Cefiderocol Retains *In Vitro* Activity Against Enterobacterales Non-Susceptible to β-Lactam–β-Lactamase Inhibitor Combinations

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ID Week 2024, Los Angeles
October 16–20, 2024

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Disclosures

This research was conducted by Element Iowa City (JMI Laboratories) and funded by Shionogi.

Boudewijn L.M. DeJonge, Sean T. Nguyen, Jason J. Bryowsky, Chris Longshaw, Miki Takemura, and Yoshinori Yamano are employees of Shionogi. Rodrigo E. Mendes and Joshua Maher are employees of Element Iowa City.

Background

- Novel β-lactam–β-lactamase inhibitor combinations, such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, are options for the treatment of infections caused by carbapenem-resistant Enterobacterales[1]
- With resistance emerging against these novel β-lactam–β-lactamase inhibitor combinations, we assessed whether the *in vitro* activity of cefiderocol, a siderophore conjugated cephalosporin with activity against a broad range of Gram-negative pathogens, including carbapenem-resistant isolates, is affected against these isolates
- Isolates were collected between 2020 and 2022 in Europe and the USA as part of the SENTRY Antimicrobial Surveillance Program

Reference
1. Tamma PD, et al. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant Gram-negative infections. Clin Infect Dis. 2024 Aug 7:ciae403.

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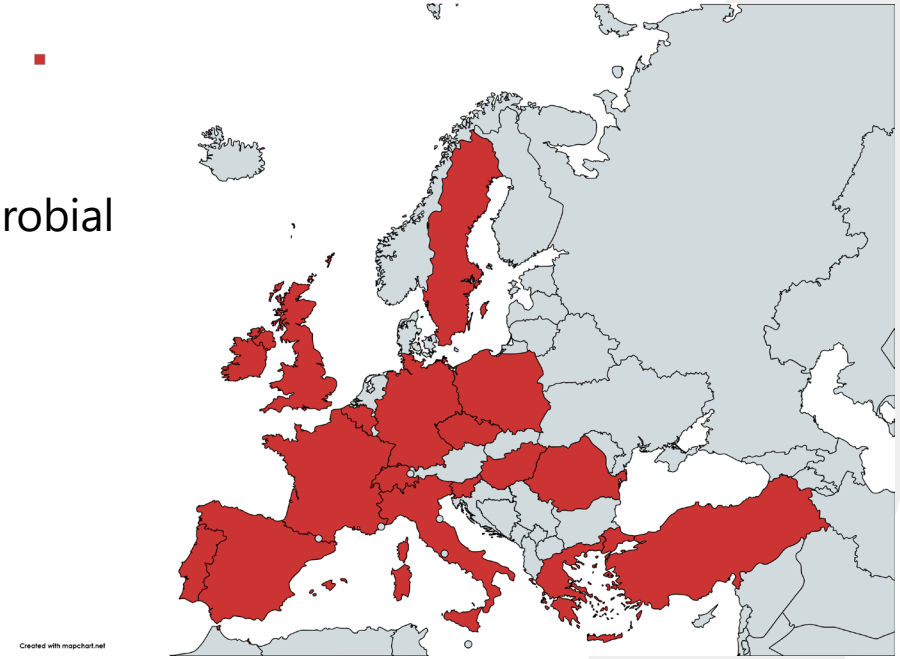
Methods

- 24,084 Enterobacterales were collected as part of the SENTRY Antimicrobial Surveillance Program
  - 2020–2022
  - 33 hospitals in the USA and 39 in Europe (17 countries + Israel)
  - Europe (n=12,200) and USA (n=11,884)
  - One (index) isolate per patient
  - Collection across different indications



- Minimum inhibitory concentration values were determined using CLSI broth microdilution methodology
  - Cation-adjusted Mueller–Hinton broth was used for the β-lactam–β-lactamase inhibitor combinations
  - Iron-depleted cation-adjusted Mueller–Hinton broth was used for cefiderocol
- Susceptibility was assessed according to 2024 CLSI, FDA, and EUCAST breakpoints
- Non-susceptibility to ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam was assessed using CLSI breakpoints
- Whole-genome sequencing was performed on cefiderocol-non-susceptible isolates (CLSI breakpoints)

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration.

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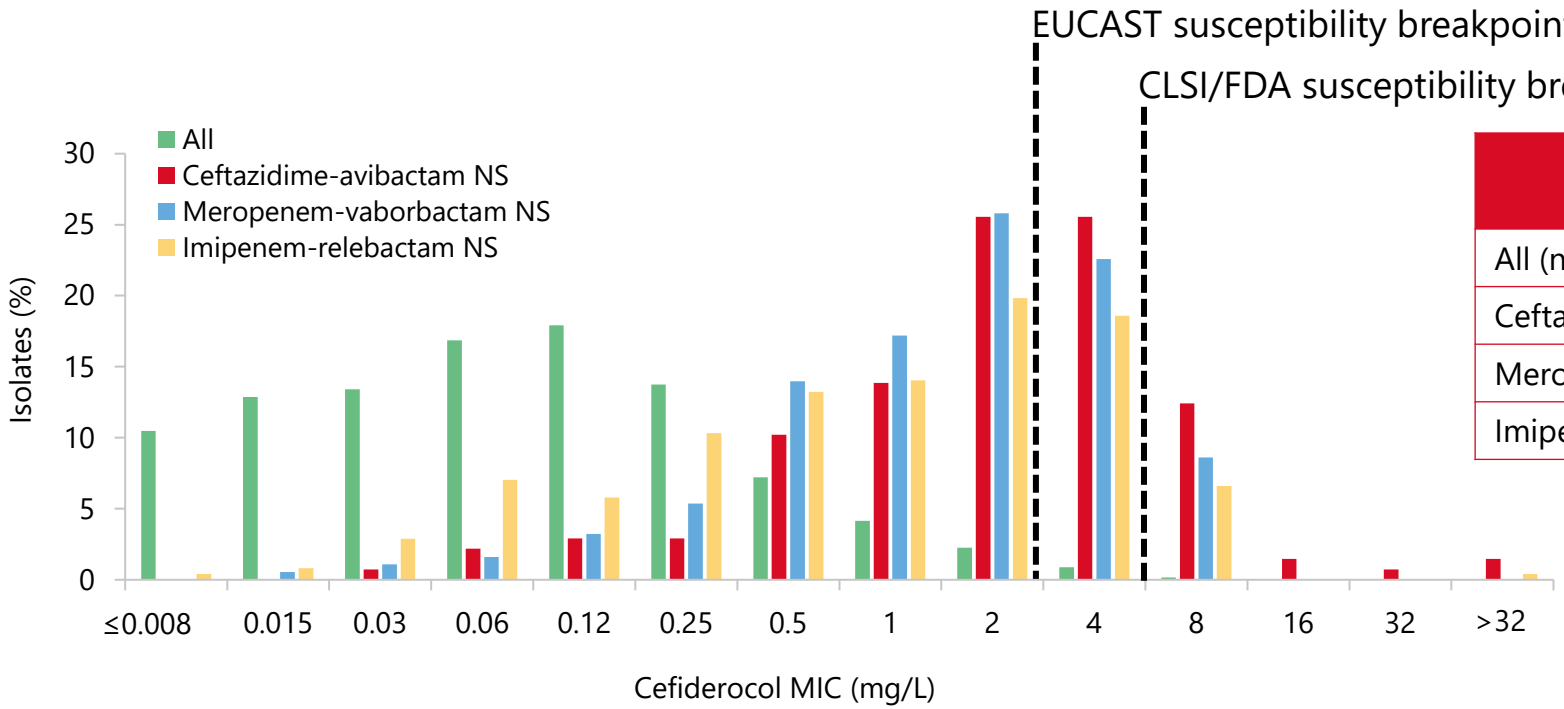
Cefiderocol MIC Distributions



	MIC_{50} (mg/L)	MIC_{90} (mg/L)
All (n=24,084)	0.06	0.5
Ceftazidime-avibactam-NS (n=137)	2	8
Meropenem-vaborbactam-NS (n=186)	2	4
Imipenem-relebactam-NS (n=229)*	1	4

**Proteus* spp., *Providencia* spp., and *Morganella* spp., which are intrinsically resistant to imipenem, were excluded.

- Isolates that were non-susceptible to β-lactam–β-lactamase inhibitor combinations showed more elevated MIC values for cefiderocol compared with the overall population
- Different breakpoints between CLSI/FDA and EUCAST resulted in different levels of susceptibility/resistance
  - Large percentage of isolates with MIC=4 mg/L, considered susceptible by CLSI/FDA but resistant by EUCAST breakpoints

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MIC, minimum inhibitory concentration; NS, non-susceptible.

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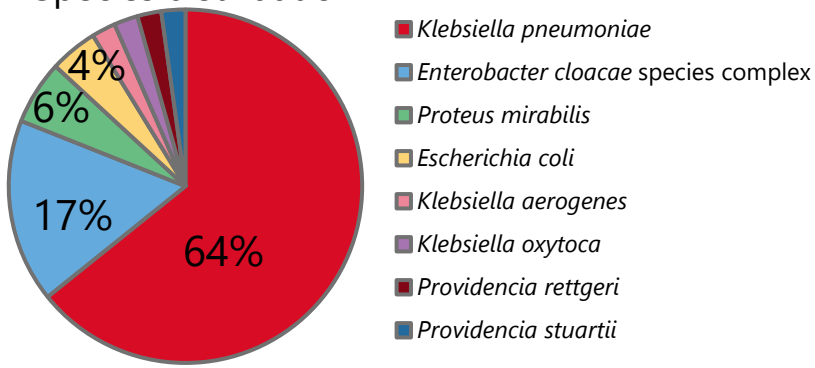
Ceftazidime-Avibactam Non-Susceptible Enterobacterales (n=137)

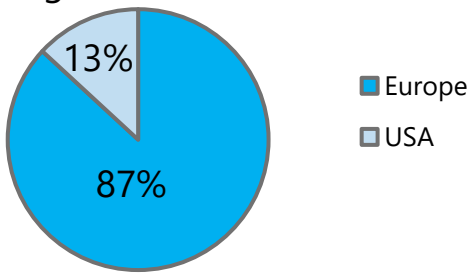
Characteristics of Isolates

0.57% of total

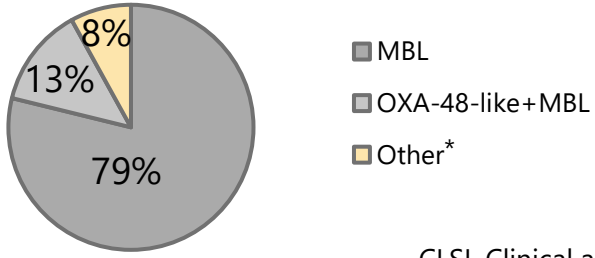
Species distribution



Origin of isolates



β-lactamase content



*Includes non-β-lactamase producers

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MBL, metallo-β-lactamase; OXA, oxacillinase.

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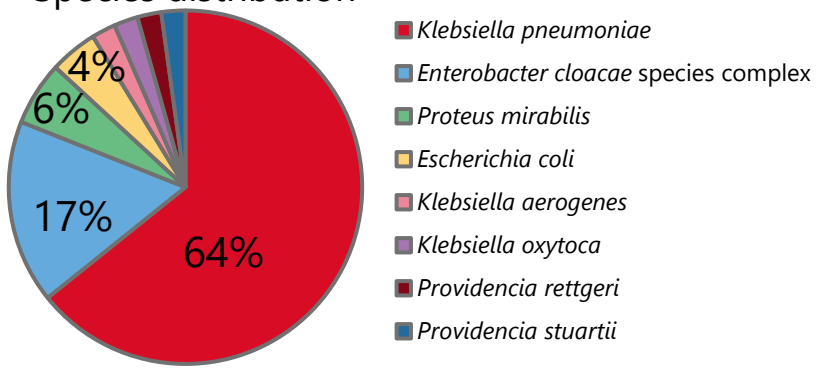
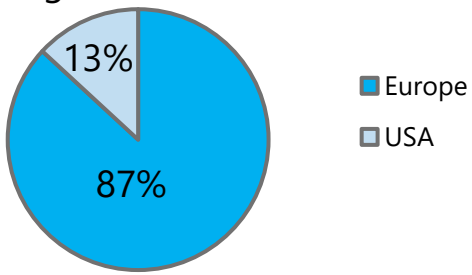
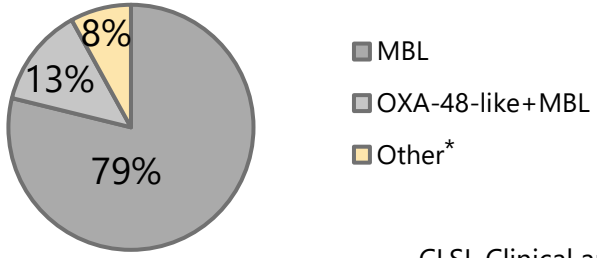


Origin of isolates

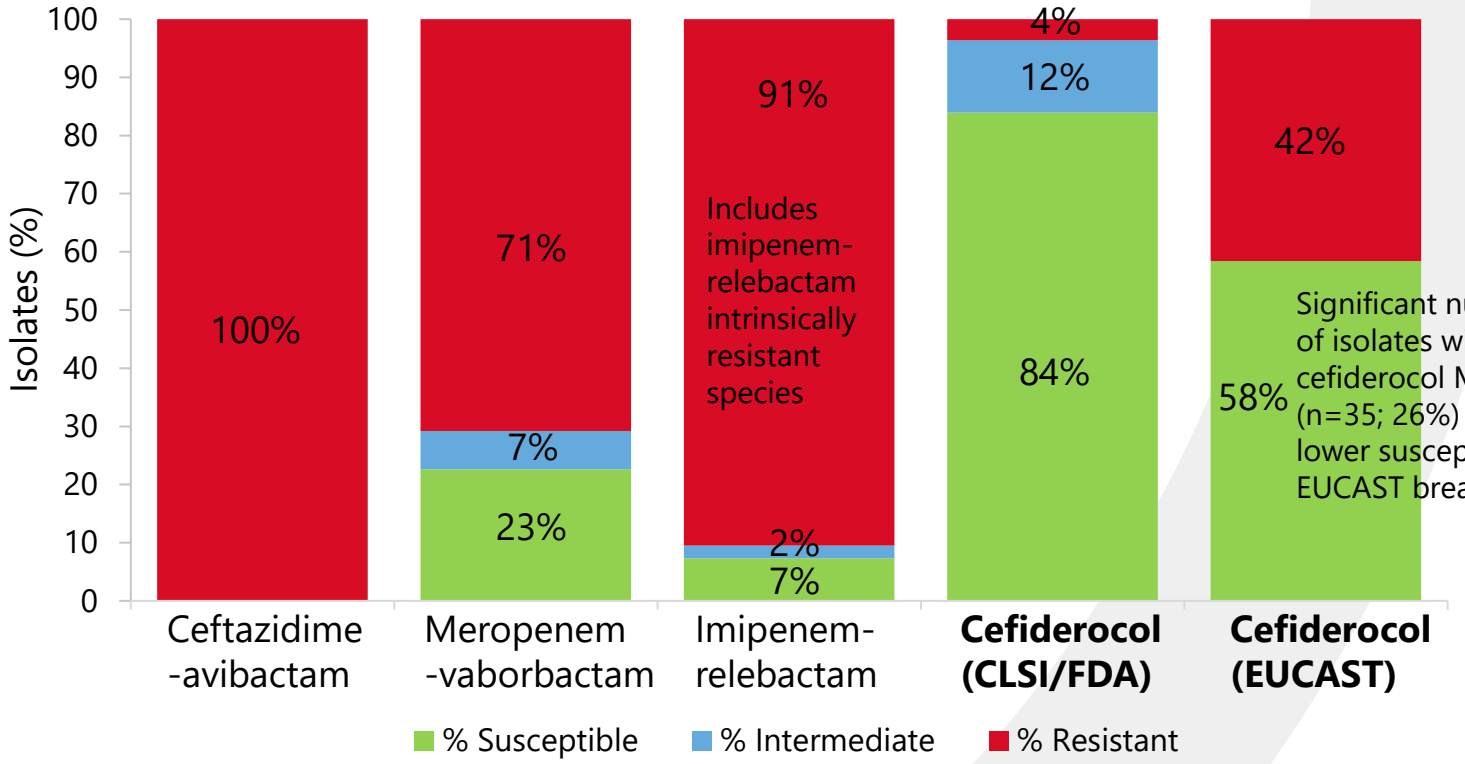


β-lactamase content



*Includes non-β-lactamase producers

Susceptibility/Resistance Profile



Significant number of isolates with cefiderocol MIC=4 mg/L (n=35; 26%) resulted in lower susceptibility using EUCAST breakpoints

- High degree of cross resistance with β-lactam–β-lactamase inhibitor combinations
- Cefiderocol remained active against isolates that were non-susceptible to ceftazidime-avibactam

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MBL, metallo-β-lactamase; OXA, oxacillinase.

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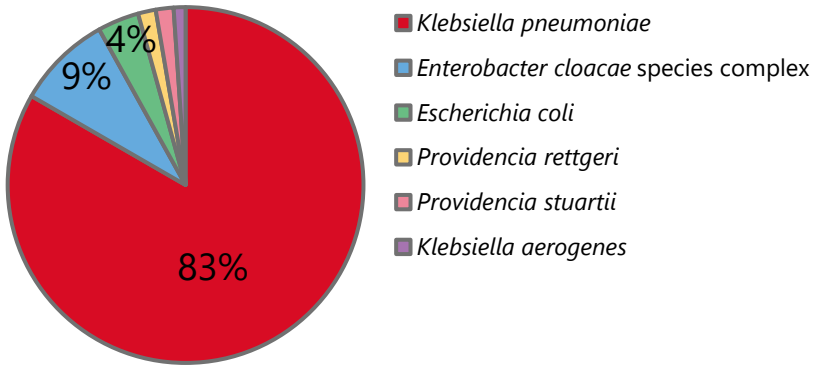
Meropenem-Vaborbactam Non-Susceptible Enterobacterales (n=186)

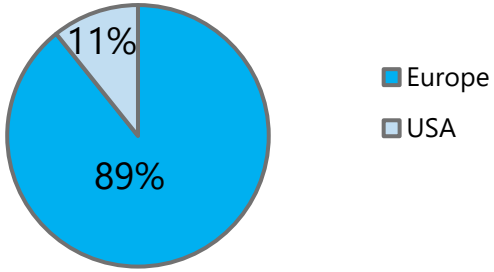
Characteristics of Isolates

0.77% of total

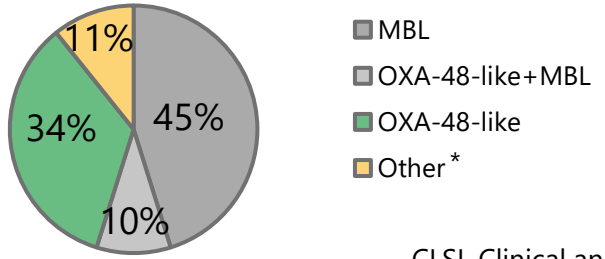
Species distribution



Origin of isolates



β-lactamase content



*Includes non-β-lactamase producers

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MBL, metallo-β-lactamase; OXA, oxacillinase.

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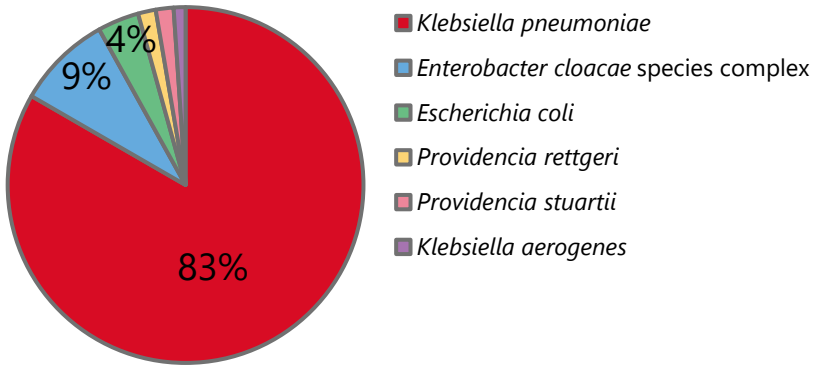
Meropenem-Vaborbactam Non-Susceptible Enterobacterales (n=186)

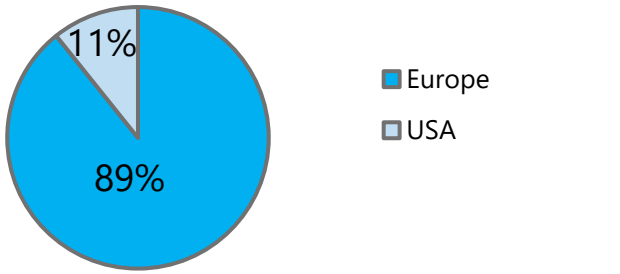
Characteristics of Isolates

0.77% of total

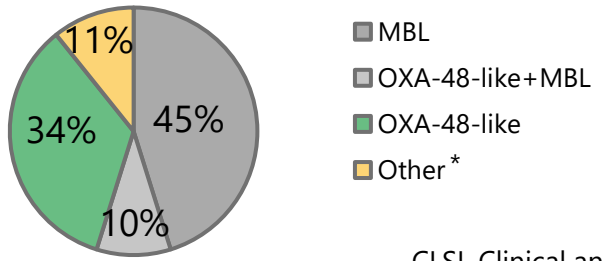
Species distribution



Origin of isolates

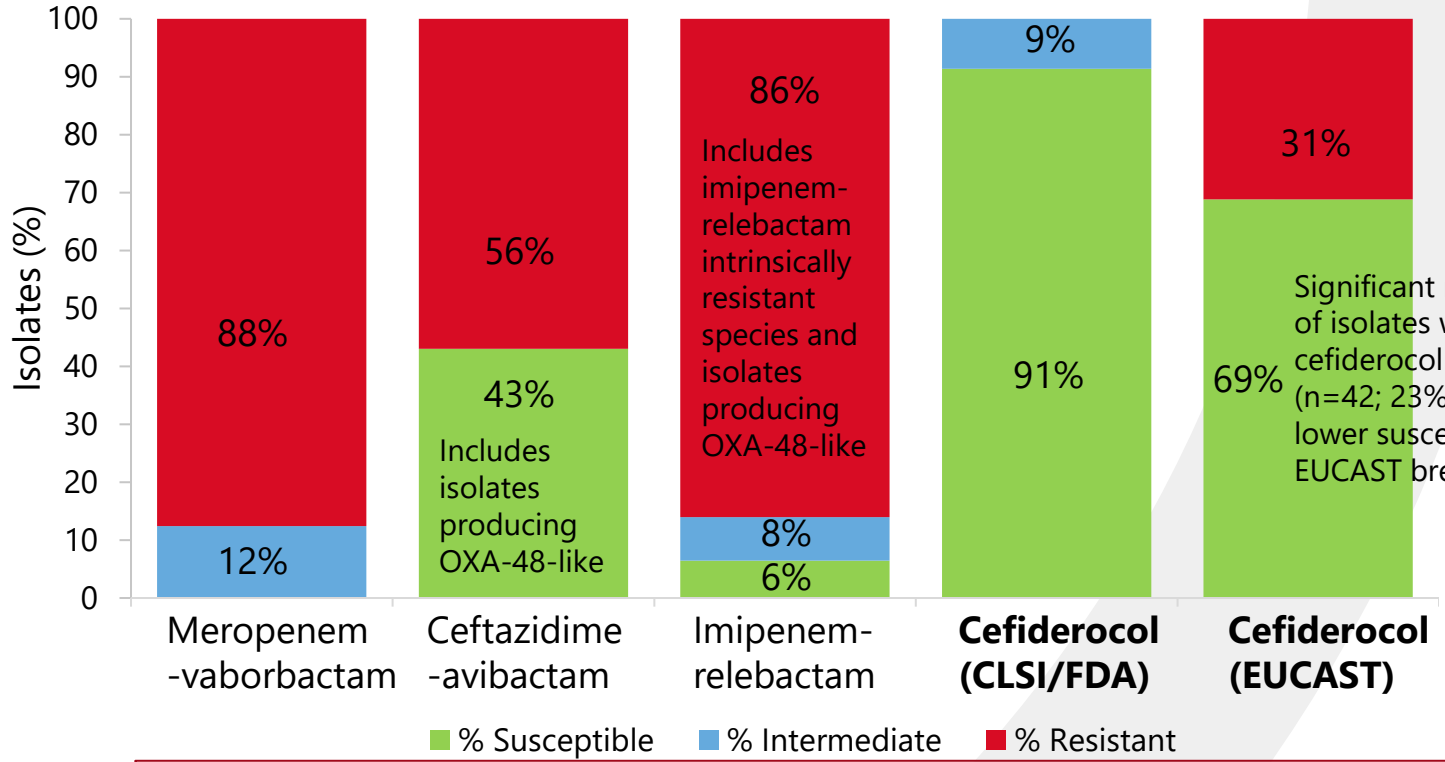


β-lactamase content



*Includes non-β-lactamase producers

Susceptibility/Resistance Profile



- High degree of cross resistance with β-lactam–β-lactamase inhibitor combinations
- Cefiderocol remained active against isolates that were non-susceptible to meropenem-vaborbactam

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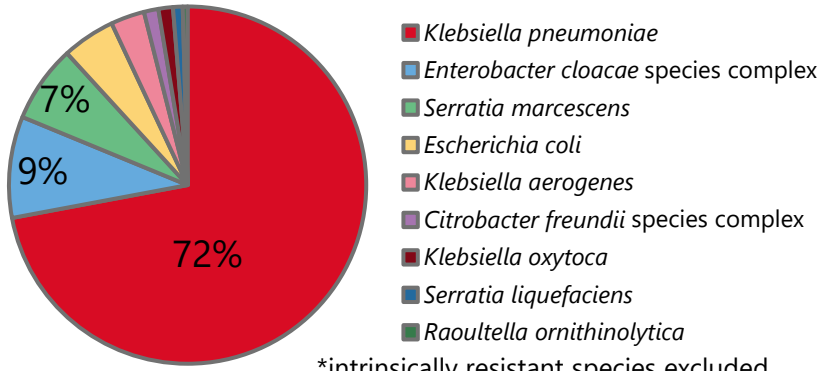
Imipenem-Relebactam Non-Susceptible Enterobacterales (n=229)

Characteristics of Isolates

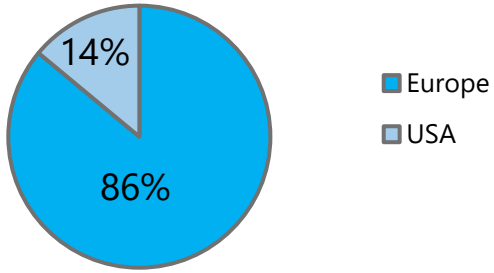
1.05% of total*

Species distribution

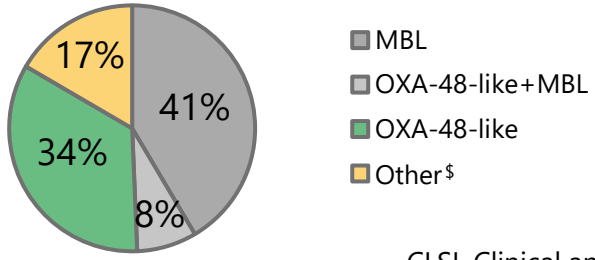


*intrinsically resistant species excluded

Origin of isolates



β-lactamase content



$Includes non-β-lactamase producers

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MBL, metallo-β-lactamase; OXA, oxacillinase.

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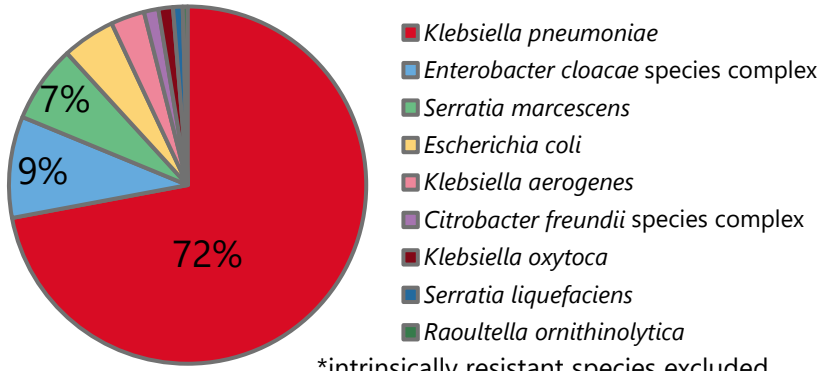
Imipenem-Relebactam Non-Susceptible Enterobacterales (n=229)

Characteristics of Isolates

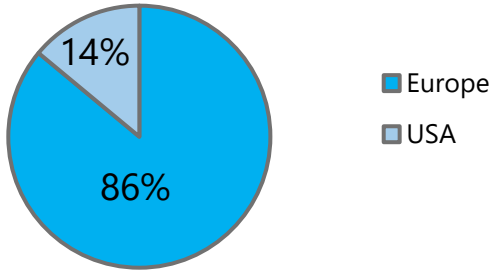
1.05% of total*

Species distribution

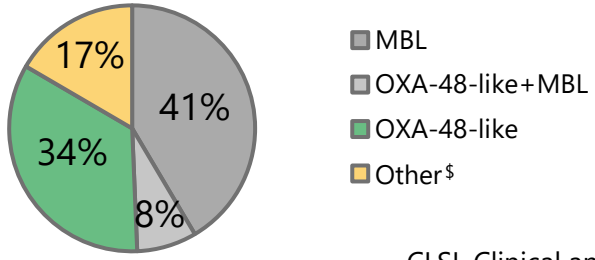


*intrinsically resistant species excluded

Origin of isolates

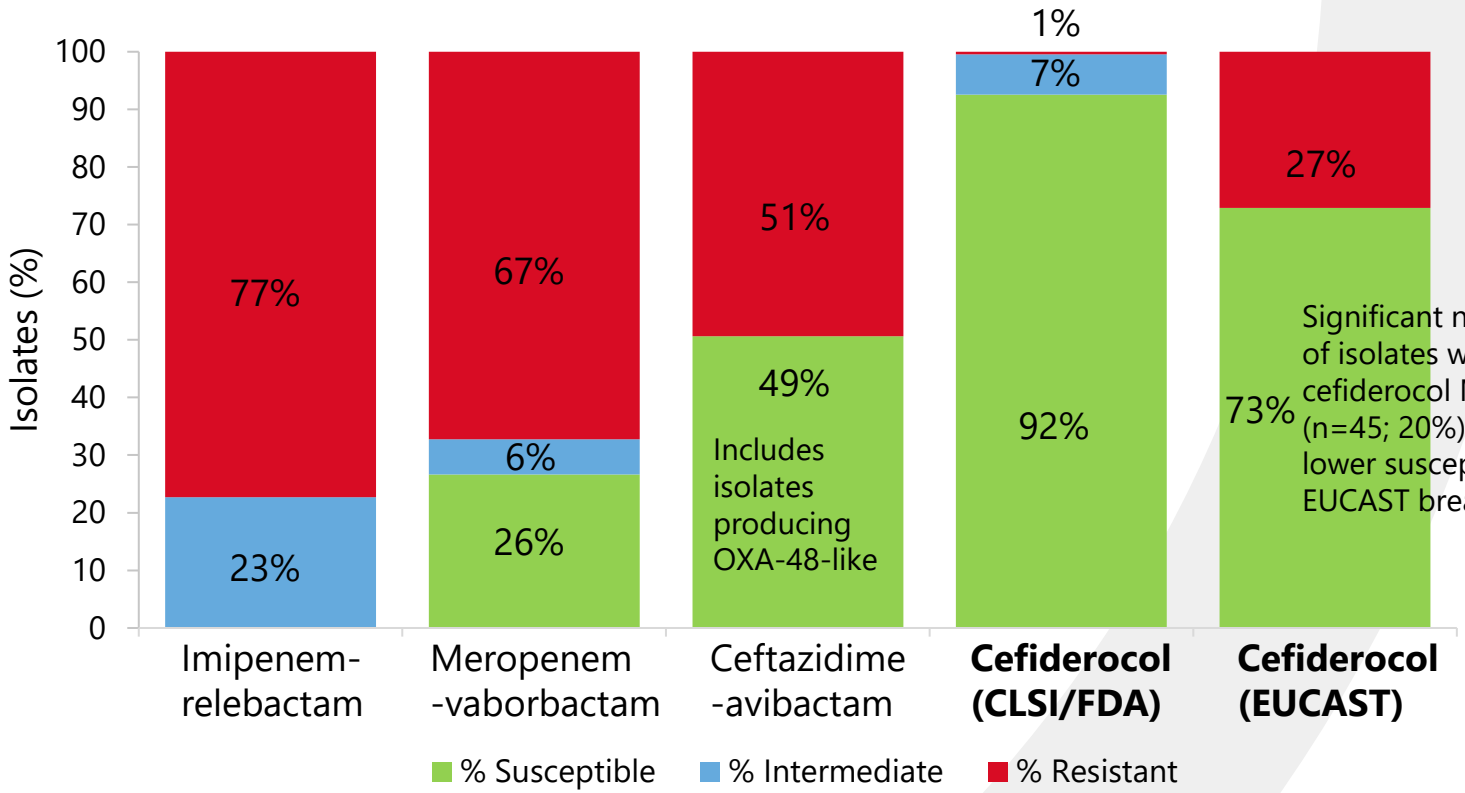


β-lactamase content



$Includes non-β-lactamase producers

Susceptibility/Resistance Profile



- High degree of cross resistance with β-lactam–β-lactamase inhibitor combinations
- Cefiderocol remained active against isolates that were non-susceptible to imipenem-relebactam

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Characteristics of Cefiderocol-Non-Susceptible Isolates

- No common theme for cross resistance between cefiderocol and β-lactam–β-lactamase inhibitor combinations could be identified, except for one isolate (out of 137) that was non-susceptible to ceftazidime-avibactam and contained KPC-31, a KPC variant known to result in ceftazidime-avibactam and cefiderocol resistance
- Most cefiderocol-non-susceptible isolates had mutations in genes previously identified as playing a role in reduced cefiderocol susceptibility: i.e., iron transporters (*cir*, *fiu*), two-component regulation systems (*bae*, *env*Z), PBP3 (*fts*I), and/or efflux systems (*acr*A), **in addition** to the presence of β-lactamases, mainly MBLs

Number and isolate characteristics of cefiderocol-non-susceptible isolates

	Cefiderocol MIC (mg/L)		
	8	16	≥32
Ceftazidime-avibactam-NS	**13 MBL+**; **2 non-MBL+**; 2 MBL–	**1 non-MBL+**; 1 non-MBL–	**1 non-MBL+**; 2 non-MBL– (1 KPC-31)
Meropenem-vaborbactam-NS	**13 MBL+**; 2 MBL–; 1 non-MBL-		
Imipenem-relebactam-NS	**13 MBL+**; 2 MBL-; 1 non-MBL–		**1 non-MBL+**

+: isolates with additional gene mutations implicated in reduced cefiderocol susceptibility.
–: isolates with no additional gene mutations implicated in reduced cefiderocol susceptibility.

KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase;
MIC, minimum inhibitory concentration; NS, non-susceptible; PBP, penicillin-binding protein.

Conclusions

- Surveillance showed low resistance against β-lactam–β-lactamase inhibitor combinations (≤1%)
  - Resistance in Europe was higher (1–1.6%) compared with the USA (0.2–0.3%).
- The most commonly encountered mechanisms of resistance were metallo-β-lactamases (all combinations) and OXA-48-like β-lactamases (meropenem-vaborbactam and imipenem-relebactam)
- Cefiderocol has activity against isolates expressing these β-lactamases and as a result it remained active against Enterobacterales that were non-susceptible to β-lactam–β-lactamase inhibitor combinations; in contrast, cross resistance was observed for the β-lactam–β-lactamase inhibitor combinations
  - Cefiderocol non-susceptibility was observed when additional mutations in genes of iron acquisition proteins, efflux pumps, and/or PBP-3 were detected
- Cefiderocol should be considered as a treatment option when Enterobacterales that are non-susceptible to one of the β-lactam–β-lactamase inhibitor combinations are encountered

OXA, oxacillinase; PBP, penicillin-binding protein.

THANK YOU FOR YOUR ATTENTION

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