentamicin (10 µg), Amikacin (30 µg), Ciprofloxacin (5 µg), Co-trimoxazole (25 µg), Norfloxacin (10 µg), Nitrofurantoin (300 µg), Piperacillin-tazobactam (100 µg/10 µg) and Meropenem (10 µg). Quality control of media and discs were performed using ATCC *E. coli* control strain 25922. ESBL production in *E. coli* was detected routinely by NCCLS phenotypic confirmatory combination disc diffusion method using Ceftazidime (30 µg) and Ceftazidime/ clavulanic acid (30 µg/10 µg). An increase in the inhibition zone diameter of ≥ 5 mm for a combination disc versus Ceftazidime disc alone confirmed ESBL production.

Results

Among 11,020 urine samples which were analysed for isolation and identification of bacterial pathogens, 3,640 were positive (33.03%).

Out of 3,640(33.03%) isolates, the most common organism was *E.coli*-2,275(62.5%), followed by *Klebsiella spp.*- 474(13%). The other isolates were *Enterococcus* 312(8.6%), *Pseudomonas* 248(6.8%), *Proteus* 86(2.4%), *Acinetobacter* 74(2.0%), *Citrobacter spp* 65(1.8%), Coagulase Negative Staphylococci (CONS) 62(1.7%) and *Candida* 44(1.2%).

The overall sensitivity pattern of all bacterial uropathogens to different antibiotics is shown in Table 1 and Table 2.

Nitrofurantoin showed better sensitivity pattern than Gentamicin, Ciprofloxacin and Co trimoxazole among both Gram-positive organisms and Gram negative uropathogens. The antibiotic sensitivity pattern of the isolates to Nitrofurantoin among GNB were *E.coli* 90.3%, *Klebsiella spp.* 62.2%, *Citrobacter spp.*87.7% and among GPCs CONS 98.4%and *Enterococcus* 94.2%.(Graph 1)

In our study ESBL detection was done for *E.coli* and *Klebsiella spp.* which is 42.3% and 34.6% respectively. We also compared the sensitivity pattern of ESBL and non ESBL producing isolates to Nitrofurantoin. However, there was not much difference in Nitrofurantoin sensitivity observed among ESBL and non ESBL strains. Among *E.coli* 91.6% of Non ESBL *E.coli* and 88.6% of ESBL *E.coli* were sensitive to Nitrofuantoin. Among *Klebsiella spp.*63.5% of non ESBL *Klebsiella a*nd 59.8% of ESBL *Klebsiella* were sensitive to Nitrofurantoin. The sensitivity pattern of ESBL and non ESBL *E.coli* and *Klebsiella* are given in Graph 2.

Table 1: Sensitivity pattern of Gram-negative organisms

	E.coli N=2275	Klebsiella N=474	Proteus N=86	Citrobacter N=65	Acinetobacter N=74	Pseudomonas N=248
Ampicillin	196(8.6%)	0	64(74.4%)	8(12.3%)	0	0
Amoxyclav	546(24.0%)	40(8.4%)	66(76.7%)	32(49.2%)	9(12.2%)	26(10.4%)
Ceftriaxone	865(38.0%)	174(36.7%)	69(80.2%)	38(58.5%)	18(24.3%)	34(13.7%)
Ceftazidime	854(37.5%)	168(35.4%)	72(83.7%)	40(61.5%)	20(27.0%)	158(63.7%)
Aztreonam	910(40.0%)	177(37.3%)	62(72.1%)	34(52.3%)	22(29.7%)	94(37.9%)
Ciprofloxacin	1024(45.0%)	258(54.4%)	67(77.9%)	36(55.4%)	24(32.4%)	142(57.3%)
Co trimoxazole	998(43.9%)	165(34.8%)	28(32.5%)	27(41.5%)	14(18.9%)	70(28.2%)
Norfloxacin	1047(46.0%)	230(48.5%)	54(62.8%)	34(52.3%)	15(20.3%)	94(37.9%)
Gentamicin	1411(62.0%)	275(58.0%)	66(76.7%)	33(50.8%)	20(27.0%)	116(46.8%)
Nitrofurantoin	**2055(90.3%)**	**295(62.2%)**	**9(10.5%)**	**57(87.7%)**	**6(8.1%)**	**29(11.7%)**
Amikacin	2002(88.0%)	370(78.0%)	86(100%)	58(89.2%)	40(54.0%)	155(62.5%)
Piperacillin-tazobactam	2016(88.6%)	378(79.7%)	86(100%)	55(84.6%)	44(59.4%)	178(71.8%)
Meropenem	2066(90.8%)	380(80.2%)	86(100%)	62(95.4%)	50(67.6%)	184(74.2%)

Table:2 Sensitivity pattern of Gram-positive organisms

	Enterococcus spp. (N=312)	CONS(N=62)
Ampicillin	130(41.6%)	-
Amoxyclav	225(72.1%)	45(72.6%)
Cefoxitin	-	48(77.4%)
Gentamicin	74(23.7%)	38(61.3%)
High Level Gentamicin	170(54.5%)	-
Co-trimoxazole	98(31.4%)	17(27.4%)
Erythromycin	85(27.2%)	32(51.6%)
Clindamycin	-	30(48.4%)
Ciprofloxacin	148(47.4%)	37(59.7%)
Ceftriaxone	130(41.6%)	49(79.0%)
Nitrofurantoin	**294(94.2%)**	**61(98.4%)**
Norfloxacin	114(36.5%)	26(41.9%)
Vancomycin	312(100%)	62(100%)
Teicoplanin	312(100%)	62(100%)

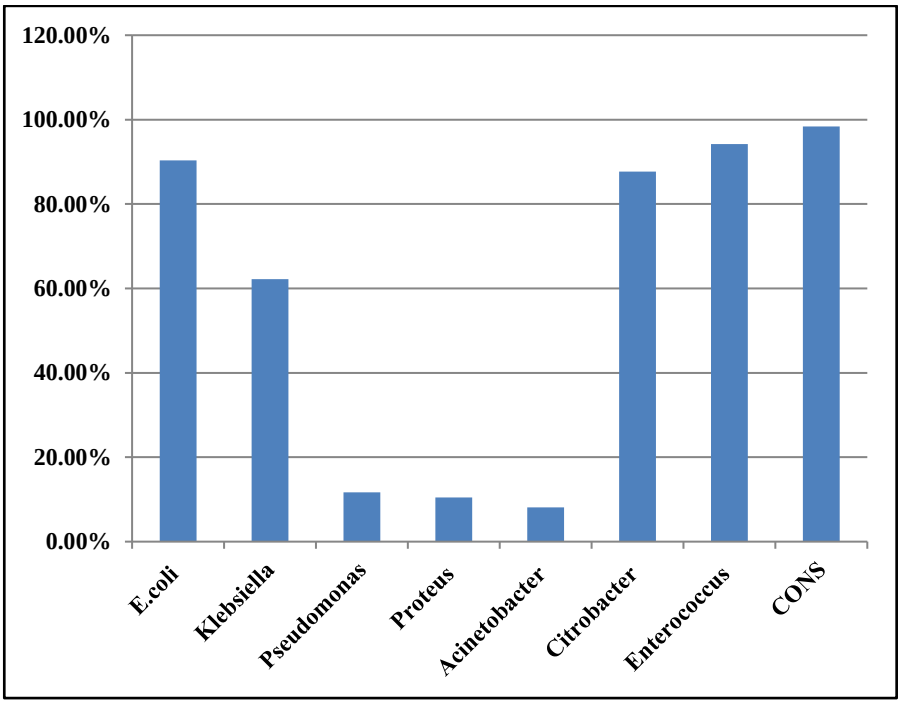

Fig 1: Nitrofurantoin sensitivity

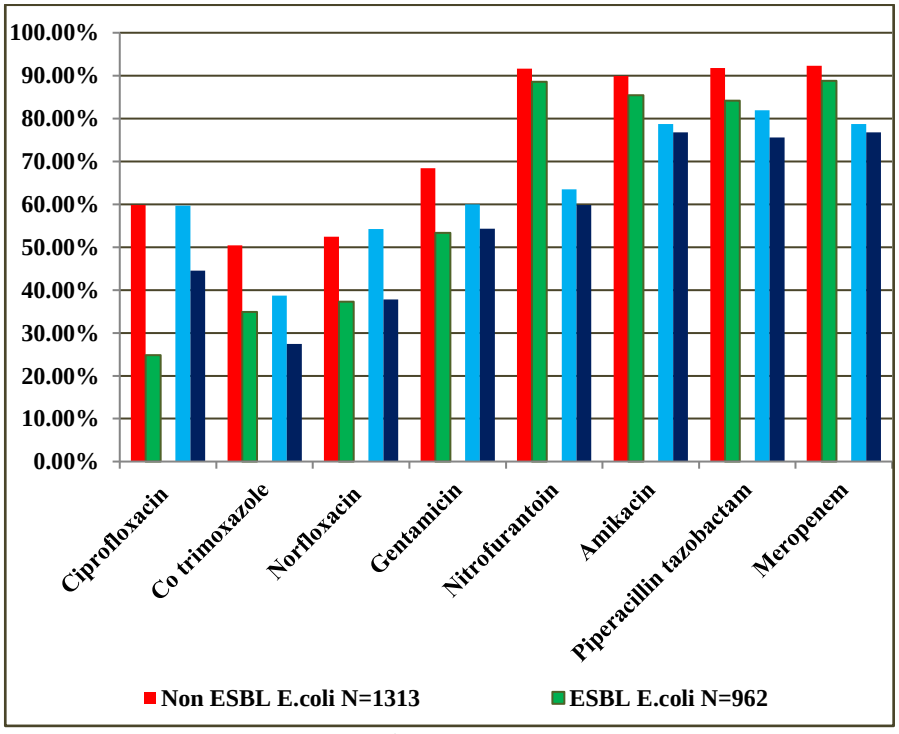

Fig 2:The sensitivity pattern of ESBL and non ESBL E.coli and Klebsiella

Discussion

The rapid development and spread of antimicrobial resistance among uropathogens is a major public health concern. Given the fact that Nitrofurantoin has no role in the treatment of other infections, it can be administered orally and is highly concentrated in urine; it may therefore be the most appropriate agent for empirical use in uncomplicated UTI in the era of antibiotic resistance. This study highlights on the susceptibility of Gram-negative and Gram-positive uropathogens to Nitrofurantoin.

The spectrum of uropathogens in our study was *E.coli* followed by *Klebsiella spp*. and *Enterococcus* which is similar to the other studies done by Saurabh Jain et al[5] and Harith kumar et al[12]. *E.coli* is the most predominant pathogen accounting 62.5% of all clinically significant urinary isolates. Similar finding that *E.coli* is most common uropathogen have been reported by Shalini et al[13], Sood S et al[14] and Neelima et al[15].

In our study 90.3% of urinary *E.coli* isolates were sensitive to nitrofurantoin which goes in accordance with a study done by Ponnammmal et al[4] with 91% sensitivity to Nitrofurantoin. In a 5yr study done by Prasada et al[16] Nitrofurantoin resistance in *E.coli* was comparatively lower ranging between 12.8–13.3% which supports the present study.

In our study 13% of uropathogens were *Klebsiella spp.* similar to the studies conducted by Saurabh et al and Ashis Kumar[17]. The sensitivity to Nitrofurantoin was shown by 62.2% of *Klebsiella spp*. which goes in accordance with the study conducted by (62.9%)Varghese A et al[18].

Our study reveals that 42.3% of *E.coli* isolates are ESBL producers which is similar to the study conducted by Bajpai T et al[19] and Eshwarappa M et al[20]. In our study 34.6% of *Klebsiella spp* are ESBL producers which is similar to studies done by Gayathri Gururajan et al[21] and Mehrishi P et al[22].

The overall prevalence of ESBL producers was found to vary greatly in different geographical areas. Bishara J et al[23] reported 10% of *E.coli* and 32% of *Klebsialla* species to be ESBL producers from Israel. In another study in SriLanka, 46% of *E.coli* isolates and 25% *Klebsiella* isolates were found to be ESBL producers[24]. This geographical difference may be due to different patterns of antibiotic usage and it may be determined by the local prescribing practices, with the resistance higher among the most commonly prescribed agents.

We also compared the sensitivity pattern of ESBL and non ESBL producing isolates to Nitrofurantoin. However there was not much difference in Nitrofurantoin sensitivity observed among ESBL and non ESBL strains. Among *E.coli* 91.6% of Non ESBL *E.coli* and 88.6% of ESBL *E.coli* were sensitive to Nitrofurantoin. Based on these findings, we suggest that Nitrofurantoin may be another alternative option for treating uncomplicated UTI caused by ESBL-*E.coli* infection. At the same time several studies have also shown that 70-95% ESBL-producing *E. coli* isolates are susceptible to Nitrofurantoin[25]. Among *Klebsiella spp*. 63.5% of Non ESBL *Klebsiella* and 59.8% of ESBL *Klebsiella* were sensitive to Nitrofuantoin with moderate degree of efficacy against ESBL-*Klebsiella*. Our findings of sensitivity to Nitrofurantoin shown by ESBL producing *E.coli* and *Klebsiella* correlates with the findings in studies done by Dusi Ratna Harika et al[26] and Tulara NK et al[27].

Nitrofurantoin showed better susceptibility pattern in Gram-positive uropathogens as well. Among Gram positive organisms 96.8% of CONS are sensitive to Nitrofurantoin. Similar findings were found in Akshaya Thrinetrapriya et al[28]. In a study done by Sourabh Jain et al[5] 100% of CONS were sensitive to Nitrofurantoin. In our study 94.2% of Enterococcal isolates were susceptible to Nitrofurantoin, the result being consistent with the several other studies done by Ponnammal et al[4] and Sanjay et al[29].

Conclusion

Nitrofurantoin should be used in uncomplicated lower urinary tract for having narrow tissue distribution, negligible serum concentration, narrow spectrum of activity, bactericidal activity against E.coli. The treatment and prophylaxis of bacterial UTI with Nitrofurantoin has gained importance during emergence of other newer Microbiol resistance due to its safety profile and resistance to this antibiotic remained virtually unchanged since its discovery. Low toxicity of the drug is also made us to choose it over any other drug during empirical or prior instrumentation.

References

1. N. Subathra, R. Radhika. An analysis on antimicrobial susceptibility pattern of uropathogens with special emphasis on nitrofurantoin in the treatment of uncomplicated lower UTI. Indian Journal of Basic and Applied Medical Research; September 2016:5(4):139-46.
2. P. Komp Lindgren, O. Klockars, C. Malmberg and O. Cars. Pharmacodynamic studies of nitrofurantoin against common uropathogens. J Antimicrob Chemother 2015; 70: 1076–82.
3. Angela Huttner, Els M. Verhaegh, Stephan Harbarth et al. Nitrofurantoin revisited: a systematic review and meta-analysis of controlled trials. J Antimicrob Chemother 2015; 70: 2456–64.
4. P. Ponnammal, Selvi. A Study on the Current Trend in Susceptibility Pattern of Uropathogens to Nitrofurantoin in a Tertiary Care Hospital.OSR Journal of Dental and Medical Sciences (IOSR JDMS), 2019; 18(3);48-52.
5. Saurabh Jain, Saurabh G. Agarwal, Sanyogita Jain et al. Study of Nitrofurantoin Susceptibility in Bacterial Isolates from Patient of Urinary Tract Infection Attending Tertiary Care Centre. Int. J. Curr. Microbiol. App. Sci. 2017 6(6): 2611-5.
6. Cortes Penfield NW, Trautner BW. 2016. Nitrofurantoin, an excellent empiric choice for outpatient cystitis. Antimicrob Agents Chemother 2016; 60:7535; 01715-16.
7. Shakti L, Veeraraghavan B. Advantages and limitations of nitrofurantoin in multidrug resistant Indian scenario. Indian J Med Microbiol 2015;33 :477-81.
8. Nitrofurantoin-clinical relevance in uncomplicated urinary tract infections. Med Monatsschr Pharm. 2014; 37(7):242-8.
9. Aliaga L, Moreno M, Aomar I, et al. Treatment of acute uncomplicated cystitis, a clinical review. Int J Fam Commun Med. 2017;1(2):33−9.
10. Squadrito FJ, del Portal D. Nitrofurantoin. [Updated 2020 Jul 10]. StatPearls Publishing; 2020 Jan.
11. Munoz-Davila MJ. Role of Old Antibiotics in the Era of Antibiotic Resistance. Highlighted Nitrofurantoin for the Treatment of Lower Urinary Tract Infections. Antibiotics (Basel). 2014;3(1):39-48.
12. Harith Kumar, Varsha A.singh, Shavi Nagpal et al. Isolation of uropathogens and their antibiotic susceptibility pattern at a tertiary care hospital in Northern India. Asian Journal of Pharmaceutical and Clinical Research, 2019; 12(12); 84-6.
13. Shalini, Joshi MC, Rashid MK, Joshi HS. Study of Antibiotic Sensitivity Pattern in Urinary Tract Infection at a Tertiary Hospital. Nat J Integr Res Med 2011; 2 (3):43-6.
14. 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):39-44.
15. Neelima A, Kiranmai. Nitrofurantoin susceptibility of ESBL gram negative isolates from patients with urinary tract infection (UTI) in a rural teaching hospital of Telangana. Trop J Path Micro 2016;2(3):159-63.
16. Prasada S, Bhat A, Bhat S, Shenoy Mulki S, Tulasidas S. Changing antibiotic susceptibility pattern in uropathogenic Escherichia coli over a period of 5 years in a tertiary care center. Infect Drug Resist. 2019;12:1439-43.
17. Ashis Kumar Saha. Pattern of antimicrobial susceptibility of Klebsiella pneumoniae isolated from urinary samples in urinary tract infection in a tertiary care hospital, Kishanganj, Bihar, 5 years' experience. International Journal of Contemporary Medical Research 2019;6(12):L25-L28
18. Varghese A, George S, Gopalakrishnan R, et al. Antibiotic susceptibility pattern of Klebsiella pneumoniae isolated from cases of urinary tract infection in a tertiary care setup. J. Evolution Med. Dent. Sci. 2016;5(29): 1470-4,
19. Bajpai T, Pandey M, Varma M, Bhatambare GS. Prevalence of extended spectrum beta-lactamase producing uropathogens and their antibiotic resistance profile in patients visiting a tertiary care hospital in central India: Implications on empiric therapy. Indian J Pathol Microbiol. 2014;57(3):407-12.

20. Eshwarappa M, Dosegowda R, Aprameya IV, Khan MW, Kumar PS, Kempegowda P. Clinico-microbiological profile of urinary tract infection in south India. Indian J Nephrol. 2011 ;21(1):30-6.
21. Gayathri Gururajan, Kathireshan A. Kaliyaperumal et al. Prevalence of Extended Spectrum Beta Lactamases in Uropathogenic Escherichia coli and Klebsiella Species in a Chennai Suburban Tertiary Care Hospital and its Antibiogram Pattern. Research Journal of Microbiology, 6: 796-804.
22. Mehrishi P, Faujdar SS, Kumar S, Solanki S, Sharma A. Antibiotic susceptibility profile of uropathogens in rural population of Himachal Pradesh, India: Where We are heading?. Biomed Biotechnol Res J 2019;3:171-5
23. Bishara J, Livne G, Ashkenazi S, Levy I, Pitlik S, Ofir O, Lev B, Samra Z. Antibacterial susceptibility of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae and Escherichia coli. Isr Med Assoc J. 2005;7(5):298-301.
24. Priyadharshana U, Piyasiri LB, Wijesinghe C. Prevalence, antibiotic sensitivity pattern and genetic analysis of extended spectrum beta lactamase producing Escherichia coli and Klebsiella spp among patients with community acquired urinary tract infection in Galle district, Sri Lanka. Ceylon Med J. 2019 ;64(4):140-5.
25. Sunite A. Ganju, Aneeta Kumari, Kiran Mokta et al. Nitrofurantoin Revisited: Susceptibility pattern of uropathogenic Escherichia coli in a tertiary care hospital, Shimla, India. World Journal of Pharmacy and Pharmaceutical Sciences 2016; 5(3): 1466-73.
26. Dusi Ratna Harika et al. Nitrofurantoin as an option in the treatment of Extended Spectrum Beta Lactamase Producing Escherichia Coli and Klebsiella Pneumoniae in Uncomplicated UTI JMSCR 2019; 07(06):848-54.
27. Tulara NK. Nitrofurantoin and Fosfomycin for Extended Spectrum Beta-lactamases Producing Escherichia coli and Klebsiella pneumoniae. J Glob Infect Dis. 2018;10(1):19-21.
28. N. AkshayaThrinetrapriya et al. Antibiotic Susceptibility Profile of Staphylococci Isolated from Clinical Samples J. Pharm. Sci. & Res. 2019;11(8): 3011-15
29. Sanjay WM, Ghorpade MV, Shivali VG et al. A study of vancomycin resistant Enterococci isolated from urinary tract infections. Int J of Pharm and P'ceutical Sci 2015; 7(5):337-9.

Conflict of Interest: Nil
Source of support: Nil