P1265
Paper Poster Session
Cefepime-tazobactam

WCK 4282 (high-dose cefepime-tazobactam) against multi-resistant Gram-negative bacteria

David Livermore*[1], Shazad Mushtaq[2], Marina Warner[2], Neil Woodford[2]

[1]*Norwich Medical School, University of East Anglia, Norwich, United Kingdom*

[2]*Public Health England, London, United Kingdom*

Background: The companies that developed □-lactamase inhibitors during the 1970 to the 90s largely combined them with their established penicillins, seeking to overcome TEM-1 and SHV-1 enzymes. Other companies developed '□-lactamase-stable' cephalosporins. Different combinations of old inhibitors and □-lactams may be more appropriate to now-prevalent □-lactamases, and their development is facilitated both by patent expiries and the market exclusivity offered by the US GAIN Act. High-dose cefepime-tazobactam is especially attractive, and was evaluated.

Material/methods: Organisms (n=270) were recent clinical isolates submitted to the UK national reference laboratory. MICs of cefepime were determined by CLSI agar dilution with tazobactam at 0, 4 or 8 mg/L.

Results: MICs of unprotected cefepime for 33 ESBL-producing Enterobacteriaceae were from 0.5->256 mg/L, with 16/33 values ≥8 mg/L. With 4 mg/L tazobactam added, only 2/33 cefepime MICs remained >1 mg/L; only 1/33 did so with tazobactam at 8 mg/L. Cefepime is relatively stable to AmpC enzymes and only 9/35 cefepime MICs for AmpC-hyperproducing Enterobacteriaceae exceeded 1 mg/L even without tazobactam; none exceeded 8 mg/L. Proportions of AmpC-hyperproducing Enterobacteriaceae with cefepime MICs >1 mg/L fell to 4/35 and 0/35 with tazobactam at 4 or 8 mg/L, respectively. Fifteen isolates with OXA-48-like enzymes were tested; 7 lacked ESBLs and were susceptible to unprotected cefepime at ≤1 mg/L; cefepime MICs for the remaining 8 were 32->256 mg/L, falling to 2-16 mg/L with tazobactam at 4 mg/L and 1-8 mg/L (with 7 of 8 at 1-2 mg/L) with tazobactam at 8 mg/L. MICs of unprotected cefepime for Enterobacteriaceae with KPC carbapenemases were 2->256 mg/L (MIC_{50}=128), falling to 1-128 mg/L (MIC_{50} 8) with tazobactam at 4 mg/L and to 0.5-128 (MIC_{50} 8) mg/L with tazobactam at 8 mg/L. MIC_{50}s of cefepime-tazobactam for MBL producers were higher, at 32 mg/L. Little potentiation of cefepime was seen for *P. aeruginosa* with derepressed AmpC, MBLs or efflux; *S. maltophilia* or *A. baumannii* with OXA carbapenemase or MBLs.

Conclusions: Based on current breakpoints for cefepime, high-dose cefepime-tazobactam has significant clinical potential against ESBL-, AmpC and OXA-48 □-lactamase producing Enterobacteriaceae.