ORIGINAL RESEARCH

CARBAPENEM RESISTANT GRAM-NEGATIVE ORGANISMS: THERAPEUTIC OPTIONS IN A RESOURCE LIMITED SETTING

Igunma, AJ[1], Robinson NI[2*], Oboro IL[2], Bob-Manuel M[2], Alex-Wele M[3]

[1]Department of Medical Microbiology and Parasitology, University of Benin Teaching Hospital, Nigeria
[2]Department of Medical Microbiology and Parasitology, Rivers State University, Nigeria
[3]Department Medical Microbiology and Parasitology, University Port-Harcourt, Nigeria

***Correspondence:** Robinson, N.I; **Email:** ndirobinson@gmail.com

Abstract

Introduction: Health care associated infections due to carbapenem resistant gram-negative bacteria (CRGNB) are on the rise with limited available therapeutic options for these infections. Therapeutic options include newer drugs and drug combinations, which are not readily accessible in low resource. Older more affordable drugs have been reported to have good antimicrobial activity against some of these pathogens. This study aimed to determine the susceptibility profile of CRGNB isolates to the recommended, readily available and affordable, antibiotics in our setting.

Methods: This cross-sectional laboratory-based study was carried out from December 2017-August 2018. *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* identified from inpatient specimens were subjected to susceptibility testing using the modified Kirby- Bauer technique. Carbapenem resistant isolates were further subjected to susceptibility tests against tigecycline, colistin, fosfomycin, polymyxin B, amikacin, and piperacillin-tazobactam. Breakpoints were read off using CLSI standards and appropriate controls.

Results: Of the 238 isolates studied, 18 (8.2%) showed resistance to ertapenem while 16 (6.7%) and 15 (6.3%) showed resistance to imipenem and meropenem respectively. Tigecycline, colistin, and polymyxin B showed impressive activity 94%, 88% and 83% activity against carbapenem resistant organisms respectively.

Conclusion: Tigecycline, colistin and polymyxin B are effective therapeutic options for treatment of infections caused by CRGNB. To optimize clinical improvement and reduce morbidity and mortality associated with these infections in resource poor countries, we recommend the use of tigecycline, colistin or polymyxin B for empirical treatment of infections caused by these pathogens.

Key words: Carbapenem resistance, Tigecycline, Polymyxin, Gram negative

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INTRODUCTION

Globally, there has been a drastic increase in the number of Gram negative organisms resistant to carbapenems .[1] Carbapenem resistant organisms (CRO) are usually multidrug-resistant strains which are resistant to all β-lactam antibiotics in addition to carbapenems.[1] These strains may also be resistant to other classes of antibiotics such as flouroquinolones and aminoglycosides.[2] Carbapenems resistance mechanisms include active transport of drug out of the cell (augmented efflux)[3], mutation or loss of outer membrane porins[4] and enzymes (carbapenemase) production[3]. However, carbapenemases production is the mechanism responsible for the multidrug resistance ability of most isolates.[3] This mechanism of resistance is more worrisome because of the reduced number of therapeutic options to treat the resultant infections.

Till date, the best (effective, affordable and available) empirical antimicrobial management for infections due to CRGNB has not been established .[5] These resistant strains are historically known to be susceptible to Tigecycline, Polymyxins (Polymyxin B and Colistin) and some aminoglycosides but their use is limited or has been out rightly abandoned, in some cases, due to high level of toxicity.[1] These previously underused drugs are being re-introduced, as a consequence of the obviously dried-up antibiotic pipeline, better understanding of the pharmacokinetics and pharmacodynamics of the drugs, as well as many findings demonstrating desirable therapeutic effects against some multidrug resistant pathogens.[6] As a result, these antibiotics are currently considered the drug of choice although none of them is as effective as the carbapenems.[1]

Other noteworthy therapeutic options include the carbapenems regime, and these have some clinical utility particularly on the background of CRE with lower MICs.[2] The notable options are; a higher dose of carbapenem mono-therapy; combination of carbapenems with other active anti-CRE agents such as tigecycline; double-carbapenem therapy (DCT)[2] and the use of extended infusions.[7]

The recently approved β-lactam/β-lactamase inhibitor combinations such as ceftazidime-avibactam, meropenem-vaborbactam and imipenem/cilastatin–relebactam) have proven, in many studies, to be excellent therapeutic options for CRE infections with minimal toxicity.[8] However, these novel β -lactamase inhibitors have a limited spectrum of coverage as each is selectively active against the products of one or two carbapenemase genes. For example, Avibactam combinations inhibit both Class A (KPC) and Class D (OXA-48) [8], while vaborbactam and relebactam combinations inhibit only Class A (KPC).[9] Consequently, molecular characterization of isolates would be needed routinely for optimal efficacy. This limited gene coverage, high cost and difficulty in accessibility are serious limitations to the use of these newer agents in our settings. Other new drugs with promising efficacies are the new tetracycline (eravacycline) and the new aminoglycoside plazomicin.[10] While these options exists in other climes, the options are more limited in our setting. Hence this study aimed to determine the susceptibility profile of carbapenem resistant Gram-negative bacterial isolates to the recommended, as well as readily available and affordable antibiotics for their treatment in our environment.

MATERIALS AND METHODS

The study was a laboratory-based cross-sectional study carried out between December 2017 and August 2018 University of Port Harcourt Teaching Hospital. Specimens, including wound swabs, urine, blood, and body aspirates from in-patients suspected to be having hospital acquired infections were submitted to the medical microbiology and parasitology laboratory of the hospital for routine analysis. Two hundred and thirty-eight (238) isolates, from these specimens, confirmed as *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* using MICROBACT 12E identification kits (Oxoid, UK) were consecutively recruited.

Susceptibility testing was performed on all isolates using the modified Kirby-Bauer disc diffusion technique according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[11] A suspension of each freshly cultured isolate was prepared to a turbidity equivalent to 0.5 McFarland standard and was inoculated on Mueller-Hinton Agar, using a sterile swab to make a lawn. The following antibiotics were tested against each isolate: ertapenem (10µg), imipenem (10µg), meropenem (10µg), ceftazidime (30µg), ceftriaxone (30µg), gentamicin (10µg), aztreonam (30µg) and piperacillin (100/10µg). Incubation parameters included ambient air at 35-37^{o}c for 16-18 hours. Thereafter, the zones of inhibition were measured and interpreted as resistant, intermediate, or susceptible using criteria recommended by CLSI 2018.

Isolates resistant to any of the carbapenems were further tested for susceptibility to tigecycline (15µg), Colistin (10µg), polymyxin B (300unit) and fosfomycin (200µg) according to CLSI and EUCAST interpretative criteria[12] *Klebsiella pneumoniae* ATCC 13883 and *Klebsiella pneumoniae* ATCC BAA-1705 as negative and positive control respectively.

Data were analyzed using SPSS version 21. Categorical data were reported using percentages. Data were presented using tables and pie charts. Ethical approval for the study was obtained from the ethical review committee of the University of Port Harcourt Teaching Hospital.

RESULTS

A total of 238 isolates comprising 141 (59.2%) from urine, while 13 (5.5%) and 10 (4.2%) were recovered from blood and body fluid aspirates respectively. Of the 238 isolates, 96 (40.3%) were *E coli*, 68 (28.6 %) *Klebsiella pneumoniae* and *Acinetobacter baumannii* was the least with 25 (10.5%) (Table I).

Table I. Proportion of gram-negative organisms from different samples

	Total number of isolates n (%)	Urine n (%)	Wound swab n (%)	Blood n(%)	Body fluid aspirate n (%)
E. coli	96 (40.3)	67(69.8)	22 (22.9)	6 (6.3)	1 (1.0)
K. pneumoniae	68 (28.6)	32(47.0)	28(41.2)	3(4.4)	5(7.4)
A. baumannii	25 (10.5)	15(60.0)	9(36.0)	0	1(4.0)
P. aeruginosa	49 (20.6)	27(55.1)	15(30.6)	4(8.2)	3(6.1)
Total (%)	**238 (100)**	**141(59.2)**	**74 (31.1)**	**13 (5.5)**	**10 (4.2)**

Results of susceptibility testing showed that 93.3%, 91.2% and 90.8% of the isolates were susceptible to meropenem, ertapenem and imipenem respectively. However, ertapenem had the highest resistance profile of 7.6% (Table II)

Table II. Susceptibility profile of isolates to carbapenems (n = 238)

	Susceptible (%)	Intermediate (%)	Resistance (%)
Meropenem	222 (93.3)	1 (0.4)	15 (6.3)
Imipenem	216 (90.8)	3 (1.3)	16 (6.7)
Ertapenem	217 (91.2)	1 (0.4)	18 (7.6)

Tigecycline showed the highest antibacterial activity with 94.4 % (17) of carbapenem resistant organisms (CRO) being susceptible to it while 88% (16), and 83.3 % (15) of CROs were susceptible to colistin and polymyxin B respectively. Only 22% (4) of CROs were susceptible to amikacin while none of the isolates was susceptible to piperacillin/tazobactam (Table III).

Table III. Susceptibility pattern of carbapenem resistant isolates (n = 18)

	Susceptible n (%)	Intermediate n (%)	Resistance n (%)
Colistin	16 (88.9)	1 (5.6)	1 (5.6)
Tigecycline	17 (94.4)	0 (0.0)	1 (5.6)
Polymyxin B	15 (83.3)	0 (0.0)	3 (16.7)
Fosfomycin	7 (38.9)	2 (11.1)	3 (16.7)
Amikacin	4 (22.2)	4 (22.2)	10 (55.6)
Piperacillin/ tazobactam	0 (0.0)	1 (5.6)	17 (94.4)

Surgical and medical wards contributed the most to the number of CROs at 39% and 27% respectively while pediatric ward contributed the least with 11% (Figure 1).

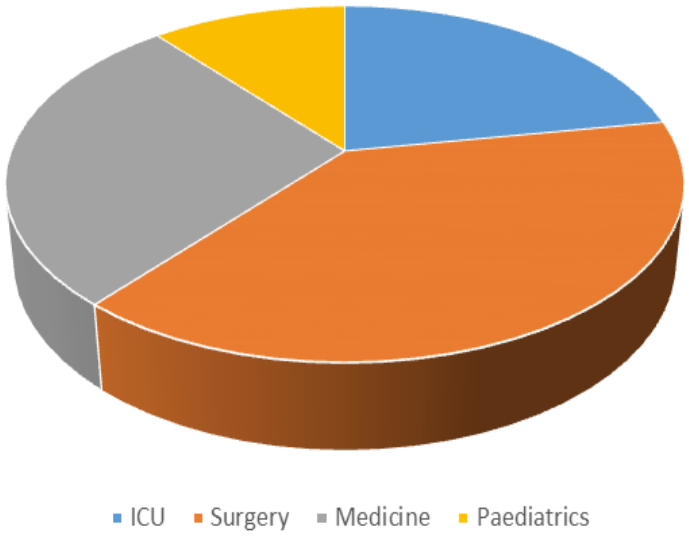

Figure 1. Distribution of CRO by source ward/unit

DISCUSSION

Our results demonstrated that tigecycline, colistin, and polymyxin B have impressive antibacterial activity against carbapenem resistant gram-negative organisms (CRO) at rates of 94%; 88%; 83% respectively. This agrees with the report by Garg*et al.* in India of high susceptibility rates to these antibiotics.[13] Lee *et al* also reported that tigecycline demonstrated excellent spectrum of activity against Klebsiella pneumoniae carbapenemases (KPC)-producing organisms in their review of 106 carbapenemase producing Enterobacteriaceae.[14] The spectrum of activity of tigecycline includes infections caused by many gram-negative, gram-positive, and anaerobic organisms. In addition, tigecycline has excellent coverage for multidrug-resistant strains of gram-positive organisms, such as methicillin-resistant *Staphylococcus*

aureus (MRSA) and Vancomycin-resistant enterococci (VRE) species [15] as well as excellent outcomes in many hospital acquired infections (HAIs). Tigecycline is bacteriostatic therefore it is advised that its use as mono therapy should be limited to complicated intra-abdominal and skin and soft tissue infections[15] while combination therapy may be required for severe infections requiring bactericidal activity such as bacteremia.[14] Other factors in favor of tigecycline include its high protein bound activity with a large area of distribution. Therefore, dosage adjustments are not required in patients with impaired renal function or those with end stage renal disease (ESRD) on hemodialysis.[16] On the other hand, it is limited by the fact that it does not have antimicrobial activity against *Pseudomonas aeruginosa* and *Proteus* species, two important pathogens in healthcare associated infections.[15]

A review of eleven (11) studies, by Trecarichi *et al*, who studied the susceptibility patterns of CROs to last resort antibiotics showed that the rates of resistance to colistin ranged from 9.7% to 51.3% (mean 22.6%) and 0 to 33% (mean 15.2%) for tigecycline.[1] Tumbarello *et al*. also documented a susceptibility rate of 89% and 91% to fosfomycin and tigecycline respectively.[17].In contrast, a study in 2013 reported lower susceptibility patterns of 73% and 75% to colistin and tigecycline respectively especially among KPC – producing carbapenem resistant Enterobacteriaceae.[18] This agrees with assertions that emergence of resistance to tigecycline and other therapeutic options for treatment of carbapenem resistant isolates are high in countries with already high rates of multidrug resistance.[18]

Colistin and polymyxin B also showed good antibacterial activity in our study. These are bactericidal, of narrow spectrum with excellent coverage for carbapenem resistant gram-negative organisms including the Enterobacteriaceae, MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa.*[19] Among the Enterobacteriaceae, *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Escherichia coli, Salmonella* and *Shigella* spp. are usually susceptible to colistin and polymyxin B. However, these antibiotics have limited activity against *Proteus* spp. and *Serretia marcescens* and no activity against gram positive organisms as well as anaerobes.[20] Colistin and polymyxin B have been recommended for treatment of blood stream infections, intra-abdominal infections and other severe hospital-acquired infections.[18] Colistin is administered as an inactive pro-drug; colistimethate (CMS), and it is believed that only a small amount of this is converted to the active ingredient colistin per time resulting in delay of up to 7 hours in achieving maximum plasma concentration of colistin. Fortunately, with Colistin, despite being a concentration dependent drug, the length of exposure of the organism to the drug as critical as the peak plasma concentration.[20] Very extensive renal tubular reabsorption of filtered colistin occurs such that it is only minimally eliminated by the kidneys. This advantageously creates ample time for exposure to pathogens[21]. The major challenge with its use in practice, is the need for renal-dose adjustment even in mild renal impairment due to nephrotoxicity.[22] Polymyxin B on the other hand still plays the role of an antibiotic of last resort because of its activities. It is anticipated that resistance to this agent will continue to emerge and so better understanding of the safest and most efficacious manner to deliver polymyxin B will remain highly beneficial. Despite its rapid bacterial clearance quality, the frequency of development of resistance while on treatment is high. For optimal therapeutic results, it is recommended that polymyxin B be used in combination with other effective antibiotics.[20] Polymyxin B requires little or no renal dose adjustment as majority of the drug is excreted through non-renal routes and since it is administered as the active drug peak plasma concentration is achieved within a very short time.[22]

Our study showed that among the CRGNB, the highest degree of resistance (8.2%) was expressed against ertapenem with imipenem and meropenem having lower rates of 7.2% and 6.3% respectively. These results are similar to the 8.4% prevalence of resistance to ertapenem reported in Port Harcourt[23] but slightly lower than the findings in a similar study done in a tertiary hospital in Abeokuta, south west Nigeria, where a 9.3% prevalence of carbapenem resistance was reported.[24] This could imply similar usage rates and parameters in both centers. A higher prevalence of 15.2% carbapenem resistance was however recorded in Lagos, Nigeria[25] and this high prevalence could be explained by the possible increased use of carbapenems in this setting as Lagos is a bigger cosmopolitan city where there may be more access to carbapenems. In northeast Nigeria, a prevalence of 12.4 % carbapenem resistance was reported, although this was seen among a more diverse group of Enterobacteriaceae[26]. Summarily, it can be said that the prevalence of carbapenem resistant organisms in Nigeria, though varied, is generally low and this may be because the use of carbapenem in clinical settings had been relatively low and limited.

Conversely, studies in other African countries recorded higher prevalence rates of resistance to carbapenems; 18.4% was recorded for meropenem in Uganda[27] while 24% and 7% were for ertapenem and meropenem respectively in Tanzania.[28] Studies in India report as high as 30% resistance to carbapenems. Interestingly, we identified a higher prevalence in our study than the 4.5% recorded in a study done by Caiet *al* in the United States of America.[29] One wonders if this could be due to better antimicrobial stewardship and infection control practices there.

Finally, our study showed that CRNBG were more prevalent in the surgical wards. Invasive procedures, instrumentation and manipulations which are common among surgical patients are predisposing factors to the development of health care associated infections and CRNBG,[3]and this was also observed in our study.

Limitations

Carbapenem-beta lactamase antibiotic disc to ascertain the susceptibility of carbapenem resistant gram-negative bacteria to these antibiotics were not available. These may have increased the options of drugs available to treat these infections.

Conclusion

Tigecycline, colistin and polymyxin B are effective therapeutic options for treatment of infections caused by carbapenem resistant gram-negative bacteria. As commonly experienced in resource

poor settings, financial constraints result in poor compliance with antimicrobial therapy with consequent increased morbidity, length of hospital stay and morbidity. To optimize clinical improvement and reduce morbidity and mortality associated with these infections in resource poor settings, we recommend the use of colistin or polymyxin B, for empirical treatment of infections caused by carbapenem resistant gram-negative bacteria.

Conflicts of Interest: The authors declare no conflict of interest

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