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THE ROLE OF FOSFOMYCIN IN INFECTIONS CAUSED BY ESBL-PRODUCING ENTEROBACTERALES

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ABSTRACT

Background : Enterobacterales is common cause of many type of infection, and for Enterobacterales ESBL producer, there are limited choice of antibiotic. Fosfomycin can be used as an alternatve especially when no other option available or when other antibiotic are less effective.

Method : All the sample in this study are collected form microbiology laboratory's culture result during 18 months period and collect sensitivity for fosfomycin, ceftriaxone, cefotaxime, and carbapenem group. Fosfomycin sensitivity are presented by each species, for both ESBL and non ESBL producer group. ESBL producer bacteria based on resistant for ceftriaxone dan cefotaxime, while carbapenemase predicted by resistant against carbapenem group.

Result : Most sample collected are urine, followed by pus and sputum. Bacteria found in this study are dominated bu E. coli and Klebsiella sp. Both bacteria are dominated by ESBL producer. Fosfomycin sensitivity from this study are high except for Klebsiella sp ESBL group and Morganella morganii.

Conclusion : Fosfomycin can be used as an consideration for choosing empiric therapy although in area with high prevalence of ESBL producer bacteria. However, it is essential to consider the recommended therapeutic doses for various types of infections

Keywords : ***Enterobacterales, ESBL, fosfomycin..***

INTRODUCTION

Infection caused by Enterobacterales, such as *Escherichia coli* and *Klebsiella pneumoniae*, are a serious concern in the medical field due to the increasing cases of antibiotic resistance, particularly through the production of Extended-Spectrum Beta-Lactamase (ESBL) enzymes. These enzymes render bacteria resistant to most beta-lactam antibiotics commonly used to treat infections.[1] Studies show that infections caused by ESBL-producing Enterobacterales increase morbidity and mortality due to the difficulty in treatment, especially in patients with comorbid conditions or compromised immune systems.[2]

The prevalence of infections caused by Enterobacterales, particularly ESBL-producing strains, is increasing worldwide and poses a major challenge to healthcare systems. This rising prevalence has led to increased use of carbapenems in therapy, which in turn has triggered the emergence of carbapenem resistance due to overuse.[3 4] A study conducted in several Asian countries also demonstrated a correlation between high community-level antibiotic use and increased cases of ESBL-producing bacterial infections.[5]

Fosfomycin acts by inhibiting an essential enzyme in bacterial cell wall synthesis and possesses a unique mechanism that allows it to remain effective against bacteria resistant to many other antibiotics. Recent studies have shown that fosfomycin is a potential and effective therapeutic option for treating urinary tract infections caused by ESBL-producing bacteria, particularly in cases where other options are limited or less effective.[4 6 – 8]

This study aims to further evaluate the effectiveness of fosfomycin against both ESBL and non-ESBL-producing Enterobacterales and to assess its potential as an alternative therapy in antibiotic-resistant infections especially for ESBL producing Enterobacterales. The results are expected to serve as a clinical guide for selecting appropriate therapy in infections involving ESBL-producing Enterobacterales.[8]

METHODS

This is a descriptive study. Samples were obtained from microbiology culture data stored in the microbiology laboratory of Hospital X. For each *Enterobacterales* species found, the following were recorded: sample type, bacterial species, and antibiotic sensitivity pattern for ceftriaxone, cefotaxime, carbapenems, and fosfomycin. Bacterial isolates without complete data were excluded. Bacteria were classified as ESBL producers if resistant to third-generation cephalosporins (ceftriaxone and cefotaxime). Carbapenemase production was inferred from resistance to carbapenem antibiotics (ertapenem/ imipenem/meropenem). All the data were collected from laboratory data only without collecting patient data.[9]

Data were collected from January 1st, 2023, to June 30th, 2024, based on the date the sample was submitted to the microbiology lab. Patient demographic or clinical details such as sex, age, or diagnosis were not recorded.

RESULT

Tabel 1. Distribution of sample types

Sample type	Number	Percentage (%)
Urine	98	62
Pus	27	17,1
Sputum	24	15,2
Blood	5	3,2
Vaginal secretion	4	2,5
Total	158	100

Tabel 2. Distribution of bacterial species

Spesies	Number	Percentage (%)
Eschericha coli	81	51,3
Klebsiella sp	52	32,9
Proteus mirabilis	10	6,3
Enterobacter sp	9	5,7
Morganella morganii	3	1,9
Citrobacter sp	3	1,9
Total	158	100

Tabel 3. MDR total per species

Species	Non-MDR (%)	ESBL (%)	Carbapenemase (%)
Klebsiella sp	16 (30,8)	35 (67,3)	1 (1,9)
Eschericia coli	29 (35,8)	52 (64,2)	0
Enterrobacter sp	5 (55,5)	4 (44,5)	0
Proteus mirabilis	9 (90)	1 (10)	0
Morganella morganii	2 (66,7)	1 (33,3)	0
Citrobacter sp	3 (100)	0	0

Tabel 4. *Fosfomycin* sensitivity in non-MDR and MDR group

Spesies	Non MDR (%)	MDR (%)
Eschericha coli	28(96,6)	47 (90,4)
Klebsiella sp	14 (87,5)	15 (41,7)
Proteus mirabilis	7 (77,8)	1(100)
Enterobacter sp	4 (80)	4 (100)
Morganella morganii	0 (0)	0 (0)
Citrobacter sp	3 (100)	-

DISCUSSION

Based on Table 1, the majority of the 158 samples in this study were from urine (62%), as fosfomycin testing is routinely performed on urine samples only, following CLSI recommendations.[9]The most frequently isolated species were *Escherichia coli* (51.3%) and *Klebsiella* sp. (32.9%). These two species far outnumbered others, consistent with a 2021 study by Suhartono et al. in Aceh, which also found *E. coli* and *Klebsiella pneumoniae* as the most common pathogens in urinary tract infections.[10]Only two species (*E. coli* and *Klebsiella* sp.) had more than 30 isolates, fulfilling analysis criteria by the Indonesian Association of Clinical Microbiologists (PAMKI). Both were also predominant ESBL producers, with a majority showing multidrug resistance (MDR). Notably, 67.3% of *Klebsiella* isolates were ESBL producers, higher than a 2022 pediatric study by Layanto et al. (42.9%).[7] One isolate was also carbapenem-resistant. Another study by Annarita et al. in Asia showed a lower ESBL rate (25.6%) in *Klebsiella pneumoniae*, but only included urine samples.[8]*Escherichia coli* was found to be ESBL-producing in 64.2% of isolates, consistent with pediatric UTI data (62.5%). In this study, *E. coli* accounted for 52 out of 92 ESBL isolates (56.5%). This is lower than Bielen and Likic's finding, which showed *E. coli* contributed to 80.9% of ESBL isolates.[11]*Enterobacter* sp. showed 4 ESBL-producing isolates from 9 samples. However, the presence of the *ampC* gene in *Enterobacter* can lead to third-generation cephalosporin resistance undetectable in vitro.[12] [13]*Morganella morganii* showed low MDR rates, consistent with studies by Alsaadi et al. (5%) and Shi et al. (9%).[14] [15] *Proteus mirabilis* had only 1 ESBL isolate here (10%), unlike Suhartono et al. (47.5%) and Mo et al. (38.2%).[16] [17] This discrepancy may be due to low sample count and different sources.All *Citrobacter* sp. isolates here were non-MDR, in contrast to Sami et al., who reported 52.4% MDR in *Citrobacter* from urine samples.[18]Table 4 shows high fosfomycin sensitivity across species, except in *Morganella morganii* (intrinsically resistant).[13] [15] However, sensitivity in MDR *Klebsiella* sp. was only 41.7%, unlike Bielen and Likic (100% sensitivity in urine-derived ESBL bacteria).[11] Falagas et al.'s review showed that 64.7% of studies reported high fosfomycin sensitivity in ESBL-producing *Enterobacteriaceae*, especially *E. coli* (91.7%).[6]Fajfr et al. in Czech Republic reported 92% sensitivity in ESBL *E. coli* and 73.6% in ESBL *K. pneumoniae*, not far from their non-ESBL counterparts.[19] Our data, however, showed a bigger drop in MDR *Klebsiella* (41.7%) vs non-MDR (87.5%).Overall, fosfomycin sensitivity was 87.5% in non-MDR and 76.3% in MDR isolates. This aligns with Falagas et al., confirming fosfomycin's potential use in both definitive and empiric therapy.[4]However, high in-vitro sensitivity does not always translate to clinical success. Bielen and Likic reported only 50% microbiological cure in patients treated for ESBL UTI with fosfomycin, despite 71.4% clinical success.[11] Oral fosfomycin yields lower plasma concentrations than intravena, potentially affecting tissue penetration and MIC (Minimal Inhibition Concentration) targets. Therefore, dosing strategies must consider infection type.[13] [20–22]

CONCLUSION

Fosfomycin is a promising alternative for treating infections caused by ESBL-producing *Enterobacterales*. However, clinicians must consider the formulation (oral vs IV) and infection-specific dosing recommendations. Further studies are needed to assess both clinical and microbiological outcomes, as well as the reinfection rate. Future research should also explore other pathogens, including gram-positive bacteria.

CONFLIC OF INTEREST

This study is not corelated to any brand of pharmacy and fully funded by author

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