International Journal of Advanced Biotechnology and Research (IJBR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-9, Issue-2, 2018, pp66-71
http://www.bipublication.com

Research Article

Effects of Polymyxin Tigecycline and Fosfomycine against Carbapenem Resistant Bacteria

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ABSTRACT

Objective: The determination of susceptibility pattern of Carbapenems Producing Enterobacteriaceae (CPE) againsttigecycline, Polymyxin – B and Fosfomycin was the research objective.
Study Design: Research design was descriptive and cross-sectional.
Place and Duration of Study: Our research was completed in the time span of eight months starting from June, 2017 to January, 2018 in the DHQ Teaching Hospital Dera Ghazi Khan.
Material and Methods: The specimens were injected on MacConkey agar and blood;aerobic incubation was carried out at 35 – 37ºC for a time of 18 – 24 hours. After gram negative identification of rods through colony morphology, biochemical reactions and Gram's staining, these were Carbapenems screened resistance with meropenem and imipenem(10µg) discs along with regular 1st and 2nd line antibiotics through Kirby – Bauer disc diffusion method as per the Clinical Laboratory Standard Institute (CLSI) regulations and guidelines. All inaccessible CPE were preserved and after that they were inoculated on the MHA (Mueller – Hinton Agar). The antimicrobial vulnerability against Tigecycline, Polymyxin – B and Fosfomycin was carried out through Kirby – Bauer disc diffusion techniquewith the help of disc Polymyxin – B (300 units), Tigecycline and Fosfomycin respectively (15µg) and (200µg). Greater than twenty-four mm zone diameters were considered sensitive for the Tigecycline (15µg), sixteen and twelve mm respectively for (Fosfomycin200 µg) and (Polymyxin – B 300 units).
Results: We collected 171 clinical specimens of all those participants who managed to comply with the criteria of the research. The age was calculated in Mean ±SD as (42.02 ± 22.367) with Confidence Interval value as (38.65 - 45.40). In total sample of 171 patients, a total of 110 were male (64%); whereas, 61 were female (36%). In our research males dominated the females in number. The outcomes of vitro susceptibility observed all 171 cases (100%) CPE isolates susceptible to Polymyxin – B; whereas, the incidence of vulnerability against the Tigecycline and Fosfomycin was observed as 49 cases (29%) and 132 cases (77%) respectively.
Conclusion: We observed CPE as (100%)Polymyxin – B susceptible; whereas, in the case of Fosfomycin it is 77% and Tigecyclinesusceptibility as 29%.

Keywords: CarbapenemsProducing Enterobacteriaceae (CPE), Polymyxin – B, Fosfomycin and Tigecycline.

INTRODUCTION

The development of bacteria resistance againstantibiotics just after antibiotics discovery, through differentenzymes production. These enzymes whether cephalosporinases or penicillinases lead to resistance progression and development.Carbapenems are taken as sole β – lactam agents which are actively against these extended spectrum B – lactamaseproducing the strains, but an irrational Carbapenems use also results in resistance development tothis antibiotics

class as well[1].These Carbapenems are mostly taken and expressed through Klebsiella pneumonae,Salmonella enterica, Klebsiella oxytoca,Enterobacteraerogenes, Citrobacter freundi, Enterobacter cloacae, Serratiamarcescens, Proteus mirabilis and in the non-fermenting Gram-negative bacilli such as Pseudomonas putida, Pseudomonas aeruginosa and Acinetobacter bauminispp.

The 1st introduction of the Carbapenems was made back in 1987. These are actually beta – lactam antibiotics, taken out from Thienamycinwhich is a product of Streptomyces cattleya. Meropenem and Imipenem are much utilized Carbapenems; whereas, others include Panipenem, Ertapenem, Faropenem and Dori-penem. The repeated beta – lactams having the most used antibacterial spectrum activity. There effectivity against gram positive is well-known and also against anaerobic bacteria and gram negative[2].

Unfortunately, antimicrobial resistance is followed by antimicrobial use &1st case ofCarbapenem resistance was observed and reported back in 1996. The GNR Carbapenems resistance has become an issue in overall the world. Carbapenem resistant prevalence GNR in United States of America is observed near (5.6%),and an increase has been observed one decade (0.6%), in India and Pakistan it is observed respectively 8% and 18.5%.Carbapenems are also considered as antimicrobials oflast option for the treatment of the infections because of the increased beta-lactamase spectrum or plasmidmediated (AmpC, pAmpC) producing the organisms for the family of Enterobacteriaceae. Thesepathogens also resist other antibioticclasses such as aminoglycosides, quinolones and trimethoprim–sulfamethoxazole and other related classes[3].

CPE Infections pose a threat serious in nature to the patients admitted in the hospital. CPE often demonstrateresistance to numerous related antibiotics classes which as a result limits the therapeutic options. Infections having CPE outcomes in poor condition and also cause burden to healthcare system specially in the clinics and hospitals.Such situation can be dealt through Tigecycline,Fosfomycin and polymyxins (Polymyxin – B and colistin)taken as the possible candidatetherapies for CPE caused infections. As per the outcomes of a research held at UK states about the pattern of sensitivity of Polymyxin-B (92%),Fosfomycin (60.5%) and Tigecycline (46.9%) against the CPE[4]. Our research rationale was the probe of a suitable antimicrobialagent against CPE for the guidance of health providers and clinicians for the overall formulation of the antimicrobial strategy of the treatment for drugresistant organisms.

MATERIAL AND METHODS

Research design was descriptive and cross-sectional. Our research was completed in the time span of eight months starting from June, 2017 to January, 2018 in the DHQ Teaching Hospital Dera Ghazi Khan. WHO calculator was used for the sample collection and calculation Tigecycline patterns sensitivity against CRE, error margin and confidence interval were respectively 46.9%, 7.5% and 95%. The total number of patients included in the research were 171 selected through non-probability sampling method. The confirmation and detection of CPE was carried out through (MODIFIEDHODGE TEST, MHT), the study was completed in the laboratory setting. Research did not include the non-CPE cases including repeated samples. Institutional permission and informed consent of the patients was also taken before the commencement of this research. Identification number allocated by the hospital, gender and age were also documented as data and information. The specimens were injected on MacConkey agar and blood; aerobic incubation was carried out at 35 – 37 ºC for a time of 18 – 24 hours. After gram negative identification of rods through colony morphology, biochemical reactions and Gram's staining, these were Carbapenems screened resistance with meropenem and imipenem (10 µg) discs along with regular 1st and 2nd line antibiotics through

Kirby – Bauer disc diffusion method as per the Clinical Laboratory Standard Institute (CLSI) regulations and guidelines. All inaccessible CPE were preserved and after that they were inoculated on the MHA (Mueller – Hinton Agar). The antimicrobial vulnerability against Tigecycline, Polymyxin – B and Fosfomycin was carried out through Kirby – Bauer disc diffusion technique with the help of disc Polymyxin – B (300 units), Tigecycline and Fosfomycin respectively (15µg) and (200µg). Greater than twenty-four mm zone diameters were considered sensitive for the Tigecycline (15µg), sixteen and twelve mm respectively for (Fosfomycin 200 µg) and (Polymyxin – B 300 units).

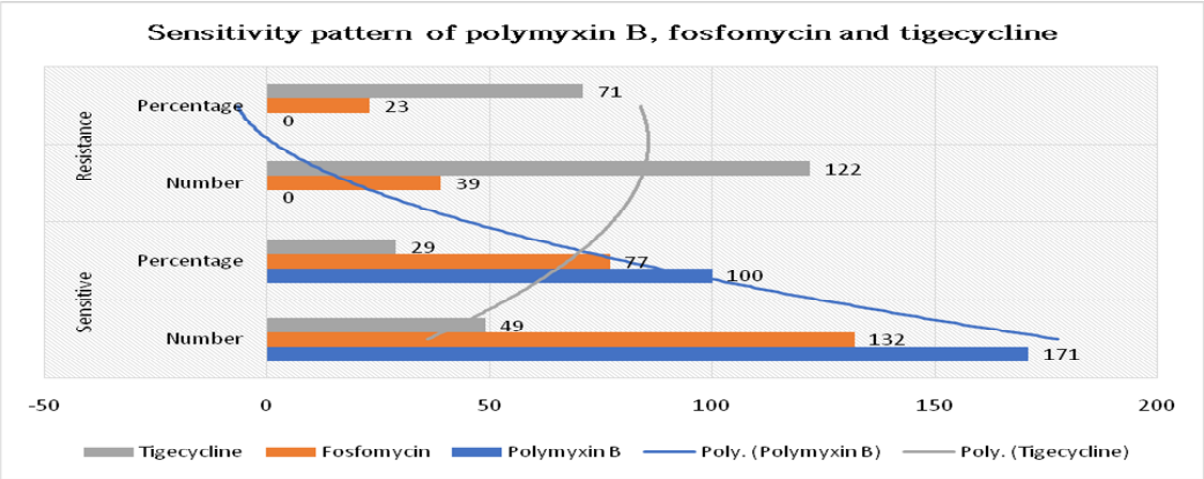
Data collection was made on a specified Performa, we observed no association and involvement of the collected specimen and also deduced that informed consent poses no conflict in this research. Collected data was entered and statisticallyanalyzed in SPSS – 17. We also calculated the values of Mean and SD for age of the participants. Percentage and frequency was calculated for the variable outcomes and gender like Polymyxin – B sensitivity pattern, Tigecycline and Fosfomycin. Through the gender and age stratification effect modifier was controlled in terms of sensitive/resistant to observed results of the variables. Post stratification was carried out through the application of Chi-Square test while the p-value was taken as (≤0.05).

RESULTS

We collected 171 clinical specimens of all those participants who managed to comply with the criteria of the research. The age was calculated in Mean ± SD as (42.02 ± 22.367) with Confidence Interval value as (38.65 - 45.40). In total sample of 171 patients, a total of 110 were male (64%); whereas, 61 were female (36%). In our research males dominated the females in number.

Table: Sensitivity pattern of polymyxin-B, Fosfomycin and tigecycline

Group	Antimicrobial susceptibility			
	Sensitive		Resistance	
	Number	Percentage	Number	Percentage
Polymyxin B	171	100	0	0
Fosfomycin	132	77	39	23
Tigecycline	49	29	122	71



Research outcomes reflect that in the total research sample 49 CPE isolates twenty-nine percent were observed as susceptible to Tigecycline; whereas,in the total of 122 isolates

resistant cases were 71%. Similarly, in the 132 CPEisolates susceptibility toFosfomycin was observed in (77.2%);whereas, in the total of 39 isolates resistant cases were (22.8%). All the cases were observed susceptible to Polymyxin – B as shown in Table-I.

DISCUSSION

Multidrug-resistant(MDR) emergence of gram-negative bacilli had provided a significant issue in the course of treatment of the infections of nosocomial type. As Carbapenems is counted as the strongest antibiotic class against resistant of the bacteria, global CPE isolates spread poses a threat serious in nature to the world's healthcare system[5]. Isolates of CPE are non-susceptiblein vitro to the β-lactams, such as β-lactam/β-lactamase combination of the inhibitors, Fluoroquinolones, Carbapenems and amino glycol sides which are frequent[6].Thus, the selected therapeutic options against Carbapenems infectionscausing the bacteria production are restricted to Tigecycline,Colistin and Fosfomycin.Polymyxin – B susceptibilityin the clinical isolates of CPE are in the range of 80 – 100 in the global perspective[7]. However, the resistance incidence is high among few of the regions because of the resistance strains clonal spread. We observed in the outcomes of our research that there was cent percent susceptibility of colistin to isolates of CPE[8]. Spain and India respectively 97.5 and 100 percent susceptibility results are observed, which are similar to the outcomes of our research. In the research outcomes held at United Kingdom the susceptibility rate was observed as 92% as isolates of CPE were susceptible to Polymyxin – B[9].Our research observed better vitro colistin efficacy against CPE, the reason behind may be the restricted use of antimicrobial because of less availability and high cost factors[10]. However,caution is to be maintained in the use of antimicrobial, it should be used judicially as the result may cause resistance emergence. The in vitro Fosfomycin activity against isolates of CPE isolates in this research was also satisfying as 74% isolates of CPE were susceptible to antimicrobial[11].Comparable outcomes have been observed in the research held at United Kingdom back in 2011 as susceptibility rate was (60.5%). A German research carried out through method of agar dilution observes that 72% isolates of CPE were Fosfomycin susceptible[12]. The Fosfomycin activity was assessed in a research of United States of America as in opposition to 68 KPC were creatingisolates of pneumonae, out of which non-susceptible to Colistin and Tigecycline were 23[13].The assessment carried out observed that rate of susceptibility was 93% in the overall group and 87% in the case of non-susceptible group to colistin and Tigecycline. An extreme resistant to drug subgroup non-susceptible to colistin and Tigecycline was observed as 83%. Whereas, in the setting our research 29% isolates of CPE were Tigecycline susceptible, other outcomes observed at various other countries were varying[14]. We observed the involvement of both Fosfomycin and colistinis potent to be used for the management of the CPE infection. Further research work is required to observe the potential of these isolates in the management of the CPE infections[15]. It is the need of the hour that healthcare facilities and policies should be executed and extended the restriction of infection spread. It is also obligatoryto the microbiologists, healthcareadministrators and clinicians to observe closely the Carbapenems use and also monitor the related antimicrobials use for the preservation of preciousantimicrobials for the management of the threatening disease and infections[16]. Instead of mono-therapy the focus and emphasis is to be put on the combined-therapy for the restriction of the progression of resistance.

CONCLUSION

We observed CPE as (100%) Polymyxin – B susceptible; whereas, in the case of Fosfomycin it

is 77% and Tigecycline susceptibility as 29%. These antimicrobials are potent to be utilized for the CPE infection treatment and management.

REFERENCES

1. Zusman, O., et al., Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy, 2016. 72(1): p. 29-39.
2. Morrill, H.J., et al. Treatment options for carbapenem-resistant Enterobacteriaceae infections. in Open forum infectious diseases. 2015. Oxford University Press.
3. Garnacho-Montero, J., et al., Optimum treatment strategies for carbapenem-resistant Acinetobacter baumannii bacteremia. Expert review of anti-infective therapy, 2015. 13(6): p. 769-777.
4. Perez, F., et al., Treatment options for infections caused by carbapenem-resistant Enterobacteriaceae: can we apply “precision medicine” to antimicrobial chemotherapy? Expert opinion on pharmacotherapy, 2016. 17(6): p. 761-781.
5. Bergen, P.J., et al., Optimizing polymyxin combinations against resistant gram-negative bacteria. Infectious diseases and therapy, 2015. 4(4): p. 391-415.
6. Doi, Y. and D.L. Paterson. Carbapenemase-producing enterobacteriaceae. in Seminars in respiratory and critical care medicine. 2015. NIH Public Access.
7. Rizek, C., et al., In vitro activity of potential old and new drugs against multidrug-resistant gram-negatives. Journal of Infection and Chemotherapy, 2015. 21(2): p. 114-117.
8. Rodríguez-Baño, J., et al., Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clinical microbiology reviews, 2018. 31(2): p. e00079-17.
9. Ni, W., et al., Efficacy of polymyxins in the treatment of carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis. Brazilian Journal of Infectious Diseases, 2015. 19(2): p. 170-180.
10. Karaiskos, I., A. Antoniadou, and H. Giamarellou, Combination therapy for extensively-drug resistant gram-negative bacteria. Expert review of anti-infective therapy, 2017. 15(12): p. 1123-1140.
11. Fan, B., et al., Activity of colistin in combination with meropenem, tigecycline, fosfomycin, fusidic acid, rifampin or sulbactam against extensively drug-resistant Acinetobacter baumannii in a murine thigh-infection model. PloS one, 2016. 11(6): p. e0157757.
12. Bergen, P.J., et al., Polymyxin combinations: pharmacokinetics and pharmacodynamics for rationale use. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2015. 35(1): p. 34-42.
13. Abid, M., et al., ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF POLYMYXIN B, TIGECYCLINE AND FOSFOMYCIN AGAINST CARBAPENAMASE PRODUCING ENTEROBACTERIACEAE (CPE). Pakistan Armed Forces Medical Journal, 2017(6): p. 1026-1029.
14. Bradford, P.A., et al., Correlation of β-lactamase production and colistin resistance among Enterobacteriaceae isolates from a global surveillance program. Antimicrobial agents and chemotherapy, 2016. 60(3): p. 1385-1392.
15. Betts, J.W., et al., In vitro and in vivo activities of tigecycline-colistin combination therapies against carbapenem-resistant Enterobacteriaceae. Antimicrobial agents

and chemotherapy, 2014. 58(6): p. 3541-3546.
16. Kaye, K.S. and J.M. Pogue, Infections Caused by Resistant Gram-Negative Bacteria: Epidemiology and Management. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2015. 35(10): p. 949-962.