ORIGINAL ARTICLE

CEFIDEROCOL: A TROJAN HORSE FOR THE MANAGEMENT OF MULTIDRUG-RESISTANT ENTEROBACTERALES IN A TERTIARY CARE HOSPITAL IN PAKISTAN

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ABSTRACT

Objective: To assess the efficacy of cefiderocol in patients with multidrug-resistant enterobacterales.

Material & Methods: A research study was carried out at Clinical Pathology Laboratory, Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan (National University of Medical Sciences). This study was completed in 6 months from June 2021 to November 2021. Data was analyzed by SPSS version 21.

Results: One hundred and fifty-eight (158) samples of blood, pus, body fluids, urine, and lower respiratory tract aspirates were analyzed. Mueller Hinton Agar (MHA) was used for antimicrobial susceptibility testing for all antimicrobials. Colistin agar was used for Polymyxin E testing. Clinical and Laboratory Standards Institute 2021(CLSI) was followed for result interpretation, among 158 MDR enterobacterales, 154 were sensitive to cefiderocol.

Conclusion: Cefiderocol came out to be the most active among all the tested antimicrobials. It had good efficacy against MDR Enterobacterales.

Key Words: Antibiotic, Cefiderocol, Bacteria, Enterobacterales, Pathology

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INTRODUCTION

Gram-negative bacteria comprise a large group including Klebsiella, Enterobacter, Proteus, Escherichia, Pseudomonas, Acinetobacter, Providencia, and several others. Among all the Gram-negative bacteria, some of them are further categorized as enterobacterales depending upon the specific criteria they follow i.e they are Gram-negative facultative anaerobic rods and can ferment glucose with the production of acid, are catalase-positive and oxidase negative. They do not produce spores and are nitrate reducers. They can grow on MacConkey Medium (bile salt-containing medium). Important genera of this family include Klebsiella spp., Escherichia spp., Enterobacter spp, and Proteus spp.[1] The inappropriate use of antibiotics has resulted in a rapid increase in antimicrobial resistance worldwide, however, the newer antibiotics are developing at a very slow pace. It has been estimated that if no new drug is discovered by 2050, these pathogens will rule the world as no antibiotic would be there to stop them,[2] Clinicians are now left with limited options of antimicrobials for these MDR bacteria. With the emergence of ESBL producers, Carbapenems were the only option left, however, New Delhi Metallo beta-lactamases (NDM-1) emerged to be resistant to Carbapenems along with klebsiella pneumonia carbapenemases (KPC).[3]

Bacteria exhibit resistance to antibiotics in various ways. The most important mechanism is the inactivation of the drug by enzymes followed by modification of the drug target or binding site. The other two mechanisms include either reduced permeability of drug caused by a mutation in porin proteins or increased export of drug by multidrug-resistance pump,[4]

MDR infections have resulted in prolonged hospital stays resulting in a significant rise in morbidity and mortality rates. Among these drug-resistant bacteria, MDR enterobacterales., Acinetobacter baumannii, and Pseudomonas aeruginosa are most commonly isolated in hospitalized patients. In judicious use of broad-spectrum antimicrobial agents is one of the factors that has resulted in the emergence as well as the spread of these MDR Gram-negative bacteria.[5]

To manage bacterial infections caused by MDR enterobacterales including Extended-spectrum βeta-lactamases (ESBL's) producers and Carbapenem-resistant enterobacterales is a challenge for health care facilities worldwide. To overcome the challenge, many new antimicrobials and their combinations have been or are in the stage of development (ceftolozane / tazobactam, ceftazidime/avibactam, imipenem /relebactam, plazomicin, cefiderocol) each having its spectrum of activity and limitations.

Cefiderocol is one of the new siderophore cephalosporin which is only available in injectable form. It has been developed by Shionogi & Co., Ltd., Japan. US FDA first approved cefiderocol for the management of urinary tract infections on 14th November 2019 and ventilator-associated and nosocomial pneumonia on 28th September 2020.[6] It is a bactericidal drug that kills the bacteria by breaking down its cell wall, as it binds to the penicillin-binding proteins (PBP's) and inhibits cell wall formation. It has a distinctive feature of entering the periplasmic space as it acts as a siderophore. and is stable against βeta-lactamases.[7] This Trojan horse strategy allows cefiderocol to reach the periplasmic space and disrupt cell wall synthesis. It have in vitro strong efficacy to manage various Gram negative bacteria.[8] This newly developed cephalosporin is highly stable against AmpC, ESBLs, and carbapenemases. It has potent activity against Acinetobacter baumannii resistant to carbapenems.[9]

Our study aimed to determine in vitro efficacy of cefiderocol against MDR enterobacterales isolated from clinical specimens processed for culture and sensitivity. Until now, only few research studies are available in the literature regarding efficacy of cefiderocol against GNB by different methods recommended by CLSI.[10,11] In Pakistan, up till now, no study has been published regarding in vitro antimicrobial susceptibility of this drug using the disc diffusion method.

MATERIAL AND METHODS

The research study was carried out at Pak Emirates Military Hospital (PEMH), Clinical Pathology Laboratory (CPL) under Army Medical College, (PEMH) Rawalpindi/ National University of Medical Sciences**.** The study was completed in 6 months from June 2021 to December 2021 and was approved by the ethics review committee and Institutional Review Board. It was a cross-sectional and non-probability convenience sampling. All clinical samples received for culture and sensitivity including blood, lower respiratory tract specimens, body fluids, urine, and pus were processed following standard microbiological procedures CMPH. (Clinical Microbiology Procedures Handbook).[12]

All the blood culture bottles incubated in BacT/ALERT BD, which flagged positively were taken out and samples from them were subcultured on 5% sheep blood agar and MacConkey agar plates. Further, they were incubated at 35°-37°C for 24 hours to allow bacteria to grow on them.

Respiratory samples were inoculated manually according to standard guidelines given by Clinical Microbiology Procedures Handbook (5% sheep blood agar, MacConkey agar, chocolate agar, and Sabouraud's agar were used). Pus samples were inoculated on 5% sheep blood agar and MacConkey agar. urine samples on cysteine-lactose-electrolyte-deficient (CLED) agar.

These plates were then incubated for bacterial growth and further, the growth was identified by Gram staining, and other biochemical tests (catalase test, motility test, oxidase test and API

20E (analytical profile index) (Biomerieux, France).[13]

Bacterial suspensions of all isolates were prepared (0.5 McFarland turbidity standards). And were inoculated on Mueller Hinton aga. and incubated at 35°-37°C for 18 hours. Antimicrobial discs of meropenem (10µg), amikacin (30µg), gentamicin (10µg), aztreonam (30µg), piperacillin-tazobactam (110µg), ciprofloxacin (5µg), ampicillin (10µg), trimethoprim/sulfamethoxazole (25µg), minocycline (30µg) amoxicillin/clavulanic acid (30µg), ceftriaxone (30µg) were applied on the Mueller Hinton agar plate for susceptibility testing of enterobacterales. For Polymyxin E /Colistin, a colistin agar test at colistin concentrations of 2ug/ml and 4ug/ml was used to test susceptibility in Enterobacterales. Following Clinical & Laboratory Standards Institute (CLSI) guidelines 2021 results were interpreted.[14]

Cefiderocol was then tested for its activity against the isolates using disc diffusion. For the control strain, we used Escherichia coli ATCC 25922.

RESULTS

In our study, 158 clinical samples were analyzed. Out of total samples, 4 (3%) were resistant to cefiderocol.

The highest number of resistances was among blood culture specimens (75%, n=12) while the remaining were isolated from pus specimens (25% n=4). All organisms which were resistant to cefiderocol were isolated from Indoor patients, with a maximum number from the neonatal ICU. The remaining organisms isolated and resistant to cefiderocol were from the Liver transplant unit, ICU, and General ward respectively. Klebsiella pneumonia was the highest in number followed by E. coli isolated among enterobacterales.

In our study, enterobacterales resistant to carbapenems were 69% and to colistin were 26%, klebsiella pneumonia being the most resistant. The increased incidence of resistance in our study is because the samples which were included were all MDR. **(Table 1)**

Table 1: Antibiotic resistance pattern of isolates tested for Cefiderocol

Antibiotics	Klebsiella pneumoniae (n=100)	Escherichia coli (n=24)	Enterobacter aerogenes (n=4)	Citrobacter freundii (n=14)	Morganella morganii n=10	Proteus mirabilis n=4
Ampicillin	IR	100%	IR	IR	IR	50%
Amoxicillin–clavulanate	100%	100%	IR	IR	IR	0%
Ceftazidime	100 %	100%	100%	0%	10%	0%
Ceftriaxone	100%	100%	100%	0%	10%	0%
Meropenem	90%	58%	75%	0%	30%	0%
Gentamicin	80%	75%	100%	0%	10%	0%
Amikacin	78%	50%	50%	0%	10%	0%
Minocycline[a]	58%	50%	50%	0%	90%	IR
Ciprofloxacin	98%	100%	100%	100%	100%	0%
Trimethoprim-sulfamethoxazole	94%	100%	50%	100%	100%	0%
Piperacillin-tazobactam	100%	92%	0%	100%	0%	0%
Colistin[a]	31%	10%	0%	0%	IR	IR
Urinary isolates (n=16)	n=10	n=4	n=0	n=0	n=2	n=0
Norfloxacin [b]	100%	25%	-	-	50%	-
Nitrofurantoin[b]	80%	0%	-	-	IR	IR
Fosfomycin[b]	NR*	0%	-	-	-	-
Cefiderocol	2%	8%	0%	0%	0%	0%

DISCUSSION

One of the most rapidly emerging threats of 21st century is antimicrobial resistance (AMR). According to the report of one of the Reviews on AMR, 10 million people would be killed by 2050 if this resistance is not controlled.[15]

Over the years' multidrug-resistant organisms (MDROs) and extensively drug-resistant (XDROs) bacteria have become a threat to the public health system globally. Invention of new antibiotics and combined antibiotic therapies, microorganisms have changed themselves and established different resistance mechanisms. Thus, the clinicians are left with limited options of antibiotics for treatment.

In our study, Carbapenem-resistant isolates among enterobacterales were 69 % out of which 57% were klebsiella pneumonia. Carbapenems were considered the drug of choice for critically ill patients due to their broad-spectrum activity,[16,17] Unfortunately, the infections associated with pathogens resistant to Carbapenems have been documented with high rates of morbidity and mortality.[18]

In a study done in Germany in 2021, 83.6% of the enterobacterales were susceptible to cefiderocol.[19] another study conducted by JMI Laboratories, North Liberty, Iowa, USA, enterobacterales susceptibility to cefiderocol was 99.8% (CLSI) similar to our study.[20]

Another method available for the in vitro activity of cefiderocol is Broth microdilution, (BMD) for which we need Mueller-Hinton broth which should be iron-depleted and cation adjusted. This is time-consuming, labor-intensive, and expensive to be carried out routinely in a laboratory in a low-income country. Hence disc diffusion (DD) serves as an easy and economical way for antimicrobial susceptibility testing of cefiderocol. Several studies have done the comparison of DD to BMD and their results showed that DD can be an alternative to BMD.

Recently in CLSI 2022, cefiderocol has been added as a category B drug for enterobacterales with slight changes in zone diameters Thus this study can be helpful for the clinicians in the treatment of patients having infections caused by resistant bacteria when no other options are available. Disc diffusion susceptibility tests cannot reproduce the extremely complex in vivo conditions as it is an in vitro technique.

The study should be done on a larger scale as the sample size for this study is small and will be conducted in a single setting.

Minimum inhibitory concentrations (MICs) are a better option to determine the in vitro activity of an antibiotic, but due to limitations of budget and unavailability of materials for MICs, the study was conducted by the disc diffusion method.

CONCLUSION

Cefiderocol can be an option for clinicians to treat infections caused by MDR GNR as it showed good efficacy against MDR enterobacterales.

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