1265. In Vitro Activity of Aztreonam-Avibactam against Klebsiella pneumoniae Isolates Analyzed by Epidemic Lineage and Hypervirulence Factors Collected in China as Part of the ATLAS Global Surveillance Study in 2019
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Session: P-72. Resistance Mechanisms

Background. Hypervirulent Klebsiella pneumoniae (hvKp), unlike classical K. pneumoniae (cKp), are often responsible for community-acquired infections in otherwise healthy individuals. The acquisition of hypervirulence genes by sequence type 11 (ST11) carbapenem-resistant (CR) Kp endemic in Asia is a grave threat. Aztreonam-avibactam (ATM-AVI) is a monobactam combined with a β-lactamate inhibitor for the treatment of infections caused by Enterobacteriaceae that carry Class A, B, C, and some Class D β-lactamases.

Methods. 487 K. pneumoniae isolates were collected from 17 sites in China in 2019 as a part of the ATLAS global surveillance study. 220 isolates with MICs >1 µg/ml to meropenem (MEM), cefazidime or ATM were selected for whole genome sequencing (Illumina Hiseq 2x150 bp reads). Analyses were carried out using the CLC Genomics Workbench (QIagen). Presence of the aerobactin synthesis locus differentiated hvKp and cKp. Antimicrobial susceptibility was determined by CLSI broths microdilution.

Results. Of the 487 isolates, MIC₅₀ values for ATM-AVI (0.5 µg/ml; Table) were lower than those for any comparator tested, with only two isolates testing with MICs >4 µg/ml. Of the isolates sequenced, 82(20%) were ST11. 53/82 (64.6%) of these ST11 isolates were hvKp (ATM-AVI MIC₅₀ 1 µg/ml; range, 0.25-4 µg/ml) and showed percentages of susceptibility <90% to three last-line agents (0% MEM-susceptible (5); 18.9% amikacin (AMK)-S; 88.7% tigecycline (TGC)-S). Isolates of other STs (Non-ST11) were less frequently identified as hvKp (24/138, 17.4%) and susceptible (S); 18.9% amikacin (AMK)-S; 88.7% tigecycline (TGC)-S). Isolates of these ST11 isolates were hvKp (ATM-AVI MIC₅₀ 1 µg/ml; range, 0.25-4 µg/ml) and showed percentages of susceptibility <90% to three last-line agents (0% MEM-susceptible (5); 18.9% amikacin (AMK)-S; 88.7% tigecycline (TGC)-S). Isolates of other STs (Non-ST11) were less frequently identified as hvKp (24/138, 17.4%) and susceptible (S); 18.9% amikacin (AMK)-S; 88.7% tigecycline (TGC)-S). Isolates of these ST11 isolates were hvKp (ATM-AVI MIC₅₀ 1 µg/ml; range, 0.25-4 µg/ml) and showed percentages of susceptibility <90% to three last-line agents (0% MEM-susceptible (5); 18.9% amikacin (AMK)-S; 88.7% tigecycline (TGC)-S). Isolates of other STs (Non-ST11) were less frequently identified as hvKp (24/138, 17.4%) and susceptible (S); 18.9% amikacin (AMK)-S; 88.7% tigecycline (TGC)-S). Isolates of these ST11 isolates were hvKp (ATM-AVI MIC₅₀ 1 µg/ml; range, 0.25-4 µg/ml) and showed percentages of susceptibility <90% to three last-line agents (0% MEM-susceptible (5); 18.9% amikacin (AMK)-S; 88.7% tigecycline (TGC)-S). Isolates of other STs (Non-ST11) were less frequently identified as hvKp (24/138, 17.4%) and susceptible (S); 18.9% amikacin (AMK)-S; 88.7% tigecycline (TGC)-S).

Conclusion. CR ST11 hvKp represented at least 10.9% of the collected Kp isolates. ATM-AVI retained potent in vitro activity against these isolates which displayed resistance to a range of last-line agents. CST and TGC also displayed some activity but are limited in utility due to nephrotoxicity and poor accumulation in blood, respectively. The spread of virulence factors leading to the complicated clinical presentation of hvKp infection into multidrug-resistant lineages warrants continued surveillance.

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1266. Melatonin for Renal Protection of Patients Treated with Polymyxin B: A Double Blind Randomized Clinical Trial
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Session: P-72. Resistance Mechanisms

Background. Polymyxins are one of the last resort treatments for carbapenem-resistant Gram-negative infections. Nephrotoxicity is a major adverse effect and has been related to oxidative stress mechanisms. Melatonin was associated to reduction in polymyxins nephrotoxicity in animal studies. Our objective is to evaluate the effect of melatonin on renal protection of patients receiving Polymyxin B.

Methods. We did a single center, double blind, randomized clinical trial (NCT03725267) of melatonin 30mg versus placebo for patients treated with polymyxin B from October 2018 to April 2021, in Porto Alegre, Brazil. Patients ≥18 years old, receiving polymyxin B for ≥548 hours, who accepted informed consent terms were included and excluded if intensive care unit (ICU) admission at enrollment, estimated glomerular rate estimated glomerular rate <10ml/min, dialysis or previous melatonin use. Treatment with melatonin or placebo was randomized in blocks of 4 and maintained until the end of polymyxin B treatment of for a maximum of 14 days. Our main outcome was any level of nephrotoxicity by RIFLE score. Secondary outcomes were renal failure and need for dialysis. We estimated a sample size of 110 patients, however the study had to be stopped earlier due to recruitment restrictions imposed by the COVID-19 pandemic.

Results. Eighty-eight patients were randomized, 44 received melatonin and 44 received identical placebo pills. Patients had a mean age of 63±17.3 years, 60.2% were male, and had a median Charlson index of 5 (3-8.3). Most infections (79.5%) were nosocomially confirmed, having 68.6% Klebsiella sp isolated. Urinary tract account for 47.7% of infection sites. Median time of polymyxin B therapy was 9.1±6.6 days. Combination therapy was prescribed for 89.8% of patients and 38.6% reached at least another nephrotoxic drug. All variables were equally distributed among groups. Nephrotoxicity rates occurred in 23 of 44 (52.3%) in both groups. Patients who developed renal failure were 8 (18.2%) vs 9 (20.5%) and dialysis occurred in 4 (9.1%) vs 5 (11.4%) of melatonin and placebo groups respectively.

Conclusion. Melatonin did not show a clinically significant renal protective effect in polymyxins treated with polymyxin B.

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