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Short Communication

High drug-pathogen mismatch in the management of invasive carbapenem-resistant *Enterobacteriaceae* infections at a tertiary hospital in Nigeria

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ABSTRACT

Objectives: This study aims to provide lacking data on antibiotics and treatment strategies used in the management of carbapenem-resistant *Enterobacteriaceae* (CRE) infections in Nigeria.
Methods: A cross-sectional study was carried out at the University College Hospital in Ibadan. CRE isolated from routine culture of specimens from hospitalized patients from December 2021 to September 2022 was identified. Treatment information and other data were collected from the patients' medical records.
Results: The hospital laboratory isolated CRE from 55 patients during the study period and 27 (49.1%) of them had data available for the study. The most frequently isolated CRE was *Klebsiella spp.* (13 of 27, 48.1%). Of the 24 patients who received empiric antibiotics, only two (8.3%) of their CRE isolates were susceptible. After receiving culture results, 18 (66.7%) patients were treated with at least one antibiotic, to which resistance was documented. Only three (11.1%) patients overall commenced or remained on an antibiotic, to which their CRE isolate was susceptible.
Conclusions: Despite culture data, we found a high prevalence of drug-pathogen mismatch in CRE treatment, including new or persistent use of antibiotics, to which resistance was documented. Antimicrobial stewardship efforts need to be strengthened to specifically address CRE treatment and effective antibiotics need to be made accessible.

Introduction

Infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) are a growing concern in developing countries and often associated with poor clinical outcomes [1]. CREs are designated as the highest level of World Health Organization (WHO) priority pathogens [2]. The optimal choice of drugs to treat CRE depends on various factors such as the mechanism of resistance to carbapenems, the minimum inhibitory concentration (MIC) and the site and severity of infection [3]. Antibiotic use guidelines, which take all these factors into consideration, as well as the local molecular and clinical epidemiology of pathogens, provide a good guide for treatment of CRE and other bacterial infections. The Africa Center for Disease Control developed treatment guidelines for bacterial infections; notably absent are recommendations for treatment of CRE infections [4]. The *WHO AWaRe antibiotic book*'s section on "Reserve" antibiotics, however, does include recommendations for treatment of carbapenem-resistant bacteria [5]. Notwithstanding, it is not clear what treatment strategies are used for managing CRE infections in most sub-Saharan African countries. We set out to describe antibiotic use in treatment of CRE infections at a tertiary hospital in Ibadan, Nigeria.

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Methods

A retrospective cross-sectional study was carried out at the University College Hospital in Ibadan, a 1000-bed tertiary hospital affiliated with the University of Ibadan. Clinical specimens obtained for culture during routine care of patients and processed at the hospital's microbiology laboratory at University College Hospital from December 2021 to September 2022 were reviewed. All microbiology records of culture reports of urine, blood, sputum, pleural fluid, cerebrospinal fluid, wound swab or biopsy, and intra-abdominal infections were included in our study and reviewed during the study period to identify CRE. No routine clinical specimens processed in the laboratory during the study period were excluded. Pathogens were isolated through bacteria culture and phenotypic identification methods. Briefly, the modified Kirby–Bauer disk diffusion method was used and it involves inoculating an agar plate with a standardized bacterial suspension, placing antibiotic-impregnated disks on the surface, incubating the plate, and measuring the inhibition zones to assess antibiotic susceptibility. The Clinical and Laboratory Standards Institute 2021 criteria were used for MIC evaluation. After the identification of CRE, a research nurse reviewed the medical records of the patient to obtain data including biodata and treatment information. Ethical approval was obtained from the University of Ibadan/University College Hospital, Ibadan, research ethics committee approval number: UI/EC/20/0009. Informed consent was waived because the study involved the use of de-identified secondary data.

Results

Over the 9-month study period, 923 isolates of *Enterobacteriaceae* were isolated from clinical specimens. A total of 55 (6%) were CRE, of which 27 (2.9%) of them had available records and were included in this report. Each of the 27 isolates were obtained from different patients. Of the 27 isolates, 19 (70.5%) were obtained from male patients and the median (interquartile range) age of the patients was 42 (25-58) years (Table 1). The most frequently cultured clinical specimen reported was urine (12, 44.4%), whereas *Klebsiella spp.* (13, 48.1%) were the most frequently isolated pathogens (Table 1). A total of 24 of the 27 patients with CRE infection had received empiric antibiotics before culture results were available and only two of these turned out to be effective against the CRE later isolated from their specimens. In both cases, there was a history of previously treated CRE infection (Table 2). Of the 24 patients on empiric antibiotics, seven (29.2%) of them discontinued antibiotics entirely after receiving culture results, including one of the patients who had empirically received an antibiotic effective against CRE. After receiving culture results, 18 (66.7%) patients added at least one antibiotic (including carbapenems), to which resistance was documented. None of these 18 patients received an antibiotic, to which susceptibility was documented after cultures were made available. Only three (11.1%) patients commenced or remained on an effective antibiotic after culture results became available. In these patients, these antibiotics were a polymyxin for two and amikacin for the third. Regarding antimicrobial susceptibility, all the CRE isolates were resistant to gentamicin and quinolones. *In vitro* susceptibility was documented to polymyxins, tigecycline, and amikacin in 21 of 27 (80.8%), 21 of 26 (77.8%), and six of 22 (27.3%) of CRE isolates, respectively.

Table 1
Characteristics of patients, culture specimens, and CRE isolates.

Characteristics	Number (%)
Gender	
Male	19 (70.4)
Female	8 (29.6)
Age group	
Child (<15 years)	6 (22.8)
Adult (≥15 years)	21 (77.8)
Specimen type	
Urine	12 (44.4)
Wound swab/biopsy	7 (25.9)
Blood	4 (14.8)
Sputum/Pleural fluid	2 (7.4)
Others	2 (7.4)
Received antibiotics before culture results available	
Yes	24 (88.9)
No	3 (11.1)
CRE isolated	
Klebsiella spp	13 (48.1)
Escherichia coli	5 (18.5)
Enterobacter spp	3 (11.1)
Serratia spp	3 (11.1)
Raoultella spp	2 (7.4)
Cronobacter spp	1 (3.7)

CRE, carbapenem-resistant *Enterobacteriaceae*.

Discussion

Our brief report describes the use of antibiotics for treatment of CRE infections in hospitalized patients in Nigeria, which, to the best of our knowledge, is the first of its kind. The number of available antibiotics for treatment of CREs worldwide has gradually increased in recent years and they are variably effective on different species and strains of pathogens [6]. Although newer agents for treating CRE are not available in Nigeria, polymyxins and tigecycline, to which CRE susceptibility has often been demonstrated *in vitro* locally, are available but are costly and scarce. Therefore, local experience with the available agents is limited. The few patients who received the appropriate empiric antibiotics (polymyxins) for CRE infection in our study had a history of confirmed CRE infections during the same admission, hence the decision to place them on a polymyxin empirically. This indicates an appropriate indication for the use of polymyxins, which are WHO Reserve antibiotics [5]. Unfortunately, several patients with confirmed CRE infection remained on antibiotics, to which resistance was documented. The reasons for this are unclear and may include poor provider knowledge of therapeutic options or unavailability or unaffordability of polymyxins and tigecycline [7]. Nevertheless, a smaller number of patients on ineffective empiric antibiotics had the antibiotics discontinued. The optimal drugs for treating CRE in this and similar settings have yet to be identified; however, using drugs without documented *in vitro* susceptibility may not be a good strategy [8]. The genes responsible for carbapenem resistance are also not well-described locally, which is important for identifying the appropriate antibiotics [9]. There are instances in which CREs with MIC values at the lower end of carbapenem resistance may still benefit from carbapenem therapy. In our study, this does not appear to be the rationale behind continued carbapenem use for CRE treatment because MIC data are not usually provided with culture results [10]. Meropenem and quinolone dual therapy was used in a few instances in our study, even though there was documented *in vitro* resistance to levofloxacin in all CRE isolates tested. Although there is evidence to suggest that dual therapy might be superior to monotherapy in certain circumstances, it does not appear to have been a guiding principle in the selection of this antibiotic combination [6]. In the cases where effective antibiotics were used after culture results became available, two of them received polymyxins, whereas the third received amikacin. Our descriptive study has some limitations. Our study was small and performed in a single center; medical records for about half of the patients with CRE infections were not available and thus not included in this report. We also do not have information on diagnosis, dosing, duration of treatment, and treatment outcomes, thus clinical information was lacking to interpret some of the treatment decisions made by the clinicians.

Table 2
Antibiotic choices before and after culture results were available.

Serial no	Empiric antibiotics before culture results were available	Empiric antibiotics given	Was CRE isolate susceptible to empiric antibiotic?	Antibiotic selected after culture results available	Was CRE isolate susceptible to newly selected antibiotic
1	Yes	gent, levo	No	**ceftriax, cefpodox**	No
2	Yes	ceftriax	No	**Pip-taz**	No
3	Yes	colis	No	**gent**	No
4	Yes	Anti-TB	No	**ceftriax**	No
5	Yes	ceftriax, levo	No	**mero,** levo	No
6	Yes	amox-clav, pip-taz	No	**ceftriax**	No
7	No		Not applicable	**ceftriax, gent**	No
8	Yes	cefotax	No	**amik, amox, pip-taz**	No
9	Yes	amik, amox, pip-taz	No	**levo**, pip-taz	No
10	Yes	gent, azith	No	**mero, levo**	No
11	No		Not applicable	**ceftriax**	No
12	Yes	levo, amik, pip-taz	No	levo	No
13	Yes	colis	Yes	**gent, pip-taz**, colis	Yes
14	Yes	gent, pip-taz, colis	Yes	No	Not applicable
15	Yes	Ceftriax, amox-clav, levo,	No	No	Not applicable
16	Yes	ceftriax, gent	No	**colis**	Yes
17	Yes	ceftaz, amik	No	**mero, levo**	No
18	Yes	levo	No	**mero,** levo	No
19	Yes	cefotax	No	No	No
20	No		Not applicable	**amik**	Yes
21	Yes	levo	No	**cefpodox**	No
22	Yes	ceftriax, amox-clav, levo,	No	**other**	No
23	Yes	cipro	No	No	Not applicable
24	Yes	ceftriax, gent, amox-clav,	No	No	Not applicable
25	Yes	ceftriax	No	**cipro**	No
26	Yes	ceftriax, amox-clav, azithro	No	No	Not applicable
27	Yes	metro	No	No	Not applicable

Amik=amikacin, amox=amoxicillin, amox-clav=amoxicillin-clavulanate, azithro=azithromycin, cefotax=cefotaxime cefpodox=cefpodoxime, ceftaz=ceftazidime, ceftriax=ceftriaxone, cipro=ciprofloxacin, colis=colistin, gent=gentamicin, levo=levofloxacin, mero=meropenem, pip-taz=piperacillin-tazobactam.

*Antibiotics commenced after availability of culture results which are different from the empiric antibiotics are highlighted in **bold font**

	No empiric antibiotics given before culture results available
	CRE isolates not found to have in-vitro susceptibility to empiric or newly selected antibiotics
	Not applicable
	CRE isolates found to have in-vitro susceptibility to empiric or newly selected antibiotics

Conclusion

The treatment of CRE infections in Nigeria is sub-optimal and existing treatment guidelines need to be adapted for institutions urgently in this and other resource-limited settings. Health care workers need to be trained as part of an antimicrobial stewardship intervention for CRE treatment. Research needs to be targeted toward understanding the local molecular epidemiology of CRE and the most effective antibiotics for treatment. Infection prevention and control practices need to be strengthened to prevent the spread of these difficult-to-treat pathogens in health care settings. Lastly, there is a need for equitable access to the most appropriate treatment agents in settings where this is not the case.

Declarations of competing interest

Olukemi Adekanmbi reports financial support from Pfizer. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

Ethical approval was obtained from the University of Ibadan/University College Hospital, Ibadan, research ethics committee approval number: UI/EC/20/0009. Informed consent was waived because the study only entailed the use of secondary data from microbiology laboratory records and clinical records.

Author contributions

OA participated in conceptualization of the research, study design, study coordination and drafted the manuscript. OP participated in the study design, statistical analysis and helped to draft the manuscript. AF participated in conceptualization of the research study, laboratory work and helped to draft the manuscript. OI participated in study design and data collection. BO participated in conceptualization of the research, data collection and helped with study coordination. SL participated in conceptualization of the research, study design and helped to draft the manuscript. IA carried out laboratory work and data collection. All authors read and approved the final manuscript.

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