IDWeek 2019 | Poster #2192

Comparative Antimicrobial Susceptibility of Gram-Negative Bacteria Isolated from Patients with Bloodstream Infections and Pneumonia When Tested against Tazobactam Combinations

Cecilia G. Carvalhaes, Rodrigo E. Mendes, Robert K. Flamm, Helio S. Sader
JMI Laboratories, North Liberty, Iowa, USA

Introduction

- The clinical efficacy of current first line empiric therapies for the treatment of Gram-negative infections has been decreasing due to increase in ESBL and/or class C expressing *Enterobacterales*; such a scenario compels clinicians to frequently use carbapenems, leading to selection of difficult-to-treat carbapenem-resistant *Enterobacterales* (CRE)
- WCK 4282 combines 2g cefepime with high dose tazobactam 2g, to be administered three times a day in extended, 90 minutes infusion
- Previous studies showed that cefepime-tazobactam retains comprehensive activity against *Enterobacterales* isolates that produce extended spectrum (ESBLs) and/or AmpC/class C β-lactamases that are resistant to first line agents, piperacillin-tazobactam and cefoperazone-sulbactam as well as recently approved combination ceftolozane-tazobactam
- Clinical indications currently approved by the US Food and Drug Administration for treatment with cefepime include moderate to severe pneumonia, complicated and uncomplicated urinary tract infections, complicated intra-abdominal infections, and uncomplicated skin and skin structure infections, as well as empiric therapy for febrile neutropenic patients
- We compared the susceptibility of Gram-negative bacilli from patients with bloodstream infections and pneumonia for cefepime-tazobactam, piperacillin-tazobactam, and ceftolozane-tazobactam

Materials and Methods

Bacterial isolates

- A total of 3,389 Gram-negative bacilli isolates were consecutively collected (1/patient) from patients with bloodstream infection (BSI; 1,349) and pneumonia (PNM; 2,040) in 40 US medical centers during 2018 by the SENTRY Antimicrobial Surveillance Program
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program

Resistant subsets

- CRE isolates were defined as displaying imipenem, meropenem, and/or doripenem MIC values at ≥4 mg/L (Clinical and Laboratory Standards Institute [CLSI], 2019)
  - Imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae due to the intrinsically elevated MIC values
- Multidrug-resistant (MDR) *Enterobacterales* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows:
  - MDR = nonsusceptible (CLSI breakpoints) to at least 3 antimicrobial classes

Susceptibility testing

- Susceptibility testing against cefepime-tazobactam (tazobactam at fixed 8 mg/L), ceftolozane-tazobactam (tazobactam at fixed 4 mg/L), piperacillin-tazobactam (tazobactam at fixed 4 mg/L), and comparators was performed by reference broth microdilution method
- The percentage of isolates inhibited at ≤8 mg/L (CLSI cefepime high dose) and at ≤16 mg/L (proposed pharmacokinetic/pharmacodynamic [PK/PD] susceptibility breakpoint based on extended infusion and high dosage) of cefepime-tazobactam were evaluated
- CLSI breakpoints were applied for comparators and for categorizing resistant subsets

Results

- The most common Gram-negative species isolated from BSI were *Escherichia coli* (47.1%), *Klebsiella pneumoniae* (17.5%), and *Pseudomonas aeruginosa* (9.0%; Figure 1)
- *P. aeruginosa* (37.1%), *K. pneumoniae* (11.9%), and *E. coli* (10.3%) were also the most frequent Gram-negative isolates recovered from patients with PNM (Figure 1)
- Cefepime-tazobactam ($MIC_{50/90}$, 0.03/0.12 mg/L; 99.7% inhibited at ≤16 mg/L for BSI, and $MIC_{50/90}$, 0.06/0.25 mg/L; 98.7% inhibited at ≤16 mg/L for PNM) was the most active tazobactam combination against *Enterobacterales* with a susceptibility spectrum similar to that of meropenem (99.3%/97.2% susceptible for BSI/PNM), ceftazidime-avibactam (99.8%/99.9% susceptible), and amikacin (99.3%/98.3% susceptible; Table 1; Figure 2)
- Cefepime-tazobactam retained good activity against *Enterobacterales* isolates not susceptible to ceftriaxone (96.9%/97.9% of BSI isolates and 92.2%/94.4% of PNM isolates inhibited at ≤8/≤16 mg/L), compared to 72.8%/47.2% susceptibility to piperacillin-tazobactam and 82.5%/56.9% susceptibility to ceftolozane-tazobactam for BSI/PNM isolates (Table 1)
- Similarly, against MDR *Enterobacterales*, cefepime-tazobactam (96.0%/90.0% [BSI/PNM] inhibited at ≤16 mg/L) and ceftazidime-avibactam (98.0%/99.2% susceptible [BSI/PNM]) demonstrated greater activity than piperacillin-tazobactam (64.4%/41.5% for BSI/PNM) and ceftolozane-tazobactam (81.8%/54.3% for BSI/PNM; Table 1)
- When tested against *P. aeruginosa*, cefepime-tazobactam inhibited 89.3%/95.0% of BSI isolates ($MIC_{50/90}$, 2/16 mg/L) and 80.7%/92.1% of PNM isolates ($MIC_{50/90}$, 4/16 mg/L) at ≤8/≤16 mg/L; ceftazidime-avibactam and ceftolozane-tazobactam were active against 96.7%/95.2% and 96.5%/94.5% BSI/PNM isolates at the respective susceptible breakpoints (Table 1 and Figure 3)
- Cefepime-tazobactam (77.8%/77.3% [BSI/PNM] inhibited at ≤16 mg/L), ceftolozane-tazobactam (81.2%/82.9% susceptible), and ceftazidime-avibactam (77.8%/84.5% susceptible) retained some activity against *P. aeruginosa* not susceptible to meropenem (Table 1)
- Cefepime-tazobactam (95.5%/79.4% [BSI/PNM] inhibited at ≤16 mg/L) and ceftolozane-tazobactam (100.0%/66.2% susceptible [BSI/PNM]) were the most active β-lactams against *Acinetobacter* spp. when the proposed cefepime-tazobactam PK/PD breakpoint was applied (Table 1)

Conclusions

- Susceptibility rates were markedly lower among isolates from PNM compared to BSI
- Cefepime-tazobactam was the most active tazobactam combination tested against Gram-negative bacilli isolated from patients with BSI and PNM from US hospitals
- Cefepime-tazobactam demonstrated greater activity than piperacillin-tazobactam and ceftolozane-tazobactam against ceftriaxone-resistant and MDR *Enterobacterales*, which was comparable to the activity of ceftazidime-avibactam against these organisms
- Against ceftriaxone-resistant and MDR *Enterobacterales* from PNM, susceptibility rates of cefepime-tazobactam were higher than that of meropenem
- Against *P. aeruginosa* from BSI and PNM, cefepime-tazobactam susceptibility rates were comparable to that of ceftolozane-tazobactam and higher than that of piperacillin-tazobactam
- Overall, activity profile of cefepime-tazobactam supports its potential role as carbapenem-sparing empirical therapy in view of rising resistance rates to current first line agents such as third and fourth generation cephalosporins and piperacillin-tazobactam
- Study results support further clinical development of high-dose extended-infusion cefepime-tazobactam for treatment of Gram-negative bacilli infections

Table 1 Antimicrobial activity of cefepime-tazobactam and comparator agents tested against Gram-negative bacilli isolated from bloodstream infection and pneumonia in the United States (2018)

Organism/organism group	BSI (no. tested)		Pneumonia (no. tested)	
Antimicrobial agent	**%S[a]**	**%R**	**%S[a]**	**%R**
Enterobacterales	(1,185)		(1,024)	
Cefepime-tazobactam	[99.5/99.7][b]		[98.2/98.7][b]	
Piperacillin-tazobactam	94.0	3.0	86.9	6.9
Ceftolozane-tazobactam	97.1	2.3	89.7	7.6
Ceftazidime-avibactam	99.8	0.2	99.9	0.1
Cefepime	88.2	9.2	87.4	9.6
Meropenem	99.3	0.6	97.2	2.6
Levofloxacin	75.1	22.8	81.5	15.9
Amikacin	99.3	0.3	98.3	0.4
Colistin[c]	88.2	11.8	73.9	26.1
Enterobacterales not susceptible to CRO	(191)		(231)	
Cefepime-tazobactam	[96.9/97.9][b]		[92.2/94.4][b]	
Piperacillin-tazobactam	72.8	13.6	47.2	28.6
Ceftolozane-tazobactam	82.5	13.9	56.9	32.5
Ceftazidime-avibactam	99.0	1.0	99.6	0.4
Cefepime	27.2	57.1	44.2	42.4
Meropenem	95.8	3.7	87.4	11.7
Levofloxacin	36.8	60.5	54.3	42.6
Amikacin	96.9	2.1	93.1	1.3
Colistin[c]	91.1[c]	8.9	79.1[c]	20.9
MDR isolates	(101)		(130)	
Cefepime-tazobactam	[94.1/96.0][b]		[86.2/90.0][b]	
Piperacillin-tazobactam	64.4	15.8	41.5	32.3
Ceftolozane-tazobactam	81.8	13.6	54.3	39.7
Ceftazidime-avibactam	98.0	2.0	99.2	0.8
Cefepime	21.8	68.3	33.1	54.6
Meropenem	92.1	6.9	77.7	20.8
Levofloxacin	13.0	80.0	31.8	62.8
Amikacin	92.1	4.0	88.5	3.1
Colistin[c]	80.2	19.8	63.6	36.4
CRE isolates	(7)		(29)	
Cefepime-tazobactam	[28.6/57.1][b]		[44.8/58.6][b]	
Piperacillin-tazobactam	0.0	100.0	0.0	89.7
Ceftolozane-tazobactam	0.0	100.0	0.0	100.0
Ceftazidime-avibactam	71.4	28.6	96.6	3.4
Cefepime	0.0	85.7	3.4	79.3
Meropenem	0.0	100.0	0.0	93.1
Levofloxacin	28.6	71.4	24.1	65.5
Amikacin	85.7	14.3	75.9	3.4
Colistin[c]	71.1	28.6	82.1	17.9
Pseudomonas aeruginosa	(121)		(757)	
Cefepime-tazobactam	[89.3/95.0][b]		[80.7/92.1][b]	
Piperacillin-tazobactam	82.6	8.3	75.2	14.3
Ceftolozane-tazobactam	96.5	1.8	94.5	3.8
Ceftazidime-avibactam	96.7	3.3	95.2	4.8
Cefepime	89.3	4.1	78.2	8.6
Meropenem	85.1	9.9	74.4	19.0
Levofloxacin	70.2	19.0	60.2	26.3
Amikacin	99.2	0.0	91.1	5.3
Colistin	100.0	0.0	99.6	0.4
P. aeruginosa not susceptible to MEM	(18)		(194)	
Cefepime-tazobactam	[66.7/77.8][b]		[49.0/77.3][b]	
Piperacillin-tazobactam	38.9	33.3	41.2	36.1
Ceftolozane-tazobactam	81.2	6.2	82.9	14.0
Ceftazidime-avibactam	77.8	22.2	84.5	15.5
Cefepime	66.7	16.7	42.8	25.3
Meropenem	0.0	66.7	0.0	74.2
Levofloxacin	16.7	50.0	18.0	59.8
Amikacin	100.0	0.0	79.4	15.5
Colistin	100.0	0.0	99.5	0.5
Acinetobacter spp.	(22)		(102)	
Cefepime-tazobactam	[95.5/95.5][b]		[67.6/79.4][b]	
Piperacillin-tazobactam	86.4	9.1	58.8	36.3
Ceftolozane-tazobactam	[100.0][c]	[0.0][c]	[66.2][d]	[20.8][e]
Ceftazidime-avibactam	[81.8][d]	[18.2][d]	[62.7][d]	[37.3][e]
Cefepime	90.9	9.1	63.7	30.4
Meropenem	95.5	4.5	65.7	33.3
Levofloxacin	95.5	4.5	65.7	34.3
Amikacin	95.2	4.8	84.3	10.8
Colistin	100.0	0.0	91.2	8.8

BSI, bloodstream infection; MDR, multidrug-resistant; CRO, ceftriaxone; CRE, carbapenem-resistant *Enterobacterales*; MEM, meropenem
[a] Criteria as published by CLSI 2019.
[b] Percentage of isolates inhibited at ≤8 / ≤16 mg/L, respectively.
[c] Percentage of wild type based on epidemiologic cutoff value, CLSI M100 (2019).
[d] Percentage of isolates inhibited at if aeruginosa breakpoint for comparison purpose.

Figure 1 Frequency of organisms isolated in US medical centers by infection type (SENTRY Program, 2018)

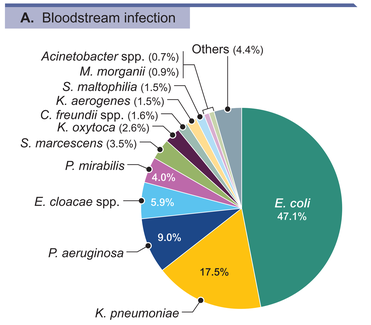
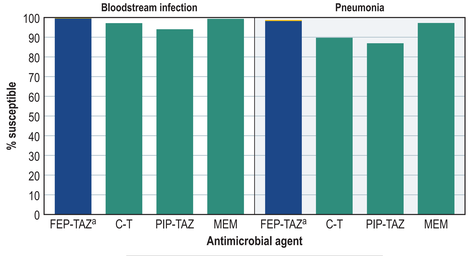
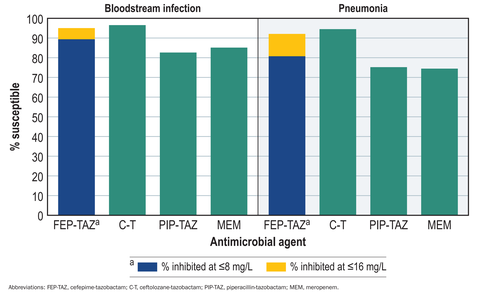


Figure 2 Antimicrobial susceptibility of *Enterobacterales* isolated from bloodstream infections and pneumonia in hospitalized patients in US medical centers (SENTRY Program, 2018)



Abbreviations: FEP-TAZ, cefepime-tazobactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem.

Figure 3 Antimicrobial susceptibility of *P. aeruginosa* isolated from bloodstream infections and pneumonia in hospitalized patients in US medical centers (SENTRY Program, 2018)



Abbreviations: FEP-TAZ, cefepime-tazobactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem.

Acknowledgements

This study was supported by Wockhardt Bio AG.

References

Burgess SV, Mabasa VH, Chow I, et al. (2015). Evaluating outcomes of alternative dosing strategies for cefepime: a qualitative systematic review. *Ann Pharmacother* 49: 311–322.

Castanheira M, Duncan LR, Rhomberg PR, et al. (2017). Enhanced activity of cefepime-tazobactam (WCK 4282) against KPC-producing *Enterobacteriaceae* when tested in media supplemented with human serum or sodium chloride. *Diagn Microbiol Infect Dis* 89: 305–309.

Clinical and Laboratory Standards Institute (2018). *M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eleventh edition*. Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2019). *M100Ed29. Performance standards for antimicrobial susceptibility testing: 29th informational supplement*. Wayne, PA: CLSI.

DHS (2018). Generating antibiotic incentives now (GAIN). Food and Drug Administration Safety and Innovations Act (FDASIA). Available at: https://www.fda.gov/media/110982/download. Accessed July 2019.

Magiorakos AP, Srinivasan A, Carey RB, et al. (2012). Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 18: 268–281.

Maxepime (2012). Maxepime Package Insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050679s036lbl.pdf. Accessed February 18, 2016.

Sader HS, Castanheira M, Mendes RE, et al. (2017). Antimicrobial activity of high-proportion cefepime-tazobactam (WCK 4282) against a large number of Gram-negative isolates collected worldwide in 2014. *Antimicrob Agents Chemother* 61: e02409.

Contact

Helio S. Sader, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: helio-sader@jmilabs.com

To obtain a PDF of this poster:

Scan the QR code or visit https://www.jmilabs.com/data/posters/IDWeek2019-cefepime-tazobactam-bacteremia-pneumonia.pdf

Charges may apply. No personal information is stored.