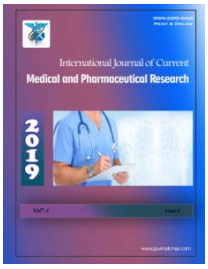
INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 5; Issue 06(A); June 2019; Page No. 4289-4292
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr201906677



Research Article

TACKLING MULTI DRUG RESISTANT GRAM NEGATIVE ORGANISMS - POSSIBLE ALTERNATIVES TO POLYMYXINS

Dr.B.Isabella Princess

Senior Registrar, Microbiology Apollo Speciality Hospitals, Vanagaram, Chennai

ARTICLE INFO

Article History:

Received 10th March, 2019
Received in revised form 2nd April, 2019
Accepted 26th April, 2019
Published online 28th June, 2019

Key words:

MDR, Tigecycline, Minocycline, Fosfomycin, Chloramphenicol, Doxycycline, Enterobacteriaceae, GNB

ABSTRACT

Introduction: Multi Drug Resistant Organisms (MDROs) pose a major threat in health care facilities across the globe as most of these bugs are recalcitrant to therapy. Polymyxins emerged as a lifesaving option to treat invasive infections with MDROs. However, in the recent past the CLSI - EUCAST joint recommendations are for the use of broth microdilution (BMD) for susceptibility testing for polymyxins. However, the procedure of BMD for polymyxins is tedious. To limit the use of polymyxins, selective reporting is done excluding polymyxins in reports.

Methods: This retrospective study was conducted at a tertiary care facility in South India over a period of two years from January 2017 to December 2018.2200Gram negative isolates were included, among which 15.8% of Multi Drug Resistant Gram negatives were further tested. Susceptibility to Chloramphenicol, Doxycycline, Tigecycline, Minocycline, Fosfomycin by Kirby Bauer disk diffusion or E-test for MIC determination was performed. Results were entered into WHONET software (2016 version) for further analysis and susceptibility pattern was determined.

Results: Among theEnterobacteriaceae,76.7% were susceptible to Fosfomycin, 32.4% to Doxycycline, 29.2% to Tigecycline, 29.1% to Chloramphenicol, 15.45% to Minocycline. Among Acinetobacterbaumanniiisolates,65% were susceptible to Minocycline, 63.6% to Tigecycline, 41.9% to Doxycycline.

Conclusion: Since there are few newer antimicrobials in the pipeline, it is wise to keep polymyxins as reserve drugs.Multidrug resistant bugs including A.baumannii show good susceptibility to the above mentioned antibiotics. Variation in species specific susceptibility was observed.Hence they can be used as alternatives to polymyxins based on their susceptibility and patient condition.

INTRODUCTION

Multi Drug Resistant (MDR) organisms are a red alert in any health care facility posing major threat at national and global levels.A simple example to this is the emergence and spread of bugs harbouring Carbapenem resistance genes which made major headlines on all forms of media. When an MDRO is isolated from a patient`s sample, many cascade of events roll out.[1]First and foremost challenge is the treatment of an MDR infection withthe available limited number of susceptible antibiotics. Next major challenge would be infection control practices such as contact isolation of the patient forcurtailing spread of the bug to other patients by following standard precautions. Next would be the prevention of a possible outbreak due to the MDRO, since Gram negative organismssurvive for days in various environmental niches. Colonization and biofilm formation of the Gram negative MDROs should be removed and re-colonization avoided by stringent cleaning and disinfection. Successful and early treatment of MDROs is the best way to cut short the deleterious sequence of events which follow.[1,2]

Treatment options for MDROs are limited and conserved in many settings to avoid emergence of resistance to these drugs. Selective reporting for antibiotics is the best way to ensure misuse and abuse of these lifesaving therapeutic options. Few drugs which have gained the limelight in the recent past for treatment of MDROs are Tetracyclines such as Doxycycline (1st generation), Minocycline (2nd generation), Fosfomycin,Phenicols (Chloramphenicol), Glycylcycline (Tigecycline). The most important attributes to these drugs are their broad spectrum of action and longhalf-life.The only noteworthy drawback is the intrinsic resistance of various organisms to these antibiotics.[3]Intrinsic resistance to Tetracyclines is noted in various Proteus species (except *Morganellamorganii*) and *Pseudomonas aeruginosa*. *Stenotrophomonasmaltophilia* is intrinsically resistant to Tetracycline but not to Tigecycline, Minocycline or Doxycycline. *Pseudomonas aeruginosa* and all Proteus species are intrinsically resistant to Tigecycline. Intrinsic resistance to Fosfomycin is seen in *Acinetobacter baumannii*, *Burkholderiacepacia* and *Stenotro phomonas maltophilia.* Organisms intrinsically resistant to Chloramphenicol are *Acinetobacter baumannii* and *Pseudomonas*

Corresponding author:* **Dr.B.Isabella Princess
Senior Registrar, Microbiology Apollo Speciality Hospitals, Vanagaram, Chennai

aeruginosa.[3]Usefulness of these antibiotics as second line in treatment of MDROs was evaluated in this study.

METHODS

This retrospective study was conducted at a tertiary care hospital in South India over a period of two years from January 2017 to December 2018. We included all multidrug resistant Gram negative isolates i.e.,organisms resistant to more than three classes of antibiotics and Carbapenem resistant organisms were also included.All MDR Gram negative isolates were evaluated for susceptibility against Chloramphenicol, Doxycycline, Tigecycline, Minocycline, Fosfomycin by Kirby Bauer disk diffusion or E-test for Minimum Inhibitory Concentration. Zones of inhibition were interpreted using CLSI 2016, 2017 and EUCAST 2016 guidelines. Since tigecycline breakpoints are unavailable in both CLSI and EUCAST,FDA breakpoints were used.

Isolates from Maytill December 2018 were tested for MIC using Vitek 2 compact system (bioMerieux, France). All susceptibility results were entered into WHONET software (2016 version) for further analysis and susceptibility percentages were analysed.

RESULTS

A total of 2200 Gram negative isolates were analysed, among which 1625 were Enterobacteriaceae.Figure 1 depicts the distribution of Gram negative isolates. Among 2200 Gram negative isolates, 15.8% were Multi Drug Resistant which was further tested for second line drugs.

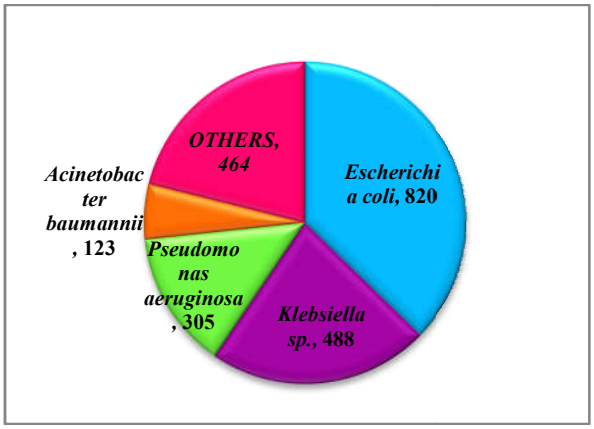


Fig 1 Distribution of Gram negative clinical isolates (n=2200)

Since Enterobacteriaceae contributed the vast majority, susceptibility of MDR Enterobacteriaceae to second line drugs are depicted in figure 2.

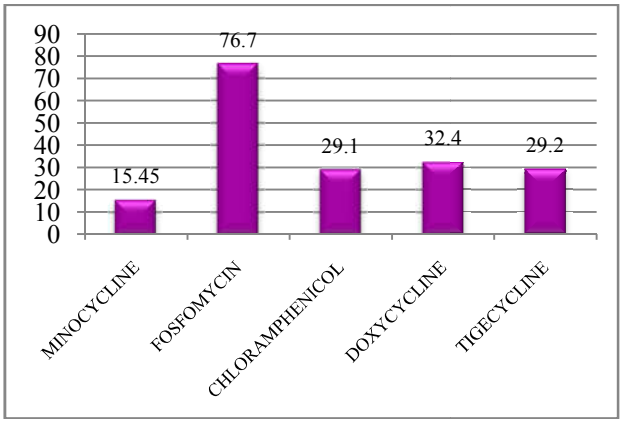


Fig 2 Percentage of susceptibility of MDR Enterobacteriaceae to antibiotics

Percentage of susceptibility of Enterobacteriaceaewas :76.7% to Fosfomycin, 32.4% to Doxycycline, 29.2% to Tigecycline, 29.1% to Chloramphenicol, 15.45% to Minocycline.

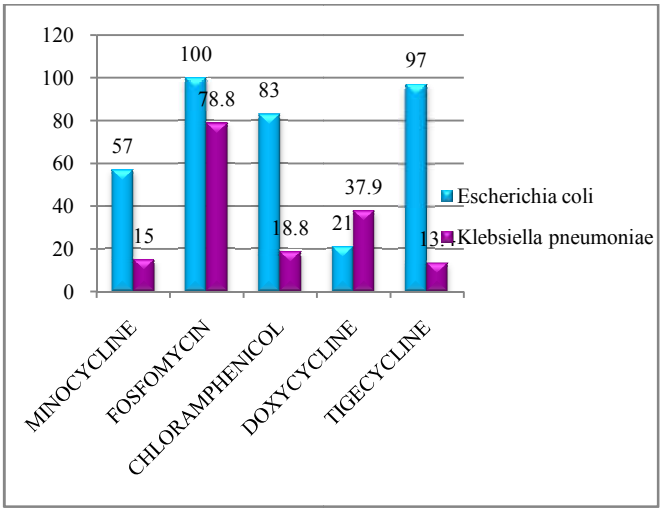


Fig 2 Percentage of susceptibility of commonest MDR Enterobacteriaceae to antibiotics

Escherichia coli and *Klebsiella pneumoniae* were the commonly isolated Enterobacteriaceae. Variation in percentage of susceptibility among these two organisms was noted to all tested antibiotics. *Escherichia coli* isolates had better percentage of susceptibility compared to *Klebsiella pneumoniae* isolates. However, only doxycycline susceptibility was contrary to this observation.

*Escherichia coli*isolates showed better sensitivity to Fosfomycin and Tigecycline, *Klebsiella pneumoniae* isolates showed better sensitivity to Fosfomycin and Doxycycline. Least percentage of susceptibility was noted among *Escherichia coli* to Doxycycline and among *Klebsiella pneumoniae*toTigecycline.

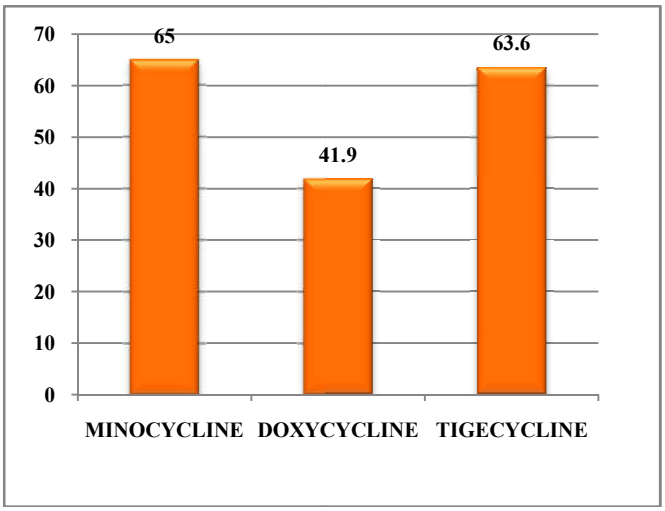


Fig 3 Percentage of susceptibility of MDR *Acinetobacter baumannii*to antibiotics

Percentage of susceptibility of *Acinetobacter baumannii*was :65% to Minocycline, 63.6% to Tigecycline, 41.9% to Doxycycline. Minocycline susceptibility of *A.baumannii* was high compared to other antibiotics.

Individual organism based susceptibility percentage of antibiotics is depicted in table 1. Intrinsic resistance of organisms to various tested antibiotics are also mentioned.

Table 1 Percentage susceptibility of microorganisms to various drugs

Organism	Antibiotic susceptibility in percentage				
	Chloramphenicol	Doxycycline	Minocycline	Tigecycline	Fosfomycin
Escherichia coli	83	21	57	97	100
Klebsiellaspecies	15.5	35.1	14.3	14.3	78
Pseudomonas aeruginosa	IR	IR	IR	IR	80
Acinetobacter baumannii	IR	41.9	65	63.6	IR
Others	0	14.3	0	40.5	50

*IR – Intrinsic Resistance, Others – includes MDREnterobacter species, MDR Proteus sp., MDR Providencia sp.

DISCUSSION

The concept of antibiotic cycling forms the basis of tackling MDR pathogens. Newer antimicrobial drugs if available should be used judiciously to conserve and prevent development of drug resistance. We have analysed the susceptibility pattern of various Gram negative isolates to drugs which we have reserved as second line. All multidrug resistant Gram negative isolates are subjected to susceptibility to these second line drugs. All these drugs have a broad spectrum of action with good bioavailability and tissue penetration.[4,5]Since these antibiotics were not in use for a brief period of time, revisiting their susceptibilities was helpful in determining their use as second line drugs.

The major class of antibiotics discovered in 1940 which gained importance due to their broad spectrum of action were tetracyclines.[6]Minocycline was discovered in 1960 and Tigecycline, the glycylcycline subclass of Tetracyclines later in 1990 as a derivative of Minocycline.[7,8]Minocycline has also been licensed for use against *Acinetobacter baumannii*due to its better pharmacokinetic/pharmacodynamics properties, long half-life, good tissue penetration and availability as oral formulation.[8]Our findings were consistent with previous reports on susceptibility percentage of *A.baumannii* isolates to Minocycline being 65%.Tigecycline showed good action against *E.coli* (97%) and *A.baumannii* (63.6%).Reason for this could be due to more recent discovery of Tigecycline compared to other tetracyclines. However their action against Klebsiella species was as low as 14.3% making their use questionable. Since the action of tigecycline is varied against each bacteria, individual organism based susceptibility should be determined.

Doxycycline which was introduced in 1967 is a broad spectrum long acting tetracycline against which MDR pathogens showed less percentage of susceptibilities. Less than 50% susceptibility was observed against doxycycline, highest being against *A.baumannii* (41.9%).Chloramphenicol a drug of class phenicol was developed in 1949 from *Streptomyces venezuelae* and other bacteria. It has a broad spectrum of activity against Gram positives, Gram negatives and atypical bacteria.In the current study chloramphenicol showed vast variation in activity against different species of MDR Gram negative isolates. *E.coli* isolates showed 83% susceptibility, whereas *K.pneumoniae* isolates showed only 15.5% susceptibility. The disadvantage with chloramphenicol is its inefficacy against most non fermenting Gram negative bacilli which are intrinsically resistant to Chloramphenicol.

Fosfomycin was an antibiotic discovered in 1969 with good spectrum of action against Gram negative and Gram positive organisms. Fosfomycin was first produced from cultures of Streptomyces species. It attains maximum concentration and is recovered unchanged in urine. Fosfomycin should therefore be reserved for treating multidrug resistant urine isolates. Susceptibility testing can be interpreted using CLSI (for *E.coli* urine isolates) and using EUCAST (for other organisms). However, fosfomycin cannot be used for treating MDR *Acinetobacter baumannii* since it is intrinsically resistant to Fosfomycin. In the current study, percentage of fosfomycin susceptibility was good against *E.coli*, Klebsiella species and *Pseudomonas aeruginosa*. Since *P.aeruginosa* is intrinsically resistant to Tetracyclines and Chloramphenicol, Fosfomycin is a good option in treatment of MDR *P.aeruginosa*.

In the current study, we observed few isolates with non-susceptibility to Colistin showing susceptibility to other tested second line drugs.Another drawback in using polymyxins is the tedious and cumbersome process of micro broth dilution for determining MIC.This makes these drugs an attractive option for treating multidrug resistant as well as colistin resistant pathogens.Taking all this into consideration, we looked for possible alternative antimicrobials for therapeutic use. We conclude by saying, Fosfomycin can be used to treat MDR Enterobacteriaceae. Since *A.baumannii* is intrinsically resistant to Chloramphenicol and Fosfomycin, other alternative drugs such as Doxycycline, Tigecycline, Minocycline can be used based on their susceptibility patterns.Other MDR Enterobacteriaceaecan be treated based on pathogen specific susceptibility to these antibiotics. Table 2 lists the details of second line drugs with spectrum of action and PK/PD properties.

Table 2 Pharmacological properties of second line antibiotics

Drug	Class/subclass	Spectrum	Pk/pd properties
Chloramphenicol	Phenicol	GNB, GPC	Oral and intravenous
Doxycycline	Tetracycline	GNB, GPC, atypical, *Plasmodium falciparum*, Rickettsiae	Oral and intravenous, long acting, good tissue penetration
Minocycline	Tetracycline (2`nd gen.)		
Tigecycline	Tetracycline (Glycylcycline)	GNB, GPC	Intravenous
Fosfomycin	Fosfomycin	GNB, GPC (Urine isolates)	Oral

CONCLUSION

A major difference in susceptibility of each pathogen exists with each antibiotic. Pathogen specific susceptibility is therefore necessary to stratify treatment plan. Rather than calling these drugs as definitive alternatives, they can be used as possible alternatives to polymyxins which can be reserved as final choice. This judgement should be made based on pathogen specific susceptibility patterns to these antibiotics, thereby warranting large scale multi centre studies to determine the same.

Reference

1. Paul M, Carmeli Y, Durante-Mangoni E, *et al*. Combination therapy for carbapenem-resistant Gram-negative bacteria. J AntimicrobChemother 2014;69:2305-9.
2. Falagas ME, Lourida P, Poulikakos P, Rafailidis PI, Tansarli GS. Antibiotic treatment of infections due to carbapenem-resistant Enterobacteriaceae: systematic evaluation of the available evidence. Antimicrob Agents Chemother 2014;58:654-63.

3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 28`th ed. CLSI Supplement M100.Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
4. Bishburg E, Bishburg K. Minocycline – an old drug for a new century: emphasis on methicillin-resistant *Staphylococcus aureus*(MRSA) and *Acinetobacter baumannii*. Int J Antimicrob Agents 2009;34:395-401.
5. Pogue JM, Marchaim D, Kaye D, Kaye KS. Revisiting "older" antimicrobials in the era of multidrug resistance. Pharmacotherapy 2011;31:912-21.
6. Devarajan V, Bansal N, Ghafur KA. Comparative analysis of tigecycline and minocycline susceptibility among Gram-negative isolates. J Contemp ClinPract. 2018;4:8-12. doi: 10.18683/jccp.2018.1029
7. Zhanel GG, Homenuik K, Nichol K, *et al*. The glycylcyclines: a comparative review with the tetracyclines. Drugs 2004;64:63-88.
8. Peterson LR. A review of tigecycline – the first glycylcycline. Int J Antimicrob Agents 2008;32:215-22.

How to cite this article:

Dr.B.Isabella Princess (2019) 'Tackling Multi Drug Resistant Gram Negative Organisms - Possible Alternatives to Polymyxins', *International Journal of Current Medical and Pharmaceutical Research,* 05(06), pp 4289-4292.

****