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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 Enterobacterales 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 MICs >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 differentiated hvKp and cKp. Antimicrobial susceptibility was determined by CLSI broth microdilution.

Results. Of the 487 isolates, MIC_{90} 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 the isolates sequenced, 82/220 (37.3%) were ST11. 53/82 (64.6%) of these ST11 isolates were hvKp (ATM-AVI, MIC_{90} 1 μg/ml; range, 0.25-4 μg/ml) and showed percentages of susceptibility < 90% to three last-line agents (0% MEM-susceptible (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 more Non-ST-11 hvKp and cKp alike were S to MEM and AMK relative to isolates of ST11 (75.0-86.8% MEM-S; 83.3-96.5% AMK-S). Likewise, the ATM-AVI MIC_{90} value (0.25 μg/ml) was 4-fold lower for Non-ST11 isolates.

Results Table

Category (number of isolates)	Agent [MIC_{90} μg/ml (S% or MIC Range)][a]					
	ATM-AVI	ATM	MEM	AMK	TGC	CST
All *K. pneumoniae* (n=487)	0.5 (≤0.015->64)	>128 (54.2%)	>16 (75.8%)	>64 (81.7%)	2 (94.9%)	1 (0.25->8)
Molecularly characterized (n=220)[b]	0.5 (≤0.015-4)	>128 (12.3%)	>16 (55.0%)	>64 (66.8%)	2 (93.2%)	1 (0.25-2)
MEM-NS (n=99)[c]	1 (≤0.015-4)	>128 (3.0%)	>16 (0.0%)	>64 (28.3%)	2 (91.9%)	1 (0.25-2)
ST11 (n=82)						
hvKp (n=53)	1 (0.25-4)	>128 (0.0%)	>16 (0.0%)	>64 (18.9%)	4 (88.7%)	1 (0.5-2)
cKp (n=29)	1 (≤0.015-2)	>128 (0.0%)	>16 (13.8%)	>64 (24.1%)	1 (100%)	1 (0.5-2)
Non-ST11 (138)						
hvKp (n=24)	0.25 (≤0.015-0.5)	>128 (29.2%)	>16 (75.0%)	32 (83.3%)	4 (83.3%)	2 (0.25-2)
cKp (n=114)	0.25 (≤0.015-0.5)	>128 (17.5%)	>16 (86.8%)	4 (96.5%)	2 (95.6%)	1 (0.25-1)

Abbreviations: S%, percent susceptible; ATM-AVI, aztreonam-avibactam; ATM, aztreonam; MEM, meropenem; AMK, amikacin; TGC, tigecycline; CST, colistin; NS, non-susceptible; ST, sequence type. hvKP, hypervirulent *Klebsiella pneumoniae* (carrying genes of aerobactin synthesis locus); cKp, classical *K. pneumoniae*.
[a]Percent susceptible determined using CLSI 2021 breakpoints or FDA breakpoints (TGC only). The observed MIC range is displayed for ATM-AVI and CST for lack of a susceptibility breakpoint.
[b]Two isolates testing with ATM-AVI MIC >4 μg/ml were not molecularly characterized.
[c]19/118 MEM-NS isolates were not molecularly characterized.

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.

Disclosures. **Mark Estabrook, PhD**, **IHMA** (Employee)**Pfizer, Inc.** (Independent Contractor) **Krystyna Kazmierczak, PhD**, **IHMA** (Employee)**Pfizer, Inc.** (Independent Contractor) **Francis Arhin, PhD**, **Pfizer, Inc.** (Employee) **Daniel F. Sahm, PhD**, **IHMA** (Employee)**Pfizer, Inc.** (Independent Contractor)

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 its main 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 ≤48 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 100 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 63.6±17.3 years, 60.2% were male, and had a median Charlson index of 5 (3-8.3). Most infections (79.5%) were microbiologically confirmed, having 68.6% Klebsiella sp isolated. Urinary tract accounted for47.7% 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, P=0.99. 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.

Disclosures. **Maria Helena Rigatto, MD, PhD**, **CNPq** (Grant/Research Support) **Diego Rodrigues Falci, MD, MSc, PhD**, **Gilead Sciences** (Grant/Research Support, Scientific Research Study Investigator, Speaker's Bureau)**GSK** (Grant/Research Support, Scientific Research Study Investigator, Advisor or Review Panel member)**MSD** (Speaker's Bureau)**Pfizer** (Speaker's Bureau)**United Medical** (Speaker's Bureau, Other Financial or Material Support) **Alexandre Zavascki, MD, PhD**, **Pfizer** (Grant/Research Support)

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

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Session: P-72. Resistance Mechanisms

Background. Plazomicin (PLZ) is novel aminoglycoside (AMG) 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 AMGs. We evaluated PLZ activity against clinical isolates of *Enterobacterales* (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] (USFDA) were applied, and breakpoints established by the USFDA/CLSI, EUCAST and USCAST were applied to other AMGs for comparison. Isolates were mainly from cUTI (37.7%), bloodstream infection (24.9%), and pneumonia (20.3%).

Results. PLZ exhibited potent activity against ENT ($MIC_{50/90}$, 0.5/1 mg/L), with S rates varying from 97.8% in 2016 to 95.8% in 2020 (96.8% overall). Against carbapenem-R ENT (CRE), S rates for PZL 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 AMGs 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; n=875; 90.6%S), TOB-NS (n=944; 92.7%S), and AMK-NS (n=60; 83.3%S) 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%S), *K. aerogenes* (100.0%S), *K. pneumoniae* (99.8%S), and *E. cloacae* (99.7%S), which had $MIC_{50/90}$ values of 0.25/0.5 mg/L, followed by *K. oxytoca* ($MIC_{50/90}$, 0.5/0.5 mg/L; 99.9%S), *E. coli* ($MIC_{50/90}$, 0.5/1 mg/L; 99.6%S), and *C. freundii* ($MIC_{50/90}$, 0.5/1 mg/L; 100.0%S).

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, GEN, or TOB against CRE and retained good activity against isolates NS to these AMGs.