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Poster Session V
Worldwide spread of carbapenem resistance

DETECTION OF AMINOGLYCOSIDE MODIFYING ENZYMES (AMES) IDENTIFIES PATTERNS OF AMINOGLYCOSIDE RESISTANCE AMONG CARBAPENEM-RESISTANT KLEBSIELLA PNEUMONIAE

R. Almaghrabi[1], C.J. Clancy[1], R.K. Shields[1], Y. Doi[1], B. Hao[1], **M.H. Nguyen**[1]

[1]Medicine, University of Pittsburgh, Pittsburgh PA, USA

Objective. We have demonstrated that gentamicin is highly-active *in vitro* against gentamicin-susceptible, carbapenem-resistant *K. pneumoniae* (CR-Kp), but not gentamicin-resistant strains. At our center, gentamicin-based regimens have proven effective in treating bacteremia due to susceptible CR-Kp strains, and gentamicin has been incorporated into a treatment algorithm. Aminoglycoside resistance among *Enterobacteriacea* is mediated by multiple mechanisms, including production of aminoglycoside modifying enzymes (AMEs). Our objective was to study the impact of AMEs on aminoglycoside resistance among CR-Kp strains.

Methods. We determined MICs of gentamicin, tobramycin, amikacin and other aminoglycosides against 50 CR-Kp strains. We screened strains for 4 common AMEs by PCR.

Results. 94% (47/50) of strains were ST258, including 80% KPC-2-producers, 10% (5/50) KPC-3-producers, and 4% (2/50) non-KPC-producers. Non-ST258 strains were non-KPC-producers. 40% (20/50), 98% (49/50) and 2% (1/50) of strains were gentamicin-, tobramycin- and amikacin–resistant, respectively; 14% (7/50) were amikacin-intermediate. Tobramycin and gentamicin MICs were closely correlated (R=0.75). Amikacin MICs did not correlate with tobramcyin or gentamicin MICs (R=-0.02). At least one AME was detected in 98% (49/50) of strains. AAC(6')-Ib was detected in each strain with an AME. The rank-order for the other AMEs was APH(3')-Ia (56%, 28/50), AAC(3)-IV (38%, 19/50), and ANT(2')-Ia (2%, 1/50). The strain without AMEs was susceptible to all aminoglycosides. All strains with AAC(6')-Ib were tobramycin-resistant. 94% (16/17) of strains with AAC(6')-Ib alone were gentamicin-susceptible. The combination of AAC(6')-Ib and ≥1 other AME was associated with higher gentamicin and tobramycin MICs than AAC(6')-Ib alone (p=0.01 and 0.0008, respectively). AAC(3')-IV made the strongest contribution to aminoglycoside MICs in combination with AAC(6')-Ib. Gentamicin and tobramycin MICs were higher against strains with AAC(3')-IV than against AME-carrying strains that lacked AAC(3')-IV (p=0.0006 and <0.0001, respectively). Moreover, the triple combination of AAC(3')-IV, APH(3')-Ia and AAC(6')-Ib was associated with higher gentamicin and tobramycin MICs than other AME-carrying strains (p=0.01, 0.001 and 0.03, respectively), whereas the double combination of APH(3')-Ia and AAC(6')-Ib was not (p=0.24 and 0.20, respectively). The presence of APH(3')-Ia in any combination was associated with higher gentamicin and tobramycin MICs than in the absence of APH(3')-Ia (p=0.03 and 0.048, respectively). The combination of AAC(6')-Ib with another AME, presence of AAC(3')-IV, and presence of APH(3')-Ia were each associated with gentamicin resistance (p=0.0002, 0.003 and 0.01, respectively). Gentamicin results for certain strains were confirmed by time-kill assays. There were no correlations between AMEs and amikacin MICs or resistance.

Conclusions. Patterns of AMEs identified CR-Kp strains that were likely to be aminoglycoside-resistant, and may serve as rapid markers for guiding treatment decision-making. In particular, detection of AAC(6')-Ib alone and AAC(6')-Ib combined with another AME (especially AAC(3')-IV) were highly sensitive for identifying gentamicin-susceptible and –resistant strains, respectively. AAC(6')-Ib can confer decreased susceptibility to amikacin, which may not be captured by MIC breakpoints.