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Original Research Article

Fosfomycin – Choice in ESBL & MBL Gram Negative Bacilli Strains?

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Abstract:

Background: The increasing antimicrobial drug resistance of bacterial pathogens, together with the relative shortage of new antimicrobial agents, call for a new look at the therapeutic options. Fosfomycin is an old antibiotic. Nowadays, many clinicians and scientists are having a re-look at its effectiveness against multi-resistant microorganisms.

Objectives:1. To test susceptibility of ESBL & MBL producing gram negative bacteria to fosfomycin, imipenem, colistin, netilmycin, and tigecycline. 2. To compare susceptibility of fosfomycin with other antibiotics.

Materials & Methods: From routine exudate samples 50 ESBL and 50 MBL isolates were included. Their susceptibility was determined to colistin, fosfomycin, imipenem, tigecycline, netilmycin.

Results: Out of 50 ESBL *E.coli* (22/50) was commonest while among MBL, *Ps. aeruginosa*(22/50)**.** Susceptibility to fosfomycin among ESBL and MBL isolates were 82% and 90% respectively. Colistin was found to be sensitive in 88% ESBL and 100% of MBL isolates. whereas sensitivity to tigecycline and netilmycin among ESBL was 34% & 68% & that of MBL was 33% & 45% respectively. The susceptibility of imipenem in ESBL isolates was 88%.

Conclusion: Fosfomycin is a good choice irrespective of ESBL or MBL. Imipenem can still be used in ESBL. Colistin is ideal for MBL.

Key words: ESBL, MBL, Fosfomycin, Colistin, Imipenem, Exudate.

Introduction

The continuously increasing problem of antibacterial resistance is well understood and much feared for its potential consequences. Clinicians often face problems in choosing appropriate
antibiotic therapy for treating infections caused by gram-positive and gram-negative bacteria, because these pathogens are often resistant to several classes of antibiotics. Drug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus*and multidrug-resistant *Pseudomonas, Acinetobacter,* and *Klebsiella*species have been frequently isolated from patients with serious infections and are associated with a considerable mortality rate. These facts created the need to discover new effective treatment solutions or even re-evaluate and re-introduce already existing therapeutic agents, such as Fosfomycin and Colistin, for addition to the list of the few remaining antibiotics used for treating infections caused by drug-resistant bacteria.[1]

Fosfomycin is a broad-spectrum antibiotic with a wide therapeutic range and characteristic pharmacological properties. It penetrates excellently into various tissues and cerebrospinal fluid and is frequently administered in combination with other antimicrobial agents in Europe to combat severe bacterial infections. It exerts bactericidal activity under anaerobic conditions, such as is the case within encapsulated purulent lesions, and has a negligible protein binding. These characteristics constituted the rationale for choosing fosfomycin in the present study. [2]

In this regard, we sought to evaluate the susceptibility of ESBL & MBL producing gram negative bacteria isolated from exudates samples to Fosfomycin, Imipenem, Colistin, Netilmycin, and Tigecyclineand To compare susceptibility of Fosfomycin with other antibiotics.

Materials and Methods

Study Design: Laboratory based prospective study.

Inclusion criteria: ESBL and MBL producing clinical isolates from routine exudates specimens, were included in the study.

Exclusion criteria: Repeat isolates from same patient from repeat specimen were excluded from study to avoid duplication of isolate. Also colistinsensitivestrains were excluded from study.

Methodology

The exudates specimens received in Microbiology Department from ICUs and wards during this period were included. Processing of the specimens was done on blood agar, chocolate agar, and Mac Conkey's agar. Bacterial colonies were identified by standard biochemical reactions and antimicrobial susceptibility testing was done as per CLSI guidelines using the Kirby-Bauer disc diffusion method. ESBL was identified by- phenotypic confirmation by placing Ceftazidime (30µg) alone and ceftazidimeclavulanic acid (30/10µg), 15-20mm apart. A difference in zone diameter of >5mm difference taken as ESBL. MBL was identified by placing Imipenem (10µg) alone and imipenem- EDTA combination, 15-20mm apart. A difference in zone diameter of>7mm difference taken as MBL. [3]

Study Period: From August 2016 to January 2017.

Settings: Study was carried out at Department of Microbiology, MMC & RI.

Further the strains were tested for their susceptibility by Kirby Bauer method for the following drugs- In ESBL strains Fosfomycin, Imipenm, Colistin, Netilmycin and Tigecycline were tested. Whereas in MBL strains same drugs were tested except Imipenem.

Results of all ESBL and MBL strains, isolated during study period were included for data analysis in the study. For this, software MS Excel was used.

Results

A total of 50 ESBL and 50 MBL isolates were included in the study (Table- 1). Among ESBL, 37 belongs to Enterobacteriaceae family and 13 were belong to non-fermenter group.

Table- 1: Number of ESBL and MBL producing bacterial isolates

	Enterobacteriaecae	Non fermenter
ESBL n=50	37	13
MBL N=50	16	34

Table - 2 shows distribution of ESBL & MBL in various Pathogens (organisms). Maximum ESBL producing 22 (44%) were *E.coli,* while *Acinetobacter* spp. 11 (22%) and *Klebsiella pneumonia* 10 (20%) were next most number of isolates. Among MBL producing organisms, most common was *Pseudomonas aeruginosa* 22 (44%), followed by *Klebsiella pneumonia* 16 (32%) and *Acinetobacter* spp. 12(24%).

Table 2: Distribution of ESBL & MBL in various Pathogens

	ESBL (N=50)	MBL (N=50)
E. Coli	22	0
Klebsiela Pneumoniae	10	16
Proteus Mirabilis	5	0
Ps. Aeruginosa	2	22
Acinetobacter Spp.	11	12
	ESBL (N=50)	**MBL (N=50)**
E. Coli	22	0
Klebsiela Pneumoniae	10	16
Proteus Mirabilis	5	0
Ps. Aeruginosa	2	22
Acinetobacter Spp.	11	12

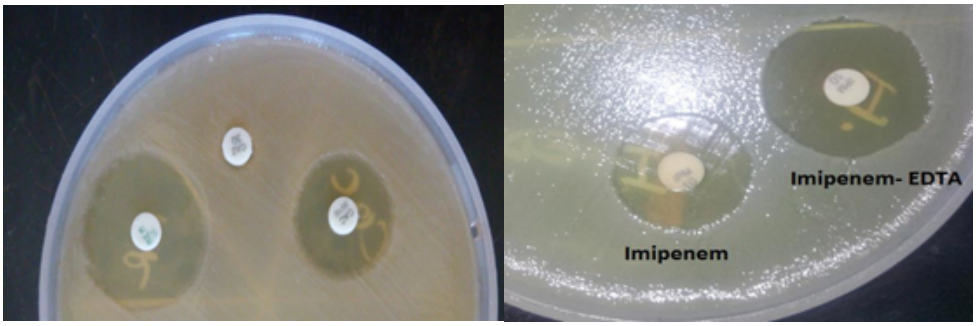


Figure 1: ESBL Figure 2: MBL

Table- 3 & 4 presents data regarding the susceptibility of the studied ESBL and MBL isolates to the antibiotics tested respectively. As shown in Table- 3, Imipenem (88%) was the most active antibiotic tested against all ESBL isolates, followed by Fosfomycin (82%) and Colistin (68%). According to Table- 4, Colistin (100%) showed good sensitivity against MBL producing pathogens followed by Fosfomycin (90%).

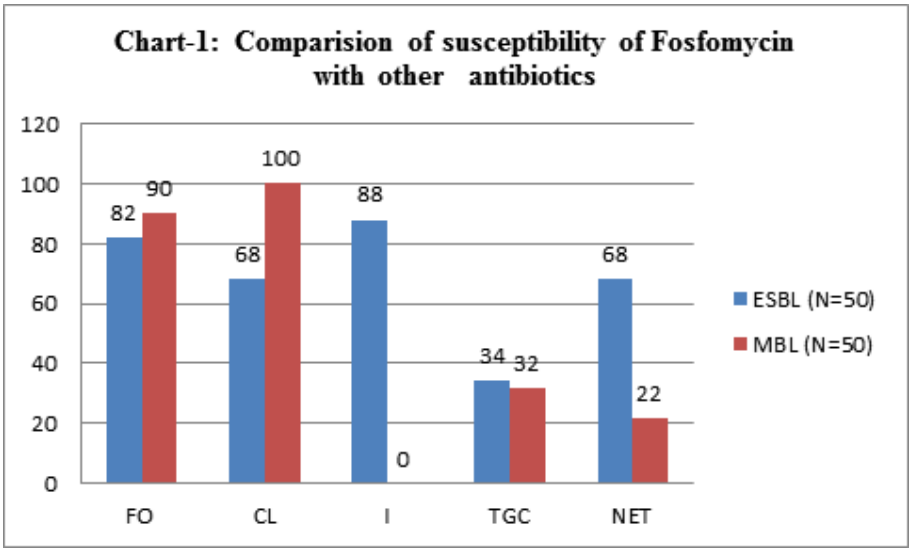
Chart- 1 showed comparison of susceptibility of Fosfomycin with other antibiotics. Fosfomycin is equally effective in ESBL and MBL, whereas Tigecyclin & Netilmycin showed less susceptibility.

Table 3: Sensitivity pattern of ESBL producing pathogens

ESBL	Fo (%)	Cl (%)	I (%)	TgC (%)	Net (%)
E.coli (22)	21(95.45)	16 (72.72)	21(95.45)	9(40.9)	19 (86.36)
K.pneumoniae(10)	10 (100)	10 (100)	9 (90)	7 (70)	10 (100)
Proteus mirabilis (5)	5 (100)	1 (20)	5(100)	0	0
Ps. aeruginosa(2)	0	2(100)	2(100)	0	2(100)
Acinetobacter(11)	5(45.45)	5(45.45)	7(63.63)	1(9.09)	3(27.27)
TOTAL (50)	41(82%)	34(68%)	44(88%)	17(34%)	34(68%)

Table 4: Sensitivity pattern of MBL producing pathogens

MBL	Fo (%)	Cl (%)	TgC(%)	Net (%)
Ps.aeruginosa(22)	22(100)	22(100)	0	0
Acinetobacter(12)	7(58.33)	12 (100)	0	0
K.pneumoniae (16)	16(100)	16(100)	16(100)	11(68.75)
TOTAL (50)	45(90%)	50(100%)	16(32%)	11(22%)



Discussion

The main finding of this study is that Fosfomycin showed substantial antimicrobial activity against a collection of pathogens with very high resistance rates to traditionally used antimicrobial agents. The antimicrobial activity of Fosfomycin did not appear

to be considerably influenced by the expression of specific resistance phenotypes (MBLs or ESBLs).

The lack of cross-resistance to Fosfomycin with other antimicrobial agents may be attributed to the unique mechanism of action of this agent, which comprises inhibition of an early step in bacterial cell wall synthesis. [4] Moreover, Fosfomycin does not
appear to be a substrate for common mechanisms of multidrug resistance such as multidrug efflux pumps.[5,6] In addition, the main type of resistance to Fosfomycinappears to be chromosomal rather than plasmid-mediated, [7] which diminishes the likelihood of co-transmission of resistance to Fosfomycin along with resistance to other agents.

A few clinical studies have evaluated the use of fosfomycin for the treatment of patients with infections caused by ESBL-producing Enterobacteriaceae. These studies have mainly focused on patients with lower urinary tract infetions and havedemonstrated substantial clinical success with orally administered fosfomycin. [8]

The accumulated clinical experience regarding the use of parenterally administered fosfomycin for various indications suggests that it may also be useful for the treatment of systemic infections. However, the appropriate dose and duration of fosfomycin therapy for such indications requires further evaluation. [9]

Conclusion

Fosfomycin is an old antibiotic and its effectiveness may be to some extent, underestimated. It is a bactericidal agent showing low levels of toxicity as well as a low level of cross resistance with other antibiotics. This study shows that fosfomycin has substantial in vitro antimicrobial activity against ESBL & MBL strains of Enterobacteriaceae and Nonfermenters.
Since therapeutic options for these types of isolates have not been well established, the potential clinical utility of fosfomycin in this regard merits further evaluation.

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