

First report of IMI-1-producing colistin-resistant *Enterobacter* clinical isolate in Ireland, March 2013

T W Boo (teck.boo@hse.ie)^{1,2}, N O'Connell³, L Power³, M O'Connor⁴, J King¹, E McGrath¹, R Hill⁵, K L Hopkins⁵, N Woodford⁵

1. Department of Medical Microbiology, Galway University Hospitals, HSE West, Ireland

2. Discipline of Bacteriology, School of Medicine, National University of Ireland Galway, Ireland

3. Department of Clinical Microbiology, Mid-western Regional Hospital, Limerick, HSE West, Ireland

4. Department of Geriatric Medicine, Mid-western Regional Hospital, Limerick, HSE West, Ireland

5. Antimicrobial Resistance and Healthcare Associated Infections Reference Unit, PHE Colindale, London, United Kingdom

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We report the first case in Ireland of an IMI-1 carbapenemase-producing *Enterobacter asburiae*, which was resistant to both colistin and fosfomycin. The circumstances under which this isolate was acquired were unclear. Several reports of IMI-producing *Enterobacter* spp. have emerged in recent years, and colistin resistance in *Enterobacteriaceae* is also increasingly reported. Laboratories should be aware of the unusual antibiograms of IMI-producing isolates.

In late March 2013, a patient was admitted to the Mid-Western Regional Hospital, Limerick, Ireland with fractured ribs. She had not been hospitalised in the previous 24 months; her last hospital stay had been in December 2010. During the admission in 2013, she received a five-day course of amoxicillin-clavulanate for an *Escherichia coli* urinary tract infection, and routine rectal screening for gastrointestinal carriage of carbapenemase-producing *Enterobacteriaceae* (CPE) was performed in accordance with the surveillance and infection control policies of the hospital. Carbapenem-resistant *Enterobacteriaceae* were isolated from the culture of the rectal swab. The isolate was identified as *Enterobacter asburiae* using matrix-assisted laser desorption/ionisation-time of flight (MALDI-TOF) mass spectrometry (BrukerDaltonics, Bremen, Germany) and was designated ME52 in this report.

Antimicrobial susceptibility testing using disc diffusion and gradient minimal inhibitory concentration (MIC) (Etest, BioMerieux, Basingstoke, United Kingdom) methods showed the isolate ME52 to be resistant to amoxicillin-clavulanate, ceftazidime, cefotaxime, ciprofloxacin, aminoglycosides and tigecycline. The isolate was resistant to colistin and fosfomycin according to interpretive criteria from the European Committee on Antimicrobial Susceptibility Testing (EUCAST), with MICs of 96 mg/L and 64 mg/L, respectively [1]. Synergy testing of meropenem with the beta-lactamase inhibitors boronic acid, dipicolinic acid, and cloxacillin was

performed (RoscoDiagnostica, Taastrup, Denmark). Significant potentiation of the meropenem inhibitory zone was observed in the presence of boronic acid, but not with dipicolinic acid or cloxacillin, implying the presence of an Ambler class A carbapenemase. Real-time PCR for various carbapenemase genes was performed in the Department of Medical Microbiology in Galway University Hospitals, and *bla* genes for KPC, GES, NDM, VIM, IMP, and OXA-48-like carbapenemases

TABLE

Antimicrobial susceptibility results of the IMI-producing *Enterobacter asburiae* ME52 isolated in the Mid-Western Regional Hospital, Limerick, Ireland, March 2013

Antimicrobial agent	MIC (mg/L)	Susceptibility ^a
Ampicillin	> 64	R
Amoxicillin-clavulanate	64	R
Piperacillin-tazobactam	2	S
Cefotaxime	1	S
Ceftazidime	1	S
Cefoxitin	> 64	R
Aztreonam	0.25	S
Ertapenem	16	R
Imipenem	64	R
Meropenem	16	R
Ciprofloxacin	≤ 0.125	S
Gentamicin	1	S
Tobramycin	1	S
Amikacin	2	S
Tigecycline	0.5	S
Fosfomycin	64	R
Colistin	> 32	R

MIC: minimum inhibitory concentration; R, resistant; S, susceptible.

^a Based on EUCAST interpretive criteria [1].

were not detected. The isolate was subsequently referred to Public Health England (PHE) Colindale, London, United Kingdom (UK), for further investigation of the mechanism of carbapenem resistance. PCR identified the presence of *bla*_{IMI} in ME52. Nucleotide sequencing confirmed the carbapenemase to be IMI-1. MICs by agar dilution also confirmed susceptibility to third-generation cephalosporins and piperacillin-tazobactam, as well as resistance to carbapenems and colistin. The Table shows the antimicrobial susceptibility profile (MICs) of the isolate.

On further review, the patient had never received either colistin or fosfomycin therapy in the past. She had travelled in Europe during the past 15 years including France and Italy, but not to the American continent where the first isolates had been reported [2,3]. The only aquatic exposure of note was a visit to the River Jordan in Israel 10 years ago. In the current hospitalisation, the patient made an uneventful recovery and was discharged home.

Discussion

This is the first report in Ireland of an IMI carbapenemase-producing *Enterobacter* clinical isolate, coupled with the phenotype of colistin and fosfomycin resistance. It seems that the isolation of ME52 was a chance finding and the period of rectal colonisation by the patient was unknown. The clinical significance of the patient's travel history and aquatic exposure with respect to the acquisition of the IMI-producing *E. asburiae* is unclear.

IMI enzymes, together with another closely related beta-lactamase NMC-A, are found in *Enterobacter* spp. and form a relatively uncommon group within the Ambler class A carbapenemases [4]. The chromosomally located IMI-1 enzyme was first reported in 1996 in two *Enterobacter cloacae* isolates in the United States (US) [2]. Subsequently, plasmid-mediated IMI-2 carbapenemase was detected in clonally related environmental *E. asburiae* isolates recovered from seven of 16 rivers in the mid-western regions of the US [3], as well as in an *E. cloacae* clinical isolate in China [5]. While IMI enzymes are relatively uncommon carbapenemases, their presence in *Enterobacter* clinical isolates have been reported in recent years in France, Finland and Singapore [6-9]. They consist mainly of *E. cloacae* isolates producing either the IMI-1 or IMI-2 enzyme. Apart from our current report, IMI-producing *E. asburiae* clinical isolates have also been found in three patients from different cities in France between 2007 and 2011 [9].

To date, the common feature with IMI-producing isolates of the *E. cloacae* complex is the retention of susceptibility to third-generation cephalosporins such as cefotaxime and ceftazidime, while being resistant to the carbapenems, particularly imipenem. Additionally, IMI-producing *E. asburiae* isolates also retain susceptibility to piperacillin-tazobactam, as shown in the

antibiograms of our isolate as well as of those isolated from US rivers from 1999 to 2001 [3].

The finding of a colistin-resistant *Enterobacter* isolate in a patient without a history of polymyxin therapy is unusual and unexpected. Unlike certain *Enterobacteriaceae* such as *Proteaeor Serratia* spp., *Enterobacter* spp. do not possess intrinsic resistance to colistin [10]. Acquired colistin resistance in *Enterobacteriaceae* has mainly been reported in *Klebsiella pneumoniae*, particularly multidrug-resistant clones producing carbapenemases such as KPC enzymes [11-13]. Prior colistin therapy has been documented in some patients, but acquisition of such colistin- and carbapenem-resistant strains in other patients is likely to be the result of cross-transmission in healthcare settings [11-13]. However, a recent study has found unexpectedly high rates of colistin resistance amongst non-multidrug-resistant *E. cloacae* complex isolates from the UK and Ireland [14]. Colistin resistance rates of 6% and 10% were found in blood and respiratory isolates, respectively [14]. Fosfomycin is another useful agent for the treatment of multidrug-resistant (MDR) *Enterobacteriaceae* [15]. However, fosfomycin susceptibility rates of *Enterobacter* spp. were lower than those of *E. coli* or *K. pneumoniae* [15,16]. Based on EUCAST interpretive criteria, fosfomycin susceptibility rates ranged from 47% to 72% in *E. cloacae* [16,17]; while one third of *E. asburiae* isolates (seven of 21) were resistant to fosfomycin in one European study [17]. Notably, our patient had not received colistin or fosfomycin therapy in the past.

Conclusion

This is the first report in Ireland of IMI-producing *E. asburiae* with co-resistance to colistin and fosfomycin. For the accurate detection of IMI-producing *Enterobacteriaceae*, laboratories should be aware of the unusual antimicrobial resistance profiles of such isolates, particularly if synergy test results with beta-lactamase inhibitors suggest the presence of a class A carbapenemase. In the era of mounting antimicrobial resistance and diminishing therapeutic options, laboratories should monitor trends in colistin and fosfomycin resistance amongst *Enterobacteriaceae* isolates, particularly in *Enterobacter* spp.

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Conflict of interest

None declared.

Authors' contributions

Teck-Wee Boo prepared the first and subsequent drafts of the manuscript and collated the clinical and laboratory data. Nuala O'Connell, Margaret O'Connor and Lorraine Power provided the clinical and epidemiological data; while Nuala O'Connell, Joanne King, Elaine McGrath, Robert Hill, Katie Hopkins and Neil Woodford provided relevant sections of laboratory data. All authors read and critically revised the first, subsequent and final drafts of the manuscript.

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