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Research Article

In-vitro antibacterial activity of Fosfomycin and Nitrofurantoin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* against clinical isolates collected from Indian tertiary care hospitals

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Abstract

The remarkable increase in resistance to currently available antibiotics to Gram-negative pathogens particularly multidrug resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* This has resulted in increasing use of older under evaluated antibiotics such as fosfomycin, nitrofurantoin, and Trimethoprime-Sulfamethoxazole for the treatment of infections caused by MDR pathogens. However, limited *in-vitro* pharmacodynamic data for fosfomycin and nitrofurantoin against *Pseudomonas* Spp., and *Acinetobacter* Spp., is available in literature. The current study demonstrates *in-vitro* activities of fosfomycin and nitrofurantoin against *Pseudomonas* and *Acinetobacter* pathogens (425 *Pseudomonas* Spp., and 352 *Acinetobacter* Spp., Total: 777 Strains), isolated from Indian tertiary care hospitals. The minimum inhibitory concentration ($MIC_{50/90}$) of fosfomycin and nitrofurantoin along with comparator antibiotics were determined using Clinical and Laboratory Standards Institute recommended agar dilution method. Fosfomycin demonstrated excellent *in-vitro* activity against *Pseudomonas* while in nitrofurantoin demonstrated poor activity against *Pseudomonas* Spp.,. Fosfomycin and nitrofurantoin did not show promising activities against *Acinetobacter* Spp.,. By applying *E. coli* breakpoints, the susceptibility rates of fosfomycin for *Pseudomonas* Spp., and *Acinetobacter* Spp., were 72.4%, and 14.8%, respectively. By applying respective breakpoints, the susceptibility rates of comparator drugs, including imipenem and meropenem, were lower than fosfomycin. Susceptibility rate of nitrofurantoin for *Pseudomonas* Spp., and *Acinetobacter* Spp., was <1.2% suggesting its poor activity. The susceptibility rate of fosfomycin was > 70% for *Pseudomonas* isolates, including strains expressing carbapenemases is encouraging finding and supports its potential use. Nitrofurantoin did not show activity against both the Spp., with susceptibility rates <1.2%.

Keywords: Fosfomycin, Nitrofurantoin Gram-negative, Multi Drug Resistant, *A. baumannii* and *P. aeruginosa.*

INTRODUCTION

The dearth in the discovery and development of newer antibiotics and rapid increase in resistance to currently available frontline antibiotics has raised serious concerns in scientific community suggesting return of pre-antibiotic era [1]. This grave situation is particularly vital for the Gram-negative pathogens such as *Pseudomonas* Spp., and *Acinetobacter* Spp. The availability of newer antibiotics is not visible in near future and rapid resistance to available resistance mechanisms to currently antibiotics is of main concern [2, 3]. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* pathogens are involved in a broad range of nosocomial and community-acquired infections, with multidrug resistant (MDR). Both the pathogens are among top six pathogens (ESKAPE) identified by the Infectious Diseases Society of America (IDSA) [4, 5, 6]. Due to the scarcity of newer antibiotics in the drug development pipeline, clinicians have been forced to reconsider older underutilized antibiotic such as fosfomycin, Trimethoprime-Sulfamethoxazole, mecillinam etc. for the treatment of infections caused by MDR Gram-negative organisms [7, 8, 9]. Among these older antibiotics, fosfomycin is gaining more attention due to its promising activity and lower resistance rates against these pathogens (especially *Pseudomonas*) either standalone or in combination with other antibiotics for the treatment of various infections caused by both MDR Gram-negative and Gram-positive organisms [10,11,12].

Fosfomycin is available in both oral (fosfomycin trometamol and fosfomycin calcium) and intravenous formulations (fosfomycin disodium). [13] while nitrofurantoin is available as oral formulation. Both the drugs are recomonded for the treatment of uncomplicated urinary tract infections (UTIs). Oral fosfomycin tromethamine (3g Single dose) is currently indicated for the treatment of uncomplicated urinary tract infections (UTIs) caused by *E. coli* and *Enterococcus faecalis* in women [14]. However, due to the rapid emergence and spread of MDR Gram-negative pathogens, renewed interest in use of the intravenous fosfomycin to treat infections other than UTIs is growing [15]. It is identified as one of the few antibiotics which possess greatest promise for the management of infections caused by MDR Gram-negative pathogens [15]. Fosfomycin and

nitrofurantoin were developed at the time where principles of modern drug development were not known. During that time, antibiotic development occurred on a trial and error basis rather than the current principles of PK/PD.[16]. Due to this, substantial knowledge gap in the area of pharmacokinetic and pharmacodynamic properties exists for both the drugs.

The purpose of this study is to evaluate the *in-vitro* antibacterial activity (MICs) of fosfomycin and nitrofurantoin against *P. aeruginosa* and *A. baumannii*, clinical isolates to understand the potential utility of both the drugs in management of MDR infections caused by these pathogens.

MATERIALS AND METHODS

Clinical isolates

The current study utilized 777 clinical isolates comprising of *Pseudomonas* Spp., (N=425), and *Acinetobacter* Spp., (N= 352). These clinical isolates were part of Wockhardt bacterial strain repository. These pathogens were collected from sixteen tertiary care hospitals across India located in geographically distinct states of India. One isolate per patient was collected from patients who were hospitalised for minimum of 48h in the hospital in one of the surgery, medicines, burns, ICUs, transplantation units and gynaecology departments. Bacterial species were confirmed by using MALDI-TOF-based VITEKVR MS (bioMe´rieux). Before MIC determination, bacterial cultures were revived and passaged twice in tryptone soya agar (HiMedia, India) medium.

Susceptibility testing and Interpretation of susceptibility results

Minimum inhibitory concentrations (MICs) of fosfomycin (Sigma, USA) and nitrofurantoin (Sigma, USA) were undertaken by employing agar dilution method by following Clinical and Laboratory Standards Institute (CLSI, M0&, A9) guidelines [17]. MIC of fosfomycin was estimated by supplementing 25 mg/L of glucose-6-phosphate (Sigma, USA) in Mueller Hinton agar. Likewise, clinical isolates were tested for susceptibility to other antibiotics such as Piperacillin-Tazobactam (PIP-TAZ), Ceftazidime-Avibactam (CAZ-AVI), Trimethoprime-Sulfamethoxazole (SXT), Ciprofloxacin, Imipenem (IME) and Meropenem (MEM) by agar dilution MIC method in the current study. Marketed formulations of comparator drugs were used. Antibiotics were recovered from commercial formulations, and purity was determined by HPLC analysis at the Wockhardt research centre. The lowest concentration which showed ≥80% reduction in growth compared to control (no drug) was considered as MIC. As per CLSI guidance (CLSI, M100, 29E) [18], the phenotypic resistance mechanisms such as the presence of β-lactamases (ESBL, Class C and MBL/OXA-48/181) were identified by employing marker antibiotic combinations such as ceftazidime + clavulanic acid (for ESBLs) and carbapenem + EDTA (for MBLs).

RESULTS

A total of 777 Gram-negative clinical isolates comprising of *Pseudomonas* Spp. [N=425] and *Acinetobacter* Spp., [N=352] collected during January 2016 to June 2018 from 16 Indian tertiary care hospitals were subjected to MIC determination. The number of isolates inhibited by fosfomycin [MIC (µg/mL)] is presented in Table 1. The MICs ranged from 2 - ≥512 µg/mL, for fosfomycin against *Pseudomonas* Spp. and *Acinetobacter* Spp.,. The $MIC_{50/90}$ of fosfomycin for *Pseudomonas* Spp. was observed to be 64/128 mg/L, whereas the $MIC_{50/90}$ of fosfomycin against *Acinetobacter* Spp., was 128/512 mg/L (Refer Table 1). Applying CLSI susceptibility breakpoints (*E.coli*), *Pseudomonas* Spp. showed moderate susceptibility rates (72.7%) while susceptibility rates of *Pseudomonas* Spp., for PIP-TAZ, CAZ-AVI, ciprofloxacin, Imipenem (IPM), and MEM were 51.8, 58.4, 40.2, 53.4, and 52.9%, respectively (Refer Table 2). In case of *Acinetobacter* Spp., fosfomycin along with comparator antibiotics including PIP-TAZ, SXT, ciprofloxacin, IPM and MEM showed lower susceptibility rates (< 22.4%) (Refer Table 2). Thus, taking into account all the *Enterobacterales* including *Pseudomonas* Spp., evaluated, fosfomycin retained better activity as compared to PIP-TAZ, CAZ-AVI, SXT, ciprofloxacin, IPM, and MEM. Such kind of activity of fosfomycin was not noted against *Acinetobacter* spp.

The susceptibility of *Pseudomonas* Spp., expressing various ESBL, ESBL and class C as well as MBL including OXA-48/181 enzymes to fosfomycin and other antibiotics were also analysed. Irrespective of *Pseudomonas* isolates expressing ESBL, ESBL and class C as well as MBL including OXA-48/181, fosfomycin showed promising susceptibility in the range of 70 to 80%. Against CAZ-S and ESBL producing strains, fosfomycin ($MIC_{50/90}$: 64/128µg/mL) susceptibility rate was in the range on 70.4 to 74.3% which was moderate in comparison with comparator drugs (87.4 to 95.1%). However fosfomycin demonstrated superior activity (Susceptibility rates: 72.7 to 80%) against *Pseudomonas* strains producing class C and MBL, or OXA-48/181like enzymes. The susceptibility rates for comparator drugs PIP-TAZ, ciprofloxacin and carbapenems (IPM & MEM) was in the range of 13.6 to 61.4% for class C β-lactamase producing strains while for same drugs it was less than 7.5% against MBL/OXA-48/181 producing strains (Refer Table 3).

The susceptibility of *Acinetobacter* Spp., expressing various ESBL, ESBL and class C as well as MBL including OXA-48/181 enzymes to fosfomycin and other antibiotics were also analysed. Irrespective of *Acinetobacter* isolates identified as CAZ-Sensitive or MBL including OXA-48/181 producing, fosfomycin showed susceptibility in the range of 11.4 and 24.4%. The susceptibility rates for comparator antibiotic for CAZ-S strains were superior (> 87%) than fosfomycin while against MBL-OXA-48/181 producers it was even poor compared to fosfomycin (Refer Table 4).

The *in-vitro* activity of nitrofurantoin was also evaluated against *Pseudomonas* spp. and *Acinetobacter* Spp. The number of isolates inhibited by nitrofurantoin [MIC (µg/mL)] is presented in Table 1. The MICs ranged from 4/8 - ≥512 µg/mL, for nitrofurantoin against *Pseudomonas* Spp. and *Acinetobacter* Spp.,.The high $MIC_{50/90}$ values for nitrofurantoin against *Pseudomonas* Spp. and *Acinetobacter* Spp., suggest its weakest activity (Table 1 & 2). The $MIC_{50/90}$ value of nitrofurantoin was 256µg/mL for both *Pseudomonas* Spp. and *Acinetobacter* Spp., based on the CLSI breakpoint, >97.4% of *Pseudomonas* Spp. and *Acinetobacter* Spp., were resistant to nitrofurantoin. Additional analyses of nitrofurantoin activity pertaining to various β-lactamases expressed also demonstrated higher resistant rates for strains expressing various β-lactamase. Overall, fosfomycin demonstrated better i*n-vitro* activity against *Pseudomonas* Spp. compared to comparator antibiotics including PIP/TAZ, CAZ-AVI, quinolone (ciprofloxacin) and carbapenems (IPM & MEM) while *in-vitro* activity against *Acinetobacter* Spp., was not evident. The susceptibility rates for nitrofurantoin were < 1.2% for both the Spp., suggesting its poor activity against *Pseudomonas* Spp., and *Acinetobacter* Spp.

Table 1: Summary of the *in-vitro* activity of fosfomycin and nitrofurantoin against *Pseudomonas* Spp., and *Acinetobacter* Spp.

No. of isolates inhibited by fosfomycin and nitrofurantoin [MIC (µg/mL)]										MIC_{50} (mg/L)	MIC_{75} (mg/L)	MIC_{90} (mg/L)	Susceptibility Rates (%)		
Fosfomycin	2	4	8	16	32	64	128	256	512				S	I	R
Pseudomonas Strains (n=425)	3	7	14	18	65	202	78	20	18	64	128	128	72.7	18.4	8.9
Acinetobacter Strains (n=352)	1		1	1	4	45	198	68	34	128	256	512	14.8	56.3	29.0
Nitrofurantoin															
Pseudomonas Strains (n=425)		4			1	2	28	355	35	256	256	256	1.2	0.5	98.4
Acinetobacter Strains (n=352)			2		2	5	18	305	20	256	256	256	1.1	1.4	97.4

MIC_{50}, MIC_{75}, MIC_{90}: Concentration inhibiting 50%, 75% and 90 of the isolates, respectively; MICs are reported in µg/mL

Table 2: *In-vitro* antibacterial activities of fosfomycin, nitrofurantoin and comparator antibiotic against *Pseudomonas* Spp., and *Acinetobacter* Spp.

Pseudomonas Strains (n=425)	Antibacterial agent	MIC (mg/L) Range	MIC_{50} (mg/L)	MIC_{75} (mg/L)	MIC_{90} (mg/L)	Susceptibility (CLSI)		
						% S	% I	% R
	Fosfomycin	2 - 512	64	128	128	72.7	18.4	8.9
	Nitrofurantoin	4 - 512	256	256	256	1.2	0.5	98.4
	PIP / TAZ	0.25 - 512	16	128	512	51.8	22.1	37.2
	CAZ-AVI	0.015 - 128	8	64	128	58.4	5.4	40.0
	SXT					NA	NA	NA
	Ciprofloxacin	0.06 - 128	16	64	64	40.2	5.2	54.6
	IPM	0.015 - 512	2	64	512	53.4	3.3	43.3
	MEM	0.06 - 512	2	128	512	52.9	3.5	43.5
Acinetobacter Strains (n=352)	Antibacterial agent	MIC (mg/L) Range	MIC_{50} (mg/L)	MIC_{75} (mg/L)	MIC_{90} (mg/L)	Susceptibility (CLSI)		
						% S	% I	% R
	Fosfomycin	2 - 512	128	256	512	14.8	56.3	29.0
	Nitrofurantoin	8 - 512	256	256	256	1.1	1.4	97.4
	PIP / TAZ	0.25 - 512	512	512	512	14.5	6.3	82.4
	CAZ-AVI					NA	NA	NA
	SXT	0.03 - 512	64	128	256	22.4	-	77.6
	Ciprofloxacin	0.12 - 128	64	64	64	12.8	0.6	86.6
	IPM	0.03 - 512	32	64	256	14.8	0.6	84.7
	MEM	0.06 - 512	32	64	128	15.3	75.0	0.0

PIP-TAZ: Piperacillin-Tazobactam, CAZ-AVI: Ceftazidime-Avibactam, IPM: Imipenem, MEM: Meropenem, SXT: Trimethoprim-sulfamethoxazole; MIC_{50}, MIC_{75}, MIC_{90}: Concentration inhibiting 50, 75 and 90% of the isolates, respectively; MICs are reported in µg/mL

Table 3: *In-vitro* activity of fosfomycin, nitrofurantoin and comparator agents against *Pseudomonas* Spp., expressing various resistance mechanisms

Pseudomonas Strains (n=425)	Antibacterial agent	MIC Range (mg/L)	MIC_{50} (mg/L)	MIC_{75} (mg/L)	MIC_{90} (mg/L)	Susceptibility (CLSI)		
						% S	% I	% R
CAZ-S (n=206)								
	Fosfomycin	2 - 512	64	128	128	70.4	23.8	5.8
	Nitrofurantoin	4 - 512	256	256	512	0.5	0.5	97.6
	PIP / TAZ	0.25 - 256	4	8	16	95.1	7.8	1.5
	CAZ-AVI	0.015 - 128	2	4	8	91.7	0.0	6.3
	SXT	0.12 - 512	16	32	128	NA	NA	NA
	Ciprofloxacin	0.06 - 64	0.5	0.5	32	72.8	10.2	17.0
	IPM	0.06 - 32	2	2	4	87.4	6.8	5.8
	MEM	0.03 - 512	0.5	1	2	91.3	2.9	5.8
ESBL producers (n=35)								
	Fosfomycin	2 - 512	64	128	128	74.3	8.6	17.1
	Nitrofurantoin	4 - 512	256	256	512	25.7	22.9	48.6
	PIP / TAZ	0.25 - 8	4	8	16	91.4	11.4	2.9
	CAZ-AVI	0.015 - 8	2	4	8	68.6	0.0	25.7
	SXT	0.5 -256	16	32	128	NA	NA	NA
	Ciprofloxacin	0.06 - 64	0.5	0.5	32	31.4	0.0	68.6
	IPM	0.06 - 2	2	2	4	94.3	2.9	2.9
	MEM	0.015 - 2	0.5	1	2	91.4	2.9	5.7
ESBL Class C producers (n=44)								
	Fosfomycin	4 - 512	64	128	128	72.7	15.9	11.4
	Nitrofurantoin	128 - 512	256	256	512	0.0	0.0	100.0
	PIP / TAZ	4 - 512	4	8	16	13.6	68.2	52.3
	CAZ-AVI	1.0--16	2	4	8	86.4	6.8	13.6
	SXT	0.5 - 256	16	32	128	NA	NA	NA
	Ciprofloxacin	0.12 - 64	0.5	0.5	32	29.5	2.3	68.2
	IPM	0.25 - 512	2	2	4	61.4	0.0	38.6
	MEM	0.12 - 256	0.5	1	2	52.3	9.1	38.6
MBL / OXA-48/181 producers (n=140)								
	Fosfomycin	4 - 512	64	128	128	80.0	7.9	12.1
	Nitrofurantoin	32 - 512	256	256	512	1.4	0.0	98.6
	PIP / TAZ	1 - 512	4	8	16	7.9	25.7	79.3
	CAZ-AVI	0.015 - 128	2	4	8	9.3	11.4	90.0
	SXT	0.12 - 512	16	32	128	NA	NA	NA
	Ciprofloxacin	0.25 - 128	0.5	0.5	32	5.0	0.0	95.0
	IPM	0.5 - 256	2	2	4	7.1	3.6	187.1
	MEM	0.12 - 512	0.5	1	2	7.1	2.1	90.7

PIP-TAZ: Piperacillin-Tazobactam, CAZ-AVI: Ceftazidime-Avibactam, IPM: Imipenem, MEM: Meropenem, SXT: Trimethoprim-sulfamethoxazole; MIC_{50}, MIC_{75}, MIC_{90}: Concentration inhibiting 50, 75 and 90% of the isolates, respectively; MICs are reported in µg/mL

Table 4: *In-vitro* activity of fosfomycin, nitrofurantoin and comparator agents against *Acinetobacter* Spp., expressing various resistance mechanisms

Acinetobacter Strains (n=352)	Antibacterial agent	MIC Range (mg/L)	MIC_{50} (mg/L)	MIC_{75} (mg/L)	MIC_{90} (mg/L)	Susceptibility (CLSI)		
						% S	% I	% R
CAZ-S (n=45)								
	Fosfomycin	32 - 512	128	256	256	24.4	46.7	28.9
	Nitrofurantoin	32 - 512	256	256	512	4.4	6.7	88.9
	PIP / TAZ	0.25 - 128	1	4	8	97.8	0.0	2.2
	CAZ-AVI	0.015 - 32	2	2	8	NA	NA	NA
	SXT	0.06 - 512	0.5	0.5	4	86.7		13.3
	Ciprofloxacin	0.12 - 64	0.25	0.5	2	88.9	0.0	11.1
	IPM	0.06 - 2	0.25	0.25	0.25	100.0	0.0	0.0
	MEM	0.03 - 1	0.25	0.25	0.5	100.0	0.0	0.0
MBL / OXA-48/181 producers (n=309)								
	Fosfomycin	32 - 256	128	256	256	11.4	59.0	29.6
	Nitrofurantoin	64 - 512	256	256	256	0.0	0.7	99.3
	PIP / TAZ	16 - 512	512	512	512	0.3	2.0	98.7
	CAZ-AVI	0.25 - 128	32	128	128	NA	NA	NA
	SXT	0.03 - 512	64	128	256	12.4		87.6
	Ciprofloxacin	0.12 - 128	64	64	64	1.3	0.0	98.7
	IPM	8 - 512	32	64	128	0.0	0.0	100.0
	MEM	16 - 512	32	64	256	0.0	0.0	100.0

PIP-TAZ: Piperacillin-Tazobactam, CAZ-AVI: Ceftazidime-Avibactam, IPM: Imipenem, MEM: Meropenem, SXT: Trimethoprim-sulfamethoxazole; MIC_{50}, MIC_{75}, MIC_{90}: Concentration inhibiting 50, 75 and 90% of the isolates, respectively; MICs are reported in µg/mL

DISCUSSION AND CONCLUSION

Emergence of MDR among Gram-negative pathogens including *P. aeruginosa* and *A. baumannii*, there has been renewed interest in older antibiotics such as fosfomycin, polymixins, aminoglycosides etc. Considering the promising activity along with minimal resistance rates, fosfomycin offers best option for the management of infections caused by MDR pathogens. The current study examined the *in-vitro* antibacterial activity of fosfomycin as well as nitrofurantoin against clinical isolates of *P. aeruginosa* and *A. baumannii*, including MDR isolates. The results of *in-vitro* antibacterial profiling in present study revealed that, fosfomycin demonstrated promising activity against *Pseudomonas* Spp., irrespective of multiple resistance mechanisms, while fosfomycin did not showed activity against *Acinetobacter* Spp., The another drug nitrofurantoin was also evaluated in the current study demonstrated poor activity against both the Spp., Based on the results observed in the current investigation, the discussion shall focus ONLY on fosfomycin activity against *Pseudomonas* Spp.,

According to MIC results of fosfomycin against *Pseudomonas*, significant variable antipseudomonal activity of fosfomycin is reported in the literature and this variability in activity is considered to be population dependent [19]. Hence it is important to understand the local susceptibility patterns of fosfomycin for its optimal use. The current study evaluates the susceptibility of *P. aeruginosa* isolates to fosfomycin within an Indian population which is represented by collecting strains from 16 tertiary care hospitals from various states of India. Based on the total 425 *Pseudomonas* clinical isolates evaluated, we found that 309 of 425 (72.7%) clinical isolates were considered susceptible to fosfomycin based upon the chosen breakpoints (64µg/mL); while 112 of 140 (80%) of only MDR isolates were susceptible to fosfomycin. The majority of the clinical isolates evaluated in the current investigation (including MDR strains) were fosfomycin susceptible, with a significant proportion being intermediate or resistant to fosfomycin.

Due to the various testing methods employed such as disk diffusion, agar dilution, broth microdilution and Etest and lack of uniform interpretive MIC breakpoints, it is very difficult to compare the susceptibility rates of *P. aeruginosa* to fosfomycin observed in the current study. Falagas et al., in his thorough review of almost 23 studies found that ≥90% of MDR *P. aeruginosa* isolates were susceptible to fosfomycin in 7 of 19 studies [14], while 4 studies reported susceptibility rates in the range of 50 – 90%. However, when the data of these studies pooled together, the overall susceptibility rate was found to be 30.2%. The overall low susceptibility rates were primarily due to the inclusion of a study conducted in France, comprising of 1348 out of 1693 isolates that were reported to be resistant in their review. Recent studies published by Perdigão-Neto and colleagues, Maraki and colleagues etc. have reported wide range of susceptibility rates (7 to 89%) to fosfomycin but they did not revealed whether isolates evaluated were MDR or non-MDR [20-29]. These results indicate need of uniform testing

methods and knowledge on pharmacodynamics of fosfomycin against *P. aeruginosa* so that proper breakpoints can be established by EUCAST or CLSI [17, 18].

The activity of any antibacterial agent is measured by its MIC, however MIC do not provide information on time course of antimicrobial activity which is generally evaluated by performing studies involving effect of higher drug concentration and duration of persistent effect which help in designing of dosage regimes. There is discordance among scientific community whether fosfomycin displays concentration or time dependent activity. In time dependent activity, effect of saturating concentration on rate of killing is minimal while concentration dependent activity displays higher rate and extent of killing at higher concentrations. For fosfomycin, recent literature suggests organism dependent activity [30, 31]. Previously couple of studies have reported time dependent activity by fosfomycin against *P. aeruginosa* and *Staphylococcus aureus* [31-33] while a study by Mazzei and collegues reported concentration-dependent activity of fosfomycin against *Escherichia coli* and *Proteus mirabilis* [31].

The *in-vitro* antibacterial activity of fosfomycin against *A. baumannii* was not promising, displaying > 85% of strains are resistant to fosfomycin hence limiting the therapeutic use of fosfomycin against *A. baumannii*. Such is the case with nitrofurantoin which has displayed > 98% resistance rates to *P. aeruginosa* and *A. baumannii* thereby suggesting its non-utility in management of infection caused by these pathogens [32-34].

In summary, the existing study has demonstrated that majority of isolates of *P. aeruginosa* from Indian tertiary care hospitals were susceptible to fosfomycin while most of *A. baumannii* isolates were resistant. Nitrofurantoin was not active against both of these pathogens thereby limiting it use.

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Conflict of Interest

The authors declare that they have no competing financial interests exist

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