Global Journal of Medicine & Public Health

Analysis of nitrofurantoin sensitivity in multi drug resistant gram negative bacilli causing UTI in a teaching hospital – A cost effective option

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ABSTRACT

Background

Antimicrobial resistance is a growing concern globally, leading to more difficult-to-treat infections and higher mortality rates. Urinary tract infections (UTI) are one of the major indications for prescribing antibiotics, with multidrug resistant Gram-negative bacilli being responsible for a growing proportion of community-acquired uncomplicated UTIs. Our goal is to determine nitrofurantoin, a less costly effective substitute in treating uncomplicated UTI caused by multidrug resistant gram negative bacilli.

Materials and method

The study included patients with UTI symptoms who have visited the Outpatient and Inpatient departments of our Institute. Sample collection and culture procedures involved midstream clean capture fresh urine samples, semi-quantitative culture on Blood agar, MacConkey, and CLED agar medium. Primary identification was made using colony morphology and Gram staining, while final identification was done using standard biochemical reactions. In vitro antimicrobial susceptibility testing was done on Mueller-Hinton agar using the Kirby-Bauer disc diffusion method.

Result

508 gram-negative UTI isolates identified among 2801 suspected patients; Escherichia coli (50.98%), Klebsiella spp(28.74%), Pseudomonas spp(9.25%), are the predominant isolates. Among the isolates Imipenem (74.61%) was found to be most effective followed by Ceftazidime clavulanic acid (73.17%) and Amikacin 70%. Nitrofurantoin was sensitive to 55.50% gram negative isolates, particularly in MDR isolates. ESBL was found to be 57.09 % (n=290) among the gram negative isolates. Nitrofurantoin is found to be sensitive to (n=152) 52.41% isolates of ESBL producer's. Among non ESBL producers nitrofurantoin was sensitive to (n =158)54.48% of the isolates.

Conclusion

In this trend of multidrug-resistant bacteria, particularly in cases of enteric bacteria, the significance of nitrofurantoin is crucial. Nitrofurantoin remains a cost effective option in treating uncomplicated urinary tract infections.

Keywords: UTI, MDR, ESBL, Antimicrobial resistance, Nitrofurantoin

GJMEDPH 2023; Vol. 12, issue 6 | OPEN ACCESS

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Conflict of Interest—none | Funding—none

INTRODUCTION

Antimicrobial resistance is flourishing globally, resulting in infections which are harder to treat and are connected with higher mortality, morbidity and increased treatment cost (1).Urinary tract infections (UTI) outcome in 8 million physician visits per year worldwide; stay one of the top current indications for prescribing an antibiotic. Multidrug resistant Gram-negative bacilli (MDR GNB) are responsible for rising proportion of community-acquired uncomplicated UTI. As a result, empiric therapy more doubtless to fail, resulting in increased numbers of patients with uncomplicated UTI needing hospitalization for intravenous antibiotics as a consequence of non-availability of oral treatment options (2).Few new antibiotics on horizon & those recently approved are mostly for intravenous use, so older 'forgotten' drugs are re-explored for treatment of cystitis (3). Despite being an older drug, nitrofurantoin can be utilized during pregnancy, especially in the first few trimesters (4). Nitrofurantoin an old antibiotic which share several essential properties such as elevated concentrations in the urinary tract, a minimal effect on gastrointestinal flora and a low propensity for resistance (2). The major strength of nitrofurantoin is its action at multiple sites and levels. This includes inhibition of bacterial enzymes involved in carbohydrate synthesis and in higher concentration DNA, RNA, and total protein synthesis by the nonspecific attack on bacterial ribosomal proteins (5). Overall, nitrofurantoin is a relatively safe medication. Based on all therapy courses, collective experience after more than three decades of intensive use demonstrates a very low reported side-effect incidence of less than 0.001 %(6).Several studies noted proliferation of drug resistant GNB, but few examined antimicrobial activity of nitrofurantoin against MDR isolates (7).There is paucity of published data - current in vitro susceptibility profiles for MDR urine isolates. UTIs - commonly treated, outpatient setting with oral agents, knowledge of susceptibility patterns in MDR urinary pathogens, critical to guide empirical treatment (8). It is necessary to have knowledge of the local bacterial etiology and susceptibility patterns in order to track any change that may have happened over time and provide updated recommendations for the best empirical treatment of UTI.

Objective

The purpose of our study is to determine the efficacy of nitrofurantoin as a less expensive alternative for treating uncomplicated urinary tract infections in multidrug resistant GNB.

Materials and methods

This research was a prospective cross-sectional study. The study was carried out between May 2022 and May 2023 over a one-year period. Approval for conducting the study was taken from institutional ethics committee .The study includes patients who had UTI symptoms and visited the Outpatient and Inpatient departments. Inclusion criteria are all consecutive Gram negative urinary pathogens isolated in last one year. Exclusion criteria are all Gram positive urinary pathogens isolated and repetitive samples from the same patient during the study period.

Sample collection and Culture procedure:

Midstream clean capture fresh samples were obtained using aseptic techniques and placed in a sterile, wide-mouth, leak-proof container with a label. For the primary isolation of organisms, a semi-quantitative approach was used, utilizing a calibrated loop with a diameter of 4 mm and delivering 0.01 ml of urine. After that, samples were grown overnight at 37°C on Blood agar, MacConkey and CLED agar medium. Samples were considered to have significant bacteriuria when the colony count was $\geq 10^5$cfu/ml. (9). The primary identification was made with basic microbiological methods using colony morphology and Gram staining. The final identification of the organism and antibiotic sensitivity pattern were done using standard biochemical reactions.In vitro antimicrobial susceptibility testing was carried out on Mueller-Hinton agar using the Kirby-Bauer disc diffusion method in accordance with the standard operating procedures. In sterile normal saline, the test organism was suspended, and the turbidity was set to 0.5 McFarland standards. Mueller Hinton agar plates were evenly seeded with the test organism. Before applying antibiotic-impregnated discs, the plates were allowed to dry for 10 minutes. The plates were incubated for 16–18 hours at 37 °C. Clear zones surrounding the antibiotic discs were measured with a ruler and recorded in millimeters after incubation. (10)

ISSN# 2277-9604

ESBL detection

For testing ESBL in isolates, Mueller Hinton agar (MHA) was inoculated with standard inoculum (0.5 McFarland) of the test isolate. It was tested for cefotaxime (30 µg) and ceftazidime (30 µg) against cefotaxime - clavulanic acid (30 µg/10 µg) and ceftazidime - clavulanic acid (30 µg/10 µg) discs. A ≥5 mm increase in zone diameter for either antimicrobial agent tested in combination with clavulanic acid vs the zone diameter of the agent tested alone is considered ESBL producers. (11).

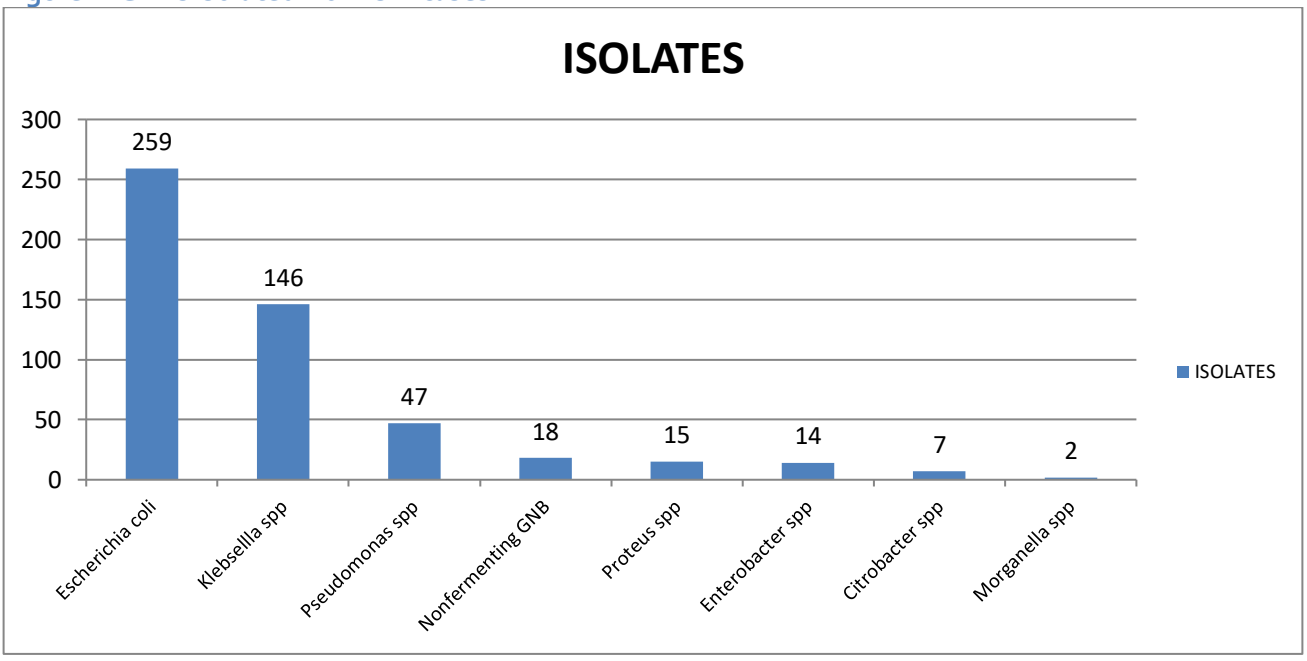
Statistical Analysis

Data was analyzed and effectiveness of nitrofurantoin over other drugs was calculated using Chi-square test. A p-value <0.05 was considered to be statistically significant.

Results

508 gram-negative isolates were isolated among 2801 suspected UTI patients. Escherichia coli 259(50.98%) was the main isolate followed by Klebsella spp 146(28.74%), Pseudomonas spp 47(9.25%), non-fermenting gram negative bacilli 18(3.54%), Proteus spp 15(2.95%), Enterobacter spp 14(2.76%), Citrobacter spp 7(1.38%), Morgenella spp 2 (0.39%) (Figure 1).

Figure 1: GNBs isolated from UTI cases



Among the total 508 isolates Imipenem(74.61%) was found to be most effective followed by Ceftazidime clavulanic acid (73.17%), Polymyxin B (70.59%) ,Amikacin (70%), , Piperacillin /Tazobactam (63.19%), Cefotaxime clavulanic acid (60.80%), Gentamicin (58.5%), Norfloxacin (52.95%), Cefepime (50.98%), Ciprofloxacin (48.22%), Ceftazidime (43.7%), Amoxicillin clavulanic acid (45.27%), Cefotaxime (41.8%), Tetracycline (40.16%), Cephalexin (28.54%), Cefuroxime (23.62%) of the isolates. It turns out that 55.51% of the gram-negative isolates were susceptible to nitrofurantoin.

ISSN# 2277-9604

Table 1 Antibiotic sensitivity pattern in isolated gram negative bacilli causing Urinary Tract Infection (total isolates = 508)

Organism	Sensitivity pattern	Escherichia coli	Klebsiella spp	Proteus spp	Pseudomon	Enterobacter sp	Non - Fermenter GNB	Citrobacter sp	Morganella sp	%	P-value
amoxicillin - clavulanic acid	S	136	59	5	9	4	12	4	1	45	0.005*
	I	3	4	0	0	1	0	1	0	2	
	R	120	83	10	38	9	6	2	1	53	
cephalexin	S	84	31	5	12	5	5	2	1	28.54	0.001*
	I	1	1	0	0	0	0	1	0	0.59	
	R	174	114	10	35	9	13	4	1	70.86	
cefuroxime	S	61	32	5	10	5	4	3	0	23.62	0.001*
	I	1	1	0	0	0	0	0	0	0.39	
	R	197	113	10	37	9	14	4	2	75.98	
cefotaxime	S	100	65	0	0	8	0	5	0	41.98	0.010*
	I	0	0	0	0	0	0	0	0	0	
	R	159	79	0	0	6	0	2	0	58.01	
ceftazidime	S	0	0	7	18	0	12	0	1	46.34	0.060
	I	0	0	0	0	0	0	0	0	0	
	R	0	0	8	29	0	6	0	1	53.65	
amikacin	S	183	101	11	32	8	13	6	2	70.07	0.001*
	I	11	3	1	1	1	1	1	0	3.74	
	R	65	42	3	14	5	4	0	0	26.18	
gentamicin	S	140	89	11	29	8	15	4	1	58.46	0.008*
	I	12	4	1	2	1	0	1	0	4.13	
	R	107	53	3	16	5	3	2	1	37.4	
ciprofloxacin	S	110	73	9	28	9	11	4	1	48.22	0.006*
	I	2	5	1	0	0	0	0	0	1.57	
	R	147	68	5	19	5	7	3	1	50.19	
pipercillin tazobactam	S	165	91	11	26	8	12	6	2	63.18	0.001*
	I	2	4	1	0	0	0	1	0	1.57	
	R	92	51	3	21	6	6	0	0	35.23	
norfloxacin	S	132	74	8	28	8	13	5	1	52.95	0.006*
	I	3	1	1	0	0	0	0	0	0.98	
	R	124	71	6	19	6	5	2	1	46.06	
	S	199	110	12	32	9	9	6	2	74.6	

ISSN# 2277-9604

imipenam	I	5	2	0	1	0	0	0	0	1.57	0.006*
	R	55	34	3	14	5	9	1	0	23.81	
cefotaxime clavulanic acid	S	151	94	0	0	8	0	6	0	61.08	0.039*
	I	5	0	0	0	0	0	1	0	1.41	
	R	101	52	0	0	6	0	0	0	37.5	
ceftazidime clavulanic acid	S	0	0	12	33	0	13	0	2	73.17	0.082
	I	0	0	0	0	0	0	0	0	0	
	R	0	0	3	14	0	5	0	0	2.68	
cefipime	S	126	76	7	27	8	8	5	2	50.98	0.007*
	I	0	2	1	1	0	0	0	0	0.78	
	R	133	68	7	19	6	10	2	0	48.22	
tetracycline	S	95	66	5	16	8	11	2	1	40.15	0.000*
	I	1	2	1	0	0	0	0	0	0.78	
	R	163	78	9	31	6	7	5	1	59.05	
polymyxin b	S	183	105	0	37	4	12	6	1	68.5	0.000*
	I	0	0	0	0	0	0	0	0	0	
	R	76	41	15	10	10	6	1	1	31.49	
nitrofurantoin	S	171	72	5	14	8	6	5	1	55.51	0.001*
	I	5	3	0	1	0	0	0	0	1.77	
	R	83	71	10	32	6	12	2	1	42.71	
total isolates		**259**	**146**	**15**	**47**	**14**	**18**	**7**	**2**	**508**	
*95% significance Level											

DISCUSSION

In the present study Escherichia coli was the predominant isolate followed by Klebsiella spp, Pseudomonas spp 47(9.25%), non-fermenting gram negative bacilli 18(3.54%), Proteus spp 15(2.95%), Enterobacter spp 14(2.76%), Citrobacter spp 7(1.38%), Morgenella spp 2 (0.39%). Nitrofurantoin is found to be sensitive in 66% of Escherichia coli and 49.3% in Klebsiella pneumoniae .The most effective antibiotic was found to be Imipenem (74.61%), which was followed by Ceftazidime clavulanic acid (73.17%), Amikacin (70%), Piperacillin/Tazobactam (63.19%), Cefotaxime/ clavulanic acid (60.80%), Gentamicin (58.5%), Norfloxacin (52.95%), Cefepime (50.98%), Ciprofloxacin (48.22%), Ceftazidime (43.7%), Amoxicillin clavulanic acid (45.27%), Cefotaxime (41.8%), Tetracycline (40.16%), Cephalexin (28.54%), and Cefuroxime (23.62%) of the isolates. The effectiveness of nitrofurantoin over other drugs was calculated using Chi-square test and p-value was found to be statistically significant (<0.05) except for Ceftazidime and Ceftazidime/Clavulanic acid. ESBL was found to be 57.09 % (n=290) among the gram negative isolates. Nitrofurantoin is found to be sensitive to (n=152) 52.41% isolates of ESBL producer's. Among non ESBL producers nitrofurantoin was sensitive to (n =158)54.48% of the isolates. Nitrofurantoin was found to be sensitive to 55.51 % of the gram negative isolates. It was found to be considerable sensitive among the MDR isolates. It was the only oral medication that had been shown to be the most effective in treating GNB isolated from UTI patients. However, due to the rise in antibiotic resistance, drugs like fluoroquinolones, which were once widely used to treat mild UTIs, appear to have lost their efficacy. As a result, nitrofurantoin is a good substitute because there are fewer instances of drug resistance.

Figure 2 ESBL in GNB Isolates

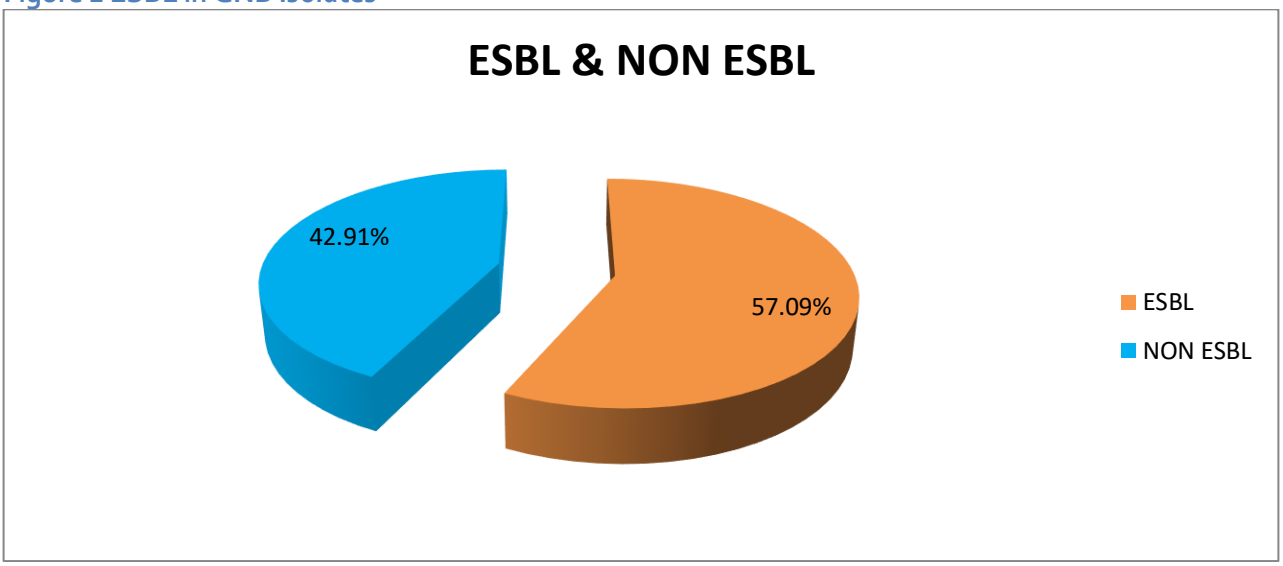
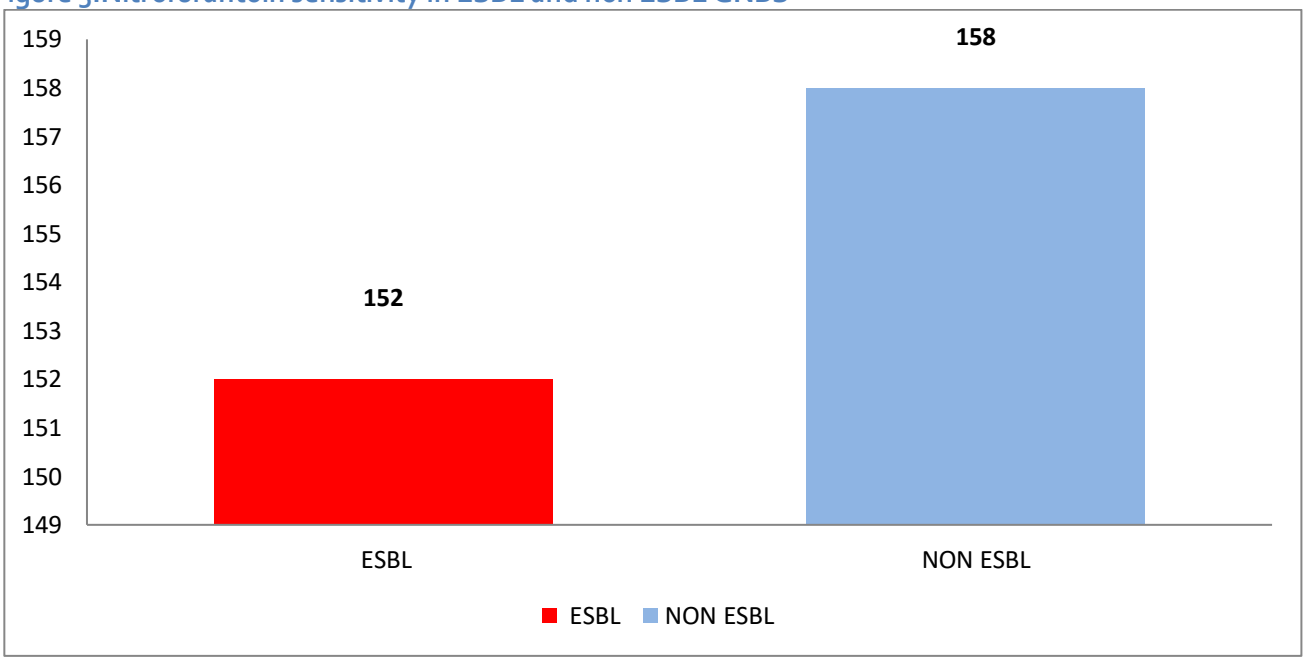


Figure 3:Nitrofurantoin sensitivity in ESBL and non ESBL GNBS



Goyal et al,2022 study Escherichia coli (22.50%) was the predominant isolate followed by Klebsiella pneumoniae followed by 56 (14.28%).Gram negative isolates showed maximum sensitivity to nitrofurantoin (88%) followed by respectively by amikacin (73%) and piperacillin/tazobactum (54%)(12). According to Bradley J Gardiner et al, 2019 uncomplicated urinary tract infection is one of the most common indications for antibiotic use in the community. However, the Gram-negative organisms that can cause the infection are becoming more resistant to antibiotics.Many multidrug resistant organisms retain susceptibility to old antibiotic nitrofurantoin(2) .Sanchez et al, 2014 found that Nitrofurantoin demonstrated consistent antimicrobial activity even against highly resistant MDR isolates. Among E.coli isolates, that demonstrated resistance to three, four & five agents, resistant to nitrofurantoin was observed in only 2.1%, 7.5% & 24.1% of the isolates respectively

ISSN# 2277-9604

(8).Mahmood et al, 2012 observed Nitrofurantoin resistance of E.coli, Klebsiella & Enterococcus isolates was only 13%, 9% & 6-17% respectively (13). In Garima Gautam et al; study 2021, the overall rate of resistance of Nitrofurantoin was 20.17% among various gram-negative uropathogens and 9.01% was intermediate sensitive according to CLSI 2019 guidelines (14). The results of study by Tasbakan et al (2012) suggest that Nitrofurantoin as treatment of ESBL-producing E. coli in Lower urinary tract infections(15).Some studies have also reported high levels of nitrofurantoin resistance rates of 24.4%(16).The limitation of this study was mechanism of drug resistances was not studied using molecular methods.

CONCLUSION

A holistic approach is necessary to address the complicated issue of AMR and "preserve the miracle" of antibiotics over the coming decades, and while re-examining older, "forgotten," medications like nitrofurantoin is indeed a valuable tactic. Similar to what we've observed historically with almost all other antibiotics, resistance is expected to develop as usage rises, either through the spread of pre-existing resistance mechanisms or the emergence of new ones.More patients will probably need microbiological testing before starting antibiotics due to the increasing failure of standard empirical therapy for urinary tract infections. This is necessary for both individualized patient management and wide-ranging epidemiological surveillance to support guideline recommendations. The significance of nitrofurantoin is extremely important in this evolving trend of microorganisms combined with multidrug-resistant bacteria, particularly in cases of enteric bacteria. Nitrofurantoin has shown to be effective in treating uncomplicated urinary tract infections.

ISSN# 2277-9604

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