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-lactamase inhibitor for the treatment of infections caused by Enterobacteriaceae isolates 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 MIC > 1 µg/mL to meropenem (MEM), ceftazidime 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 differed-intenstely hvKp and ckp. Antimicrobial susceptibility was determined by CLSI broth microdilution.

**Results.** Of the 487 isolates, MIC₉₀ values for ATM-AVI (0.5 µg/mL; Table) were lower than those for any comparator tested, with only two isolates testing with MIC > 4 µg/mL. Of these isolates sequenced, 82/220 (37.3%) were ST11, 53/82 (64.6%) of these ST11 isolates were hvKp (ATM-AVI MIC₉₀ 1 µg/mL; range, 0.3-4.5 µg/mL and showed percentages of susceptibility < 90% to three last-line agents (0% MEM-S; 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 showed percentages of susceptibility < 90% to three last-line agents (0% MEM-S; 83.3%-96.5% AMK-S). Likewise, the ATM-AVI MIC₉₀ value (0.25 µg/mL) was 4-fold lower for Non-ST11 isolates.

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**Background.** Polymyxin B is one of the last resort treatments for carbapenem-resistant (CRE) infections. Nephrotoxicity is a major adverse effect and has been related to oxidative stress mechanisms. Melatonin was associated to reduction in polymyxin B 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, with severe nosocomial infections, who accepted informed consent terms were included and excluded if intensive care unit (ICU) admission at enrollment, estimated glomerular rate estimated glomerular rate < 30ml/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 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 100 patients, however the study had to be stopped earlier due to recruitment limitations 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 63.6±17.3 years, 60.2% were male, and had a median Charlson index of 5 (3-8.3). Most infections (79.5%) were nosocomially acquired, having 68.6% Klebsiella sp isolated. Urinary tract account for 74.7% 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% received 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 patients treated with polymyxin B.

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1267. Five-Year Trend on the Susceptibility of Enterobacteriaceae to Plazomicin and Other Aminoglycosides in Hospitals in the United States (2016–2020)

Hileo S. 19, 39, 45, 39, 39

Session: P-72. Resistance Mechanisms

**Background.** Plazomicin (PLZ) is a novel aminoglycoside (AGM) that was approved by the US FDA in June 2018 to treat complicated urinary tract infection (cUTI), including pyelonephritis. This agent is active against most isolates resistant to other AGMs. We evaluated PLZ activity against clinical isolates of Enterobacteriaceae (ENT) from US hospitals.

**Methods.** 10,008 ENT isolates (1/patient) were collected from 35 US medical centers in 2016-2020 and susceptibility tested by the broth microdilution method at a central laboratory. PLZ breakpoints of ≤2/8 mg/L for susceptible [S]/resistant [R] USEFDA were applied, and breakpoints established by the USFDA/CLSI, EUCAST and USCAST were applied to other AGMs for comparison. Isolates were mainly from cUTI (37.7%), bloodstream infection (24.9%), and pneumonia (20.3%).

**Results.** PLZ exhibited potent activity against ENT (MIC₉₀ ≤ 0.5/1 mg/L), with >90% S rates from 2017 in 2016 to 95.8% in 2020 (96.8% overall). Against carbapenem-resistant ENT (CRE), S rates for PLZ increased from 96.3% in 2016 to 100.0% in 2020 (Figure: 97.3% overall) and were markedly higher than amikacin (AMK; 75.2% overall), gentamicin (GEN; 48.7%), and tobramycin (TOB; 23.0%). The discrepancies between S rates for PLZ and other AGMs were greater when applying breakpoints generated using the same stringent contemporary methods applied to determine PLZ breakpoints. CRE S rates for AMK were 62.8% as per EUCAST and 52.2% as per USCAST. PLZ retained activity against GEN non-S (NS; 87.5; 90.6%), TOB-NS (n=94; 92.7%), and AMK-NS (n=60; 83.3%) isolates. Among isolates from cUTI (n=3,774), 96.9% were PLZ-S, varying from 97.8% in 2017 to 95.8% in 2020. The ENT species most S to PLZ (lowest MIC values) were C. koseri (100.0%), K. aerogenes (100.0%), K. pneumoniae (99.8%), and E. cloacae (99.7%), which had MIC₉₀ values of 0.25/0.5 mg/L followed by K. oxytoca (MIC₉₀ 0.5/0.5 mg/L; 99.9%), E. coli (MIC₉₀ 0.5/1 mg/L; 99.6%), and C. freundii (MIC₉₀ 0.5/1 mg/L; 100.0%).

**Conclusion.** PLZ demonstrated potent activity against a large collection of contemporary ENT isolates from US hospitals with 4-fold lower MIC values than AMK. PLZ was markedly more active than AMK, TOB, or GEN against CRE and retained good activity against isolates NS to these AGMs.

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