29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

P1834 Comprehensive thermal stability data and optimal supplement dosing schemes for *in vitro* time-kill experiments with 10 beta-lactams and 3 beta-lactamase inhibitor in Mueller-Hinton broth

Yuli Qian[1], Xun Tao[1], Tae Hwan Kim[1], Jieqiang Zhou[1], Yinzhi Lang[1], Bartolome Moya[1], Dhruvitkumar Sutaria[1], Yuanyuan Jiao[1], Nirav Shah[1], Jürgen Bulitta*[1]

[1] University of Florida, Orlando, United States

Background: Beta-lactam antibiotics and beta-lactamase inhibitors are commonly used in *in vitro* time-kill experiments to assess antibacterial efficacy. While stability data are available for selected beta-lactams in saline or clinical formulations, comprehensive stability data of these compounds in cation-adjusted Mueller-Hinton broth (MHII) are not publicly available. We aimed to determine the stability of ten beta-lactams and three beta-lactamase inhibitors in MHII at various pH and to propose feasible supplement dosing schemes which assure relatively constant drug concentrations over 24h.

Materials/methods: We determined the rate of degradation in filter-sterilized MHII at 36 °C with pH adjusted to 6.8, 7.0, 7.25, 7.4, and 7.8. Drugs included imipenem, meropenem, doripenem, biapenem, ceftazidime, cefepime, cefsulodin, piperacillin, ticarcillin, aztreonam, tazobactam, sulbactam and avibactam. Drug concentrations were determined via LC-MS/MS. The lower limit of quantification was 0.025 or 0.05 mg/L for all drugs except biapenem, sulbactam and avibactam which had an LLOQ of 0.25 mg/L. Supplement dosing schemes were developed to minimize the variation of the actual drug concentrations over time around the nominal (i.e. targeted) drug concentration. Schemes included either one supplement dose at 9h or two supplement doses at 6 and 10h.

Results: For all compounds, the degradation half-life became gradually shorter at higher pH. Aztreonam, avibactam, sulbactam, ticarcillin, ceftazidime, and tazobactam were very stable with degradation half-lives of 74.3h or (considerably) longer at all pH. The half-lives at pH 7.25 indicated intermediate stability for piperacillin (60.2h), cefepime (50.2h), meropenem (47.6h) and doripenem (41.3h); the least thermally stable beta-lactams were imipenem (17.0h), biapenem (20.6h) and cefsulodin (22.8h). For a single supplement dose at 9h, the optimal dose was 60% of the original dose for imipenem, 51% for biapenem, 46% for cefsulodin, 27% for doripenem, 23% for meropenem, 22% for cefepime, and 18% for piperacillin. Optimal supplement doses at 6 and 10h were: Imipenem (30/36%), biapenem (25/30%), cefsulodin (23/27%), doripenem (13/15%), meropenem (11/13%), cefepime (11/12%), and piperacillin (9/10%).

Conclusions: This study identified feasible supplement dosing schemes to achieve as-constant-as-possible beta-lactam and beta-lactamase inhibitor concentrations over 24h. Beta-lactamase related drug degradation will additionally have to be considered for *in vitro* time-kill studies with multidrug-resistant strains.