The emergence of carbapenem resistance in *Enterobacteriaceae* in South Africa

The high levels of extended-spectrum β-lactamase (ESBL) production recorded among invasive *Enterobacteriaceae* in South Africa, especially documented for *Klebsiella pneumoniae*, in both the public sector (55-74%), as reported by Bamford et al in this edition of the *SAJEI*, and in the private sector (55-60%) shown previously, is disconcerting. Carbapenemases are the cornerstone of therapy for patients with serious infections caused by ESBL-producing organisms. The high ESBL prevalence amongst bacteraemic pathogens places a tremendous strain on the use of these agents as directed therapy, and empirically as well. In the private sector, the use of imipenem, meropenem and ertapenem, more than doubled in terms of monthly units sold, between January 2009 and June 2011. Not only is this consumption, through selective pressure, creating the ideal environment for the development of carbapenem resistance among the enterobacteriaceae, but at the same time, carbapenem use has been shown to be a risk factor for subsequent infections with ESBL-producing organisms. Excessive use, including inappropriate duration of therapy, is therefore selecting for the very resistance that the class is being used for. A vicious cycle is established in the process. Therefore, the emergence of carbapenem resistance among *Enterobacteriaceae* in South Africa is inevitable, and as documented for the public sector in this edition of the *SAJEI*, of major concern.

In the private sector in South Africa, *K. pneumoniae*, with reduced susceptibility to carbapenems due to CTX-M ESBLs, in conjunction with porin loss, was previously reported. Carbapenemases, among the *Enterobacteriaceae*, have been described in all four classes of beta-lactamases, but epidemiologically, most relevant carbapenemases fall into three of these. Class B includes the metallo-beta-lactamases (MBL) and the recently described New Delhi metallo-β-lactamases, NDM-1. In class A, *K. pneumoniae* carbapenemase (KPC) is clinically and epidemiologically the most important enzyme, whereas Class D includes the OXA-type carbapenemases, such as OXA-48, which occur in *Enterobacteriaceae*. Carbapenemases, from all three of these important classes, have recently been detected in South Africa. With the exception of our index patient infected with a *K. pneumoniae* isolate that produced OXA-48 (unpublished), the origins of the NDM-1 and KPC-2 strains are not known at this stage. The emergence of carbapenemases in South Africa poses a formidable challenge to clinical microbiologists, infection control and prevention (IPC) practitioners, and treating clinicians. A high index of suspicion is needed in the laboratory to detect these genotypes, as phenotypic expression may vary. Furthermore, the automated systems that are widely used for susceptibility testing, have a poor sensitivity and specificity for detecting carbapenemases. Screening tests for the detection of carbapenemases are still evolving, and are complicated by the heterogeneity of both enzymes and hosts. Rapid molecular confirmation of resistance mechanisms with PCR is considered to be the gold standard, but the limitation of PCR is that it will only detect the specific mechanisms targeted in the PCR reaction.

The rapid detection of KPC and NDM-1, as well as OXA-48, is essential in order to institute appropriate antibiotic treatment, as well as implement timely infection control measures, to prevent their transmission. KPCs, and increasingly OXA-48, are among the most prevalent carbapenemases worldwide, and have been documented to cause institutional outbreaks. NDM-1 has the ability to spread, unlike any resistance mechanism that has ever been seen in clinical microbiology. The plasmids that have been described to carry the NDM-1 gene are of a broad host range, implying that they can disseminate easily between other *Enterobacteriaceae*, and even unrelated species.

Furthermore, horizontal transfer of the NDM-1 gene itself to different plasmids can also occur, playing a major role in its widespread dissemination. The mobility of the NDM-1 genotype poses unprecedented challenges to IPC practitioners in containing its spread within institutions, and also limits the value of traditional DNA fingerprinting tests, such as pulsed field gel electrophoresis, that are widely used to determine the clonality of isolates in an outbreak situation.

Antibiotic treatment options for carbapenem-resistant *Enterobacteriaceae* are limited, as these organisms are often extensively drug resistant. Optimal treatment of these infections has not been established in clinical trials, but from case reports in the literature, combination therapy with two active drugs has been recommended. Colistin, tigecycline, and intravenous fosfomycin (which is currently not available in South Africa, are often the only treatment options. The emergence of resistance to colistin is rendering infections with organisms carrying these genotypes, virtually untreatable.

In conclusion, as stated by Bamford et al, ongoing surveillance and regular publication of antimicrobial resistance patterns of key invasive pathogens, is essential. However, further
molecular elucidation of carbapenem resistance mechanisms is crucial to improve understanding of the underlying risk factors for acquisition, including the potential role of antibiotic stewardship in conserving the class, and to prevent the spread of these resistant genotypes.

Currently, the emergence of carbapenem resistance among Enterobacteriaceae is still low in South Africa, but there is no time like the present. Carpe diem!

Jennifer Coetzee and Adrian Brink
Department of Clinical Microbiology and Molecular Biology, Ampath National Laboratory Services, Gauteng
E-mail: coetzeej@ampath.co.za

References


