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Susceptibility of MDR/XDR Pseudomonas aeruginosa to ceftolozane-tazobactam, Germany, 2013-2014

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Background: Therapeutic management of drug resistant *Pseudomonas aeruginosa* infections is a challenge due to an increasing prevalence of drug-resistant isolates and an increased mortality. Therefore, there is a strong interest in marketed, new antimicrobial drugs that could be effective against drug resistant *P. aeruginosa*. The objectives of our study were to study (1) the susceptibility of multi- (MDR) and extensively drug resistant (XDR) *P. aeruginosa* to ceftolozane-tazobactam (CT) and (2) the clonal relation of CT resistant vs. susceptible isolates.

Material/methods: Isolates were collected at the University Hospital Münster between 2013–2016. Eligible were all *P. aeruginosa* isolates being resistant to at least three out of four of the following antimicrobial agents: piperacillin, ceftazidime, meropenem/imipenem and ciprofloxacin according to Vitek 2 routine testing. Isolates (one per patient) were re-tested using broth microdilution against multiple *P. aeruginosa* active antibiotics and only those isolates were included in the final analysis that met the definition of MDR or XDR as suggested by the joint initiative of ECDC and CDC (Magiorakos et al. 2012, Clin Microbiol Infect). Susceptibility of MDR and XDR *P. aeruginosa* to CT was tested by broth microdilution method and interpreted using EUCAST clinical breakpoints. The clonal relation was analyzed in a random subset of isolates using whole genome sequencing.

Results: In total, 112 *P. aeruginosa* (MDR: n=44, XDR: n=68) met the inclusion criteria and represent a cross section of patients from intensive care units (n=42), intermediate care (n=2), normal care units (n=45), bone marrow transplantation units (n=17) and outpatient departments (n=6). In total, 66.1% (n=74) were susceptible to CT (MIC_{50}: 2 mg/L, MIC_{90}:256 mg/L, range: 0.5–>256 mg/L). CT susceptibility was significantly higher in MDR (95.2%, MIC_{50}: 1 mg/L, MIC_{90}: 4 mg/L, range: 0.5–8 mg/L) than in XDR *P. aeruginosa* (50%, MIC_{50}: 4 mg/L, MIC_{90}: 256 mg/L, range: 0.5–>265 mg/L, $p<0.0001$). In the majority of wards, at least 50% of isolates were susceptible to CT. However, all isolates from the bone marrow transplant unit were CT resistant. In general, the isolates were highly diverse and CT resistant isolates were found in different clusters. However, one cluster (ST235) consisted exclusively of CT resistant *P. aeruginosa* accounting for one fourth of all isolates.

Conclusions: The susceptibility to CT ranged between 95.2% (MDR) and 50% (XDR) among *P. aeruginosa* isolates. However, high resistance rates against CT in *P. aeruginosa* from high-risk patients (i.e. after bone marrow transplantation) should be taken into account in the therapeutic management.