696. Cefiderocol Susceptibility Against Molecularly Characterized Carbapenemase-Producing Gram-Negative Bacteria in North America and Europe Between 2014 and 2017: SIDERO-WT-2014 to -2016 Studies

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Background. Antibiotic susceptibility surveillance is the foundation for selecting treatment options as well as immediate and long-term strategies for combating antimicrobial resistance. We have conducted three surveillance studies SIDERO-WT-2014/-2015/-2016 with approximately 30,000 Gram-negative strains isolated in North America and Europe between 2014 and 2017. Here, we present the latest data of molecular analysis on acquired carbapenemase genes and antibiotic susceptibility of 3691 meropenem-nonsusceptible strains in the surveillance studies.

Methods. Meropenem-nonsusceptible strains isolated in North America (*n* = 1009) and Europe (*n* = 2,682), consisting of 1,897 *Acinetobacter baumannii*, 1,154 *Pseudomonas aeruginosa*, 447 *Klebsiella pneumoniae,* and 193 other Enterobacteriaceae were tested. Conventional PCR was used to detect known carbapenemases. Cefiderocol MICs were determined by broth microdilution method using iron-depleted cation-adjusted Mueller–Hinton broth.

Results. The percentages of known carbapenemases detected in 3 main pathogens are shown in the Table. In *A. baumannii* complex, OXA-23 was predominant followed by OXA-24 in most countries. The detection rates of VIM in *P. aeruginosa* were ≥40% in Greece and Russia, but none of the strains in the United States carried VIM. In *K. pneumoniae*, the predominant carbapenemase varied among the countries, with KPC predominating in the USA, Greece and Italy, while OXA-48-like was dominant in Russia, Spain and Turkey. Cefiderocol MIC_{90} were ≤4 µg/mL against these 3 pathogens in all 6 countries, except for *A. baumannii* strains in Russia.

Conclusion. Carbapenemase detection rates, especially in *P. aeruginosa* and *K. pneumoniae*, were quite different among the countries. Cefiderocol demonstrated potent *in vitro* activity against meropenem-nonsusceptible strains irrespective of the presence of specific carbapenemases.

Table.

	A. baumannii complex			*P. aeruginosa*			*K. pneumoniae*			
Country	N	OXA-23 % of strains	OXA-24 % of strains	N	VIM % of strains	GES % of strains	N	KPC % of strains	OXA-48-like % of strains	NDM % of strains
USA	448	46.7	25.7	369	0	0.5	56	82.1	0	0
Greece	302	84.1	1.0	54	40.7	1.9	102	70.6	8.8	6.9
Italy	325	92.3	4.9	87	13.8	2.3	94	87.2	3.2	0
Russia	202	26.7	66.8	140	48.6	0.7	65	0	70.8	21.5
Spain	160	46.9	38.8	73	20.5	1.4	33	3.0	54.5	3.0
Turkey	291	94.2	4.5	80	6.3	0	75	1.3	76.0	24.0

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697. Evaluation of Contezolid Activity to Anaerobic and Gram-positive-cocci Isolates from a Phase 3 Acute Bacterial Skin and Skin Structure Infection Clinical Trial (MRX-I-06)

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Background. Contezolid (MRX-I) is an oxazolidinone in development for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). In this study, *in vitro* susceptibility (S) for Contezolid and comparator agents for Gram-positive (GP) and anaerobic isolates from Phase 3 ABSSSI clinical trials were determined.

Methods. 313 isolates were collected from 65 participated sites and sent to a central laboratory for MIC testing. Clinical isolates included 34 anaerobes (15 *Finegoldia magna*, 8 *Actinomyces* spp., 4 *Prevotella* spp., 3 *Propionibacterium avidum,* 2 *Peptostreptococcus* spp., 1 *Veillonella* spp. *and* 1 *Bacteroides fragilis*), 187 *S. aureus* (59. 7%). 12 *S. pyogenes, 5 Enterococcus* and 75 other Gram-positive organisms. Broth micro-dilution method was used to determine the MIC of contezolid, linezolid and other comparators to facultative isolates. Agar dilution was carried out for the anaerobes.

Results. For both 33 MRSA and 154 MSSA $MIC_{50/90}$ values of contezolid and linezolid were 2 mg/L. One *E. faecalis* showed decreased susceptibility to oxazolidinones (both MIC = 4). 1 mg/L contezolid and linezolid could inhibit 12 *S. pyogenes*. 2 mg/L contezolid and linezolid could inhibit 15 *Finegoldia magna*. 0.5 mg/L contezolid and linezolid could inhibit *8 Actinomyces spp. To* one *Bacteroides fragili,* two *Prevotella bivia* and one *Leuconostoc lactis* (Intrinsic resistant to vancomycin) the MIC of contezolid were 4 or 8 mg/L. In general, Contezolid had lower or equal $MIC_{50/90}$ values against both GP and ANA species compared with linezolid for all organisms.

Conclusion. Contezolid demonstrated potent *in vitro* antibacterial activity against Gram-positive and anaerobic isolates tested. These data suggest that contezolid might be a beneficial supplement to the arena against MDR Gram-positive infection.

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698. *In vitro* Activity of a New Generation Oxopyrazole Antibiotic Against Multidrug-Resistant Gram-Negative Bacilli

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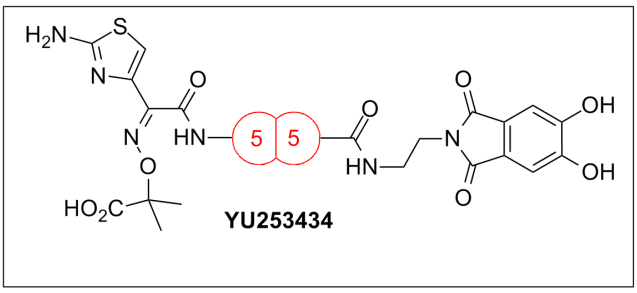
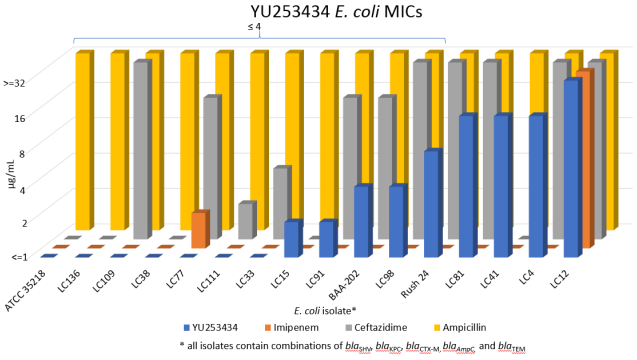
Background. Multidrug-resistant Gram-negative bacilli (MDRGNB) are emerging as a challenging cause of hospital-acquired infections and represent a critical need for innovative antibacterial development. New oxopyrazole agents targeting penicillin-binding proteins (PBPs) based on a non-β-lactam core and incorporating a siderophore moiety (Figure 1) which facilitates transport to the periplasm are being developed that show promise against Gram-negative organisms including multidrug-resistant strains of *E. coli, K. pneumoniae* and *P. aeruginosa.*

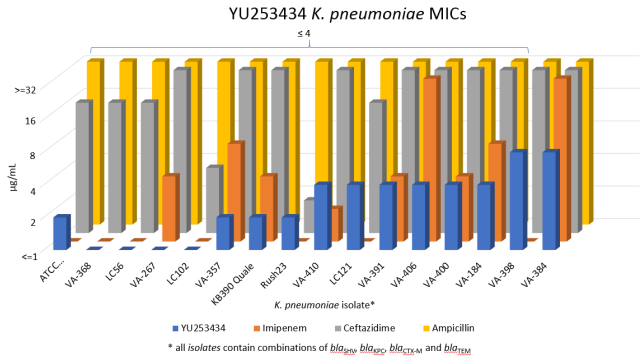
Methods. YU253434, an example of this new class of antibacterials, was investigated *in vitro*. Minimum inhibitory concentrations (MICs) were determined by broth microdilution against a representative panel comprising 15 strains each of *E. coli, K. pneumoniae* and *P. aeruginosa*, which contain extended-spectrum β-lactamase (ESBL) and/or carbapenemases genes.All studies were performed according to current Clinical & Laboratory Standards Institute (CLSI) guidelines using iron-depleted media. Ceftazidime breakpoints were arbitrability chosen as a reference for YU253434 (susceptibilities ≤4 µg/mL for *Enterobacteriaceae* and ≤8 µg/mL for *P. aeruginosa*).

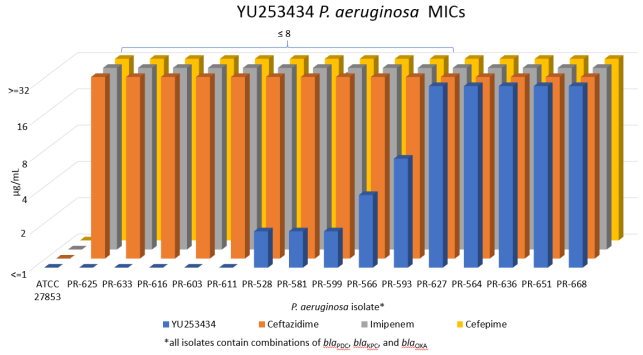
Results. MIC testing (Figures 2–4) against *E. coli* showed 11 strains were YU253434 susceptible (compared with 6 for ceftazidime, and 3 for imipenem); against *K. pneumoniae* 13 strains were YU253434 susceptible (compared with 2 for ceftazidime and 6 for imipenem); against *P. aeruginosa* 10 strains were YU253434 susceptible (compared with 0 for both ceftazidime and imipenem). There appeared to be no correlation between YU253434 resistance and the presence of specific lactamase genes.

Conclusion. YU253434, a new generation oxopyrazole antibiotic, demonstrated promising *in vitro* potency against a panel of *E. coli*, *K. pneumonia*, and *P. aeruginosa* strains which contain ESBL and/or carbapenemases genes.









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699. Hepatobiliary Safety in Adults With Community-Acquired Bacterial Pneumonia (CABP) Treated With Lefamulin (LEF) or Moxifloxacin (MOX): Pooled Analysis of Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Study Results

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Background. LEF efficacy and safety were shown in 2 noninferiority trials (LEAP 1/2) vs. MOX in adults with CABP. We assessed the hepatobiliary safety of LEF based on pooled analyses of LEAP 1/2 data.

Methods. In LEAP 1, PORT III–V patients received LEF 150 mg IV q12h for 5–7 days or MOX 400 mg IV q24h for 7 days, with optional IV-to-oral switch (600 mg LEF q12h or 400 mg MOX q24h). In LEAP 2, PORT II–IV patients received oral LEF 600 mg q12h for 5 days or oral MOX 400mg q24h for 7 days. Exclusion criteria included infection with HBV/HCV, acute hepatitis, cirrhosis, AST or ALT >5xULN, total bilirubin >3xULN (unless Gilbert's disease), AST or ALT >3xULN and total bilirubin >2xULN, and manifestation of end-stage liver disease. Hepatic safety was assessed from baseline (BL) and multiple post-BL blood samples using a central laboratory, TEAEs, and expert consultant adjudication. Pooled analyses included all randomized/treated patients (safety population).

Results. Of 1282 randomized/treated patients, 1251 had BL and post-BL hepatobiliary data (table). Post-BL distribution of ALT/AST was generally similar for both groups, although ALT >AST in the absence of muscle injury or alcohol use. Overall, rates of patients experiencing an increase in ALT/AST >3xULN, ALP >2xULN, or total bilirubin >1.5xULN were low (table). Patients with elevated vs. normal BL transaminases (TAs) were more likely to have post-BL elevations >3xULN, but the vast majority remained <5xULN. Among patients with ALT >5xULN, peak increases were generally seen in the first week after the first LEF dose and declined to within/near normal levels by late follow-up (day 28); for MOX, time to peak ALT was less consistent (figure). No LEF pt and 1 MOX pt met laboratory criteria for Hy's Law. Elevations in TAs were reversible, with no evidence of chronic injury. The LEF injury pattern was predominantly hepatocellular (50.0%)/mixed (40.0%), with no apparent gender, age, or ethnic predominance. TEAEs in the hepatobiliary disorders system organ class were reported in 6 (0.9%) LEF patients and 6 (0.9%) MOX patients, with similar levels seen in patients with elevated BL TAs. There were no symptomatic patients, severe disease, or evidence of hypersensitivity.

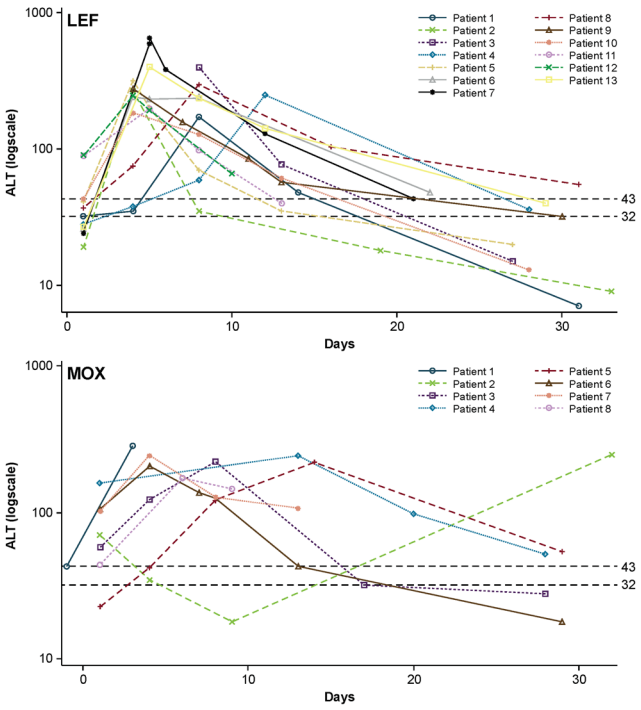
Conclusion. Low incidences of hepatobiliary parameter elevations and TEAEs were observed, with no apparent differences between LEF and MOX.

Table. Maximum Postbaseline Increases in Hepatobiliary Parameters

	LEAP 1		LEAP 2		Pooled	
n (%)	LEF (n=268)	MOX (n=267)	LEF (n=355)	MOX (n=361)	LEF* (n=623)	MOX† (n=628)
ALT >3×ULN	19 (7.1)	17 (6.4)	15 (4.2)	17 (4.7)	34 (5.5)	34 (5.4)
ALT >5×ULN	6 (2.2)	5 (1.9)	7 (2.0)	3 (0.8)	13 (2.1)	8 (1.3)
ALT >10×ULN	1 (0.4)	0	1 (0.3)	0	2 (0.3)	0
AST >3×ULN	11 (4.1)	7 (2.6)	12 (3.4)	8 (2.2)	23 (3.7)	15 (2.4)
AST >5×ULN	2 (0.7)	2 (0.7)	6 (1.7)	5 (1.4)	8 (1.3)	7 (1.1)
AST >10×ULN	1 (0.4)	0	1 (0.3)	0	2 (0.3)	0
ALP >2×ULN	5 (1.9)	5 (1.9)	14 (3.9)‡	6 (1.7)‡	19 (3.0)‡	11 (1.7)‡
Total bilirubin >1.5×ULN	3 (1.1)	3 (1.1)	3 (0.8)	3 (0.8)	6 (1.0)	6 (1.0)
Total bilirubin >2×ULN	0	2 (0.7)	2 (0.6)	0	2 (0.3)	2 (0.3)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LEF=lefamulin; MOX= moxifloxacin; ULN=upper limit of normal.
*Lefamulin 150 mg IV / 600 mg oral.
†Moxifloxacin 400 mg IV / 400 mg oral.
‡For LEAP 2: LEF, n=357; MOX, n=362. For pooled analysis: LEF, n=625; MOX, n=629.

Figure. Individual ALT Values for Patients With Postbaseline ALT >5xULN



ALT=alanine aminotransferase; LEF=lefamulin; MOX=moxifloxacin; ULN=upper limit of normal.
Note: The ALT ULN range for the central laboratory is 32-43 U/L, depending on age and sex.

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700. Safety and Efficacy of Omadacycline in Patients with Diabetes in Phase 3 Clinical Studies

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Background. The risk of serious infections and poor treatment outcomes is reported to be higher in patients with diabetes compared with the general population. Omadacycline (OMC) is an intravenous (IV) and oral aminomethylcycline antibiotic approved in the US to treat acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in adults. Here we assessed safety and efficacy results from OMC Phase 3 studies (ABSSSI: Omadacycline in Acute Skin and skin structure Infections Study [OASIS]-1 and OASIS-2; CABP: Omadacycline for Pneumonia Treatment In the Community study [OPTIC]), by diabetes history.

Methods. In OASIS-1 (IV to optional oral medication) and OASIS-2 (oral only), patients were randomized to OMC or linezolid (LZD) for 7–14 days. In OPTIC, patients were randomized to IV OMC or moxifloxacin (MOX) for 7–14 days, with optional transition to oral medication. Data from OASIS-1 and OASIS-2 were pooled, and patient