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Activity of Aztreonam-Avibactam and Comparators against Difficult-to-Treat Resistant (DTR) Enterobacterales from Patients with Pneumonia or Intra-abdominal Infections (IAI) in European Medical Centers (2020–2024)

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Background

- Treatment options for infections caused by difficult-to-treat resistant (DTR) isolates, defined as bacterial isolates expressing nonsusceptibility to all first-line agents, are very limited.
- These infections are associated with high clinical failure and mortality rates, especially in vulnerable patients.
- Delay on the introduction of appropriate therapy is one of the strongest predictors of mortality in patients with DTR infections.
- We evaluated the activity of aztreonam-avibactam and comparators against DTR Enterobacterales from European medical centers.

Methods

- A total of 9,144 Enterobacterales isolates were consecutively collected (1/patient) from 41 European medical centres in 19 countries in 2020–2024. The participating countries (no. of isolates) were:

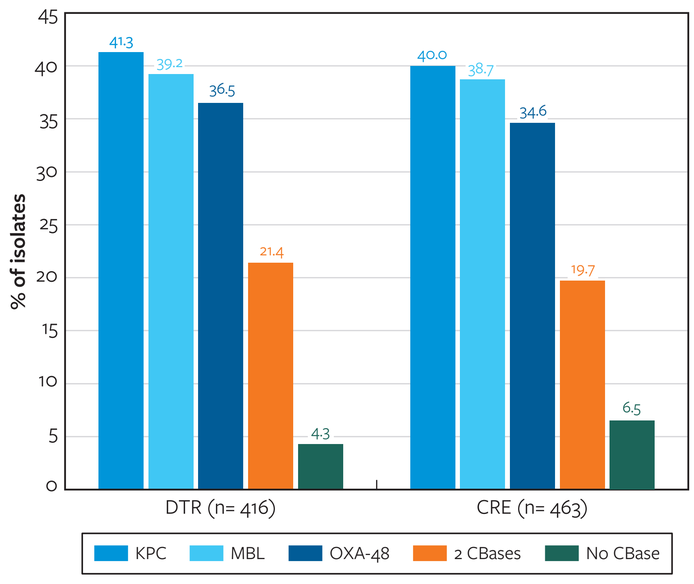
Belgium (328)	Hungary (180)	Portugal (304)	Sweden (90)
Czech Republic (156)	Ireland (325)	Romania (75)	Switzerland (517)
France (1,007)	Israel (264)	Slovakia (81)	Turkey (640)
Germany (1,737)	Italy (954)	Slovenia (283)	United Kingdom (617)
Greece (368)	Poland (285)	Spain (933)	

- The isolates were collected from patients with pneumonia (n=6,561) or intra-abdominal infections (n=2,583).
- Isolates were susceptibility tested by CLSI broth microdilution and MIC interpreted according to EUCAST breakpoints.
- The collection included:
  - 416 DTR, defined as nonsusceptible to cephalosporins (excluding cefiderocol), carbapenems, piperacillin-tazobactam, ceftolozane-tazobactam, and fluoroquinolones.
  - 463 carbapenem-resistant Enterobacterales (CRE), defined as resistant to meropenem or imipenem per CLSI criteria. Thus, all DTR isolates were CRE.
- All DTR and CRE isolates were screened for β-lactamase genes by whole genome sequencing.

Results

- Aztreonam-avibactam was active against 99.8% of DTR and 99.1% of CRE isolates (Table 1), with $MIC_{50/90}$ values of 0.25/0.5 mg/L for both groups.
- Aztreonam-avibactam retained potent activity against DTR isolates nonsusceptible to ceftazidime-avibactam (99.4% susceptible), meropenem-vaborbactam (99.6% susceptible), and/or cefiderocol (100.0% susceptible; Table 1), with $MIC_{50/90}$ values of 0.25/0.5 mg/L for all 3 groups.
- Cefiderocol was active against 74.0% of DTR and 74.8% of CRE isolates (Table 1).
- Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, and the aminoglycosides exhibited limited activity against DTR and CRE (Table 1).
- All MBL producers (100.0%) were susceptible to aztreonam-avibactam and 61.5% were susceptible to cefiderocol (Table 1).
- DTR and CRE rates were generally higher among isolates from pneumonia (5.4% and 6.0%, respectively) than IAI (2.3% and 2.7%, respectively; Table 2).
- DTR and CRE rates were considerably higher in Greece, Poland, Slovakia, and Turkey compared to other countries (Table 2).
- Greece, Italy, Poland, and Turkey contributed with 83.2% of DTR and 79.5% of CRE isolates.
- The most common carbapenemase (CBase) genes identified among DTR isolates were bla_{KPC} (41.3% of isolates) and bla_{NDM} (34.1%).
- DTR and CRE isolates exhibited similar frequencies of CBase types (Figure 1).
- An MBL gene was observed in 39.2% of DTR and 38.7% of CRE isolates (Figure 1).

Figure 1. Distribution of carbapenemase (CBase) types among DTR and CRE isolates



Abbreviations: DTR, difficult-to-treat resistant; CRE, carbapenem-resistant Enterobacterales; MBL, metallo-β-lactamase; CBase, carbapenemase.

Table 1. Antimicrobial susceptibility of selected resistant subsets

Antimicrobial agent	% Susceptible per EUCAST criteria (no. of isolates)					
	DTR (416)	CRE (463)	MBL producers (179)	CAZ-AVI-NS (161)[a]	MEM-VAB-NS (235)[a]	Cefiderocol-NS (77)[a]
ATM-AVI	99.8	99.1	100.0	99.4	99.6	100.0
CAZ-AVI	61.3	61.8	2.8	0.0	36.6	14.3
MEM-VAB	43.5	47.7	12.3	7.5	0.0	3.9
IMI-REL	44.4	46.4	5.0	1.6	17.0	7.1
Cefiderocol	74.0	74.8	61.5	58.5	64.1	0.0
Gentamicin	42.1	42.5	31.3	31.7	29.4	20.8
Amikacin	40.4	44.3	33.5	29.8	24.3	16.9
Colistin	62.6	65.2	62.4	60.6	55.3	48.1

[a] Includes only DTR isolates. Abbreviations: DTR, difficult-to-treat resistant; CRE, carbapenem-resistant Enterobacterales; MBL, metallo-β-lactamase; CAZ-AVI, ceftazidime-avibactam; NS, nonsusceptible; MEM-VAB, meropenem-vaborbactam; IMI-REL, imipenem-relebactam.

Table 2. DTR and CRE rates by country

Country (no. of isolates: pneumonia/IAI)	DTR rate (%)		CRE rate (%)	
	Pneumonia	IAI	Pneumonia	IAI
Belgium (258/70)	0.8	0.0	1.2	0.0
Czech Republic (156/0)	1.9	NT	1.9	NT
France (635/372)	0.5	0.5	0.9	0.5
Germany (1,310/427)	0.2	0.9	0.6	1.2
Greece (231/137)	34.2	11.7	36.8	12.4
Hungary (152/28)	0.7	0.0	0.7	0.0
Ireland (277/48)	0.7	0.0	1.1	0.0
Israel (207/57)	2.9	0.0	3.9	0.0
Italy (689/265)	3.5	4.5	3.9	6.0
Poland (195/90)	24.6	8.9	26.2	10.0
Portugal (196/108)	4.6	0.0	7.2	0.0
Romania (75/0)	8.0	NT	8.0	NT
Slovakia (81/0)	16.0	NT	19.8	NT
Slovenia (283/0)	0.0	NT	0.0	NT
Spain (599/334)	1.2	2.1	1.5	2.4
Sweden (71/19)	0.0	0.0	0.0	0.0
Switzerland (384/133)	0.0	0.0	0.0	0.0
Turkey (428/212)	34.6	5.2	35.0	6.1
United Kingdom (334/283)	0.6	0.0	0.9	0.0
Overall (6,561/2,583)	**5.4**	**2.3**	**6.0**	**2.7**

Abbreviations: CRE, carbapenem-resistant Enterobacterales; IAI, intra-abdominal infection.

Conclusions

- Aztreonam-avibactam retained potent activity against DTR Enterobacterales and CRE from European medical centres.
- Aztreonam-avibactam activity was not adversely affected by clinically relevant CBases or resistance to agents currently used to treat CRE and MDR Enterobacterales.
- The activities of other β-lactamase inhibitor combinations and cefiderocol were compromised by the increased occurrence of MBL producers among DTR and CRE isolates.

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