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Paper Poster Session VI

New data on new cephalosporin/beta-lactamase inhibitor combinations

Antimicrobial activity of ceftolozane/tazobactam and comparator agents tested against Enterobacteriaceae isolates from 15 European countries and Israel (2013)

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Objective: To evaluate the activity of ceftolozane/tazobactam, ceftazidime, meropenem and other comparator agents against Enterobacteriaceae isolates from 15 European (EU) countries and Israel. Ceftolozane is a novel oxyimino-aminothiazolyl cephalosporin with potent anti-pseudomonal activity. The addition of tazobactam broadens coverage to include most extended-spectrum β-lactamase-producing Enterobacteriaceae. Ceftolozane/tazobactam is currently in clinical development in patients with ventilator-associated bacterial pneumonia, complicated intra-abdominal infections or complicated urinary tract infections.

Methods: A total of 4875 Enterobacteriaceae isolates were consecutively collected in 2013 from 34 medical centres located in 15 EU countries, including Russia, Turkey and Ukraine, plus Israel. Susceptibility testing was performed by CLSI broth microdilution methods and MIC interpretations for comparator agents were as published by EUCAST and CLSI. Ceftolozane/tazobactam was tested at a fixed 4 mg/L concentration of tazobactam.

Results: The number of isolates per country varied from 41 in Ukraine to 838 in Germany. Ceftolozane/tazobactam ($MIC_{50/90}$, 0.25/2 mg/L) demonstrated similar potency as ceftazidime ($MIC_{50/90}$, 0.25/32 mg/L) against ceftazidime-susceptible isolates but remained active against most ceftazidime-non-susceptible strains and inhibited 94.9% of all isolates, and >90% of isolates in 13 countries, at MIC of ≤8 mg/L. In contrast, ceftazidime susceptibility was 78.0% overall and >90% only in Sweden (94.8%; Table). Non-susceptibility (by EUCAST criteria) to ceftazidime was very high (>50%) in Poland and Russia, and ceftolozane/tazobactam also showed lower activity against Enterobacteriaceae from these countries. Susceptibility to meropenem was high overall (97.4%) and >95% in 13/16 countries, but lower in Poland (75.3%), Italy (90.8%) and Greece (93.1%). Overall susceptibility rates (by EUCAST criteria) to piperacillin/tazobactam, cefepime, ciprofloxacin and gentamicin were 81.8, 81.7, 71.8 and 86.1%, respectively, below ceftolozane/tazobactam at ≤8 mg/L (94.9%). The overall MDR rate was 15.7% and varied widely ranging from 3.0% in Sweden to 50.0% in Poland. The overall XDR rate was 2.8% and also varied widely ranging from 0.0% in Sweden to 31.3% in Poland. Two PDR isolates were found (both *Klebsiella pneumoniae* from Italy and Turkey).

Country (no. tested)	Ceftolozane/tazobactam $MIC_{50/90}$ (% at ≤8 mg/L)	Ceftazidime $MIC_{50/90}$ (% at ≤8 mg/L)[a]	Meropenem $MIC_{50/90}$ (% at ≤2 mg/L)[a]	%MDR/%XDR/ %PDR[b]
Belgium (40)	1/>32 (72.5)	8/>32 (50.0)	4/>8 (41.0)	52.5/35.0/0.0
Czech Republic (22)	0.5/4 (100.0)	1/>32 (81.8)	0.5/8 (63.6)	27.3/18.2/0.0
France (76)	0.5/2 (100.0)	2/32 (77.6)	0.5/4 (88.2)	14.5/9.2/0.0
Germany (168)	0.5/2 (99.4)	2/32 (85.7)	0.5/8 (74.4)	17.9/10.7/0.0
Greece (44)	0.5/8 (90.9)	2/16 (88.6)	0.5/8 (84.1)	15.9/9.1/0.0
Ireland (46)	0.5/2 (100.0)	2/8 (91.3)	0.5/4 (82.6)	15.2/4.4/0.0
Israel (66)	0.5/4 (98.5)	4/>32 (72.7)	0.5/>8 (71.2)	31.8/19.7/0.0
Italy (160)	0.5/4 (94.4)	4/>32 (71.9)	0.5/>8 (72.3)	31.9/25.6/1.3
Poland (71)	2/16 (85.9)	16/>32 (46.5)	8/>8 (22.5)	64.8/53.5/0.0
Portugal (60)	1/32 (73.3)	2/>32 (60.0)	2/>8 (51.7)	38.3/36.7/0.0
Russia (71)	1/>32 (73.2)	8/>32 (52.1)	1/>8 (63.4)	40.9/33.8/0.0
Spain (197)	0.5/4 (96.5)	2/32 (80.7)	0.5/8 (78.7)	18.3/14.2/0.0
Sweden (42)	0.5/2 (100.0)	2/8 (90.5)	0.25/2 (90.5)	9.5/2.4/0.0
Turkey (111)	1/4 (95.5)	2/32 (82.9)	0.5/>8 (73.6)	23.4/13.5/0.0
UK (81)	0.5/2 (100.0)	2/32 (84.0)	0.5/>8 (75.3)	13.6/6.2/0.0
Ukraine (11)	0.5/2 (100.0)	4/32 (63.6)	0.25/0.5 (100.0)	0.0/0.0/0.0
Overall (1266)	**0.5/4 (93.4)**	**2/>32 (75.4)**	**0.5/>8 (71.0)**	**26.0/18.6/0.2**

a. Susceptible breakpoint established by EUCAST (2014).

b. Multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria were classified according to Magiorakos AP, et al. (2012). *Clin Microbiol Infect.* 18:268-81.

Conclusion : In 2013, antimicrobial susceptibility of MDR and XDR Enterobacteriaceae varied widely among EU countries. MDR, XDR resistance rates to ceftazidime were generally elevated and particularly high in some Eastern EU nations. At a MIC of ≤8 mg/L, ceftolozane/tazobactam had higher susceptibility rates than β-lactams (except for carbapenems) currently available for treatment of infections caused by Enterobacteriaceae and could represent a valuable treatment addition for these pathogens.