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Heteroresistance to Carbapenems in New Delhi Metallo-β-Lactamase-1–Producing Isolates: A Challenge for Detection?

To the Editor—The worldwide dissemination of bacteria producing New Delhi metallo-β-lactamase (NDM) is a major public health concern owing to its worldwide dissemination. NDM-1 has now been detected in some South American countries, including Brazil.[1]

The first Brazilian NDM-1-producing isolate was a *Providencia rettgeri* isolate that had an unexpected susceptibility profile, with susceptibility to ertapenem (minimum inhibitory concentration [MIC], 0.5 mg/L) and meropenem (MIC, 0.75 mg/L) and only a low-level resistance to imipenem (MIC, 4 mg/L) by epsilometer test (E-test);[1] the latter finding might be expected since higher imipenem MICs are common to wild-type *Providencia* spp.

The susceptibility of the Brazilian *P. rettgeri* was reassessed by broth microdilution, showing similar MICs to those previously reported by E-test: 0.25, 0.5, and 8.0 mg/L for ertapenem, meropenem, and imipenem, respectively. Considering such an unusual susceptibility profile, a population analysis profile (PAP) was performed to detect the presence of possible ertapenem- and meropenem-heteroresistant subpopulations.[2] Briefly, a 20-μL aliquot from a 24-h culture serially diluted in saline with approximately 10^8 bacterial colony forming units was spread on Mueller-Hinton agar plates containing 0, 0.125, 0.25, 0.5, 1, 2, 3, 4, and 6 mg/L of meropenem and ertapenem. Colonies were counted after 48 h of incubation at 35°C.

The PAP experiments revealed the growth of colonies up to the concentrations of 0.5 and 2 mg/L of ertapenem and meropenem, respectively. However, the MICs of ertapenem and meropenem of these subpopulations were greater than 32 mg/L for both carbapenems, and the same elevated MICs were observed after daily subculture in antibiotic-free medium for 4 days.

We report an ertapenem- and meropenem-susceptible NDM-1-producing *P. rettgeri* harboring subpopulations highly resistant to both drugs by PAP. Interestingly, there was no subpopulation growth in plates with ertapenem and meropenem concentrations greater than 0.5 and 2.0 mg/L, respectively; nonetheless, when MICs of these colonies were performed, high-level resistance was demonstrated. An ertapenem-susceptible NDM-1-producing *P. rettgeri* has also been previously reported in Israel, but no experiment for heteroresistance was performed for that isolate.[3]

Although other carbapenemase-producing isolates have shown heteroresistance to carbapenems,[2,4,5] to our knowledge, this is the first description of an NDM-1-producing Enterobacteriaceae with such a resistance profile. Beyond the potential clinical impact of heteroresistance to carbapenems, this finding has important epidemiological consequences. From an infection control perspective, if this isolate had not demonstrated resistance to imipenem, it would have been managed as another carbapenem-susceptible Enterobacteriaceae. Infection control measures would not have been implemented, nor would the presence of NDM-1 have been detected, potentially contributing to further spread of this resistance mechanism.

In summary, we showed that an isolate carrying the $bla_{\text{NDM-1}}$ gene might seemly demonstrate susceptibility to carbapenems, including ertapenem, by conventional methods. NDM-1-producing isolates may actually harbor subpopulations detected only by PAP experiments. The prevalence of

heteroresistance in these organisms must be further evaluated, since its occurrence may greatly impact infection control practices.

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