Emergence of Candida tropicalis resistant to caspofungin

Tim Pasquale1, Jon Rupert Tomada1*, Mahmoud Ghannoun2, Joseph Dipersio1 and Hector Bonilla1

1Summa Health System, 75 Arch Street, Akron, OH 44304, USA; 2University Case Medical Center, 11100 Euclid Avenue, LKS 5028, Cleveland, OH 44106, USA

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Sir, Candida species is the fourth leading cause of nosocomial bloodstream infection in the USA. The incidence and mortality of invasive candidiasis (IC) remain high despite new antifungal agents. Although Candida albicans remains the most common isolated species causing IC, the incidence of IC caused by non-albicans species is increasing.1 Caspofungin, an echinocandin, is approved for treatment of IC.2 Resistance to caspofungin has been rarely reported.

We admitted a 28-year-old female with acute myelogenous leukaemia (AML) for fever and otitis media. She was started on caspofungin [70 mg intravenous (iv) loading dose followed by 50 mg iv daily] on her first hospital day due to persistent fever despite iv broad-spectrum antibiotics. Defervescence was noted and she was started on induction chemotherapy for AML on the sixth hospital day. She again developed fever with symptoms of oesophagitis on her 21st hospital day. Oesophagogastroduodenoscopy with oesophageal biopsy was performed and showed invasive candidal oesophagitis. Caspofungin was switched to liposomal amphotericin B. Her repeat blood cultures grew Candida tropicalis susceptible to fluconazole. Amphotericin B was switched to fluconazole and the patient improved slowly. She completed 4 weeks of fluconazole treatment.

We subsequently performed additional in vitro MIC testing for echinocandins on the isolated C. tropicalis using the CLSI (formerly NCCLS) M27-A2 standard methods.3 This method has been proven to be reproducible and reliable in the study of MIC trends and patterns of antifungal medications.4 MICs of caspofungin, micafungin and anidulafungin were 4.0, 8.0 and 1.0 mg/L, respectively.

This is the first documented case of C. tropicalis infection clinically resistant to caspofungin. This suggests that all Candida species are capable of developing resistance to echinocandins. The CLSI has established an echinocandin MIC of >2 mg/L to identify ‘non-susceptible’ Candida species.5 Our isolated strain’s caspofungin MIC is consistent with this breakpoint.

We also observed cross-resistance of the isolated species to micafungin. This pattern of cross-resistance is similar to the observations made by Mougdal et al.6 for Candida parapsilosis. This may suggest a similar mechanism of resistance of Candida species to echinocandins, specifically caspofungin and micafungin.

Four mechanisms of reduced susceptibility to caspofungin have been suggested: (i) fks1 gene mutation; (ii) efflux-based mechanism; (iii) Sbe2p overexpression; and (iv) paradoxical or eagle effect.1,7 Only the fks1 gene mutation, however, is proven to cause clinical failure with caspofungin therapy.1 Further investigation of the fks1 gene of our isolated strain would help support Candida species’ similarity of mechanism for echinocandin resistance.

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Transparency declarations

None to declare.

References


Detection of blaVIM-2 carbapenemase in Pseudomonas aeruginosa in Ireland

F. Walsh* and T. R. Rogers

Department of Clinical Microbiology, Trinity College Dublin, St James’s Hospital, Dublin 8, Ireland

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*Corresponding author. Tel: +353-1-896-3620; E-mail: walshfl@tcd.ie

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Sir,

*Pseudomonas aeruginosa* is one of the most frequently isolated Gram-negative pathogens associated with hospital-acquired infections. The carbapenems, imipenem and meropenem, have a broad spectrum of activity and are considered the agents of choice for the treatment of *P. aeruginosa* infections. However, metallo-β-lactamases (MBLs), which readily hydrolyse most β-lactams, including carbapenems, are increasingly being identified among *P. aeruginosa* clinical isolates. The VIM-type MBLs have been widespread in Asia, Southern Europe and North America.1 Since 2000, the Antibiotic Resistance Monitoring and Reference Laboratory has received approximately 80 isolates, mostly *Pseudomonas* species, from the UK, which tested positive for *bla* 

*bla* VIM (Dr Neil Woodford, Health Protection Agency, London, personal communication). This study describes the first identification of *bla* VIM2 in Ireland.

*P. aeruginosa* isolates 32297 and 15488 were isolated from a swab and a sputum sample, respectively, from the same patient at St James’s Hospital, Dublin, Ireland. These isolates were 74.3% similar with more than three band differences, as determined by *XbaI* restriction digest and separation using PFGE, and thus considered unrelated. Both isolates were resistant to imipenem and meropenem using the CLSI guidelines.2 Isolate 32297 had imipenem and meropenem MICs of 64 and 16 mg/L, respectively. Isolate 15488 had imipenem and meropenem MICs of >128 mg/L for both carbapenems. Both isolates had a reduction in imipenem and meropenem MICs of greater than 3 doubling dilutions in the presence of EDTA (320 mg/L), suggesting the presence of an MBL. This was confirmed by the MBL Etest (AB Biodisk, Solna, Sweden). *bla* VIM- and *bla* IMP-positive controls were included in each test. Isoelectric focusing was performed using the methods of Matthew et al.3 *bla* VIM- and *bla* IMP-positive controls were included in the gels. The *bla* VIM control had pI values of 8.65, 6.85 and 6.75. Isolate 15488 had pI values of 8.65, 7.2 and 6.65 and isolate 33075 had values of 8.15 and 7.85. Both isolates were screened by PCR for the presence of *bla* VIM, *bla* IMP, *bla* SPM and *bla* GIM genes. Isolate 15488 was *bla* VIM-positive by PCR. The *bla* VIM gene was amplified by PCR and sequenced using primers forward 5' GCA GCA GCA AG-3' and reverse 5'-AAG CAG ACT TGA CA CGT CTG CCT GA-3' for the amplification of the entire gene, which yield an 800 bp PCR product. The PCR product of 15488 had 100% identity with the *bla* VIM-2 gene, GenBank accession number AY943084.1. Sequencing results also revealed that the *bla* VIM-2 gene of 15488 was inserted as a single gene cassette into a class 1 integron. The two isolates were tested phenotypically for the presence of efflux pumps by measuring the meropenem MIC in the presence of efflux pump inhibitors carbonyl cyanide m-chlorophenylhydrazone (50 mg/L) and phenyl-arginine-β-naphthylamide (20 mg/L).4,5 There were no changes in the carbapenem MICs in the presence of the efflux pump inhibitors. The outer membrane proteins of the two clinical isolates, the *bla* VIM and *bla* IMP controls and the susceptible strain ATCC 27853 were extracted from exponentially growing cells. Both clinical isolates, in contrast to the susceptible ATCC 27853 strain, had loss of a 46 kDa protein band, which corresponds to the OprD porin. Isolate 33075 was PCR-negative for the tested MBLs, although a reduction in carbapenem MIC in the presence of EDTA has been detected. Such false-positive results could be attributed to the EDTA interference with the cell wall permeability as EDTA affects the regulation of the OprD porin and may facilitate the entry of carbapenems.6

To the best of our knowledge, this is the first report of an MBL-producing *P. aeruginosa* isolate from Ireland. The MBL was not associated with an outbreak. The integron did not contain other resistance gene determinants. Although this isolate was not associated with an outbreak, the identification of this carbapenemase on a mobile element poses a threat to infection control. Carbapenem-resistant *bla* VIM2-producing *P. aeruginosa* clones have emerged in several countries such as Portugal, Poland, Spain, Italy, Greece and Japan and can be attributed to the spread of *bla* VIM2-producing *P. aeruginosa*. Therefore, continued monitoring and surveillance of *P. aeruginosa* for MBLs is required to minimize the threat of outbreaks. The identification of *bla* VIM2 in Ireland also indicates that MBLs from their original reports in southern Europe have been further spread within Europe.

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References