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Cadazolid activity against contemporary antibiotic-resistant Clostridium difficile isolates and prevalent ribotypes from Europe

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Background: Cadazolid is a novel antibacterial currently in phase III clinical trials for the treatment of *C. difficile* infections. This study evaluated the activity of cadazolid against recent clinical isolates of *C. difficile* from Europe based on resistance to other antibiotics and also based upon prevalent ribotypes.

Material/methods: Clinical isolates of *C. difficile* (n=652) were collected in 2014/2015 from Belgium (1 site), Czech Republic (2), France (9), Germany (3), Hungary (1), Poland (1), Romania (3), Spain (5), Sweden (1) and the United Kingdom (3). Minimum inhibitory concentrations (MICs) for cadazolid and antibiotic comparators were determined by agar dilution following CLSI guidelines. MIC_{50} and MIC_{90} (concentrations to inhibit 50% & 90% of isolates, respectively) were calculated and susceptibility was determined according to CLSI breakpoints, except for linezolid where higher MIC isolates were defined as those with linezolid MIC ≥8 mg/L (based on the CLSI breakpoint for Gram-positive aerobes). All isolates were ribotyped by PCR amplification of the 16S-23S intergenic spacer regions and size of fragments determined. PCR-ribotypes were assigned by comparison with those in the CDRN UK PCR-ribotype library.

Results: Summary MIC results (mg/L) for cadazolid against the four most common ribotypes observed and against antibiotic-resistant *C. difficile* are shown in the Table below. Cadazolid MIC was very consistent irrespective of ribotype or antibiotic resistance with MIC_{50} and MIC_{90} of 0.5 mg/L except ribotype 078 where MIC_{50} was 0.25 mg/L. The highest cadazolid MIC was 1 mg/L for one isolate from Spain which was also resistant to imipenem and clindamycin and had an MIC of 8 mg/L to linezolid.

Group/cadazolid MIC (mg/L)	N	MIC_{50}	MIC_{90}	Min MIC	Max MIC
All isolates	652	0.5	0.5	0.12	1
Ribotype 027	100	0.5	0.5	0.12	0.5
Ribotype 014	53	0.5	0.5	0.25	0.5
Ribotype 001	49	0.5	0.5	0.12	0.5
Ribotype 078	34	0.25	0.5	0.12	0.5
Imipenem-resistant (MIC ≥16 mg/L)	600	0.5	0.5	0.12	1
Clindamycin-resistant (MIC ≥8 mg/L)	498	0.5	0.5	0.12	1
Moxifloxacin-resistant (MIC ≥8 mg/L)	259	0.5	0.5	0.12	0.5
Higher linezolid MIC (≥8 mg/L)	38	0.5	0.5	0.25	1

Conclusions: Cadazolid was very active against European *C. difficile* isolates with MICs over a very narrow range between 0.12 and 1 µg/ml, and displayed a mode of 0.5 mg/L across all subgroups regardless of ribotype or reduced susceptibility to other test agents. This activity included isolates from hypervirulent ribotypes 027 and 078. A large proportion of isolates were resistant to imipenem or clindamycin but this did not affect cadazolid activity. Furthermore, reduced susceptibility to moxifloxacin or linezolid did not affect cadazolid MIC values, indicating no cross resistance to these agents. These data support the ongoing investigation of cadazolid as a new treatment for *C. difficile*-associated diarrhoea.