Cefiderocol Activity for Carbapenem Non-Susceptible Bacteria From Intensive Care Unit Pneumonia Patients

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Conflicts of Interest

I have the following conflicts of interest:

Boudewijn L.M. DeJonge, Sean T. Nguyen, Jason J. Bryowsky, Miki Takemura, Yoshinori Yamano are employees of Shionogi.

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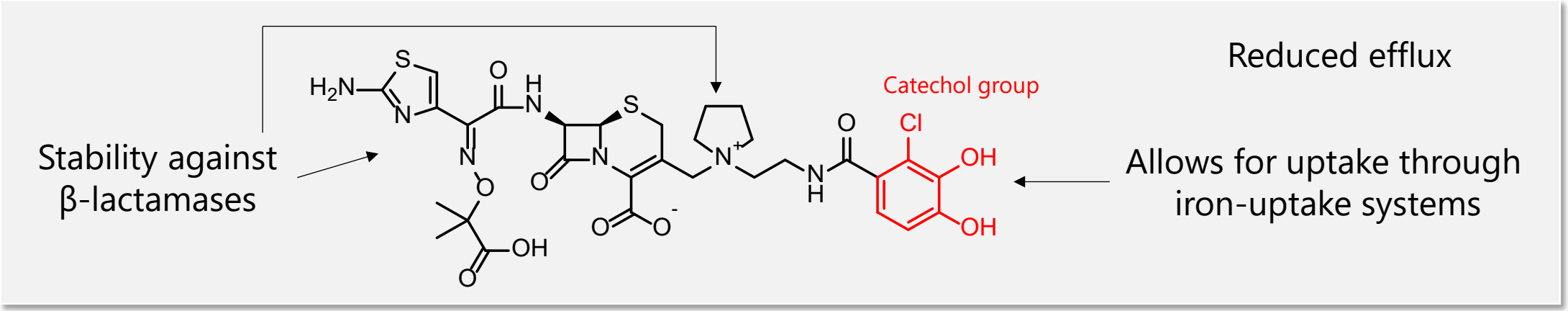
Introduction

- Treatment of pneumonia caused by Gram-negative bacteria in the intensive care unit (ICU) is complicated by increased antimicrobial resistance limiting the choice of antibiotics.[1]
- Cefiderocol is a catechol-siderophore cephalosporin;[2,3] its unique structure allows for good activity against aerobic Gram-negative species, including carbapenem-resistant isolates.[4]



- Cefiderocol is approved by the US Food and Drug Administration (FDA) for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia.[5]

1. Hetzler L, et al. Curr Opin Crit Care. 2022;28(5):522-533; 2. Aoki T, et al. Eur J Med Chem. 2018;155:847-868; 3. Sato T, et al. Clin Infect Dis. 2019;69(Suppl 7):S538-S543; 4. Shortridge D, et al. Microbiol Spectr. 2022;10(2):e0271221; 5. Fetroja (cefiderocol). Prescribing information. Shionogi Inc., 2021.

Objective

- To evaluate the susceptibility of cefiderocol and comparator agents against contemporary carbapenem non-susceptible Gram-negative isolates, collected from patients with pneumonia in intensive care units in the USA.

Methods

- A total of **2,977 Gram-negative bacterial isolates** were collected **between 2020 and 2022** from **patients with pneumonia in intensive care units** in **40 US medical centers** as part of the SENTRY surveillance program.
  - 1,565 Enterobacterales
  - 886 *Pseudomonas aeruginosa*
  - 233 *Acinetobacter baumannii-calcoaceticus* complex
  - 293 *Stenotrophomonas maltophilia*.
- Minimum inhibitory concentrations were determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines, and susceptibility was assessed using CLSI and FDA breakpoints.

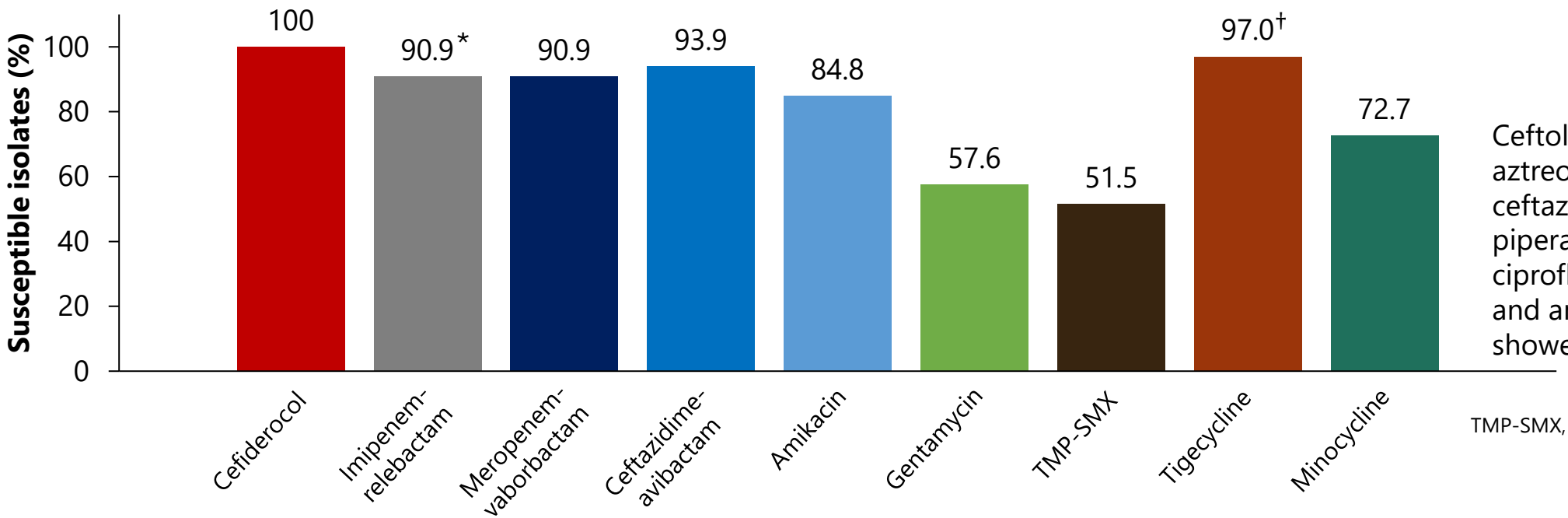
Cefiderocol Susceptibility Breakpoints*	**Enterobacterales**	P. aeruginosa	A. baumannii	S. maltophilia
CLSI	≤4	≤4	≤4	≤1
FDA	≤4	≤1	≤1	None

- Carbapenem non-susceptible isolates were defined as those non-susceptible to meropenem and imipenem.

*Susceptibility breakpoints for comparator agents are the same for CLSI and FDA, unless otherwise indicated.

Activity of Cefiderocol and Comparator Agents Against 33 Carbapenem Non-Susceptible Enterobacterales Isolates

- 2.1% of Enterobacterales (33/1565) isolates were carbapenem non-susceptible.



Ceftolozane-tazobactam, aztreonam, ceftriaxone, ceftazidime, cefepime, piperacillin-tazobactam, ciprofloxacin, levofloxacin, and ampicillin-sulbactam showed <50% susceptibility.

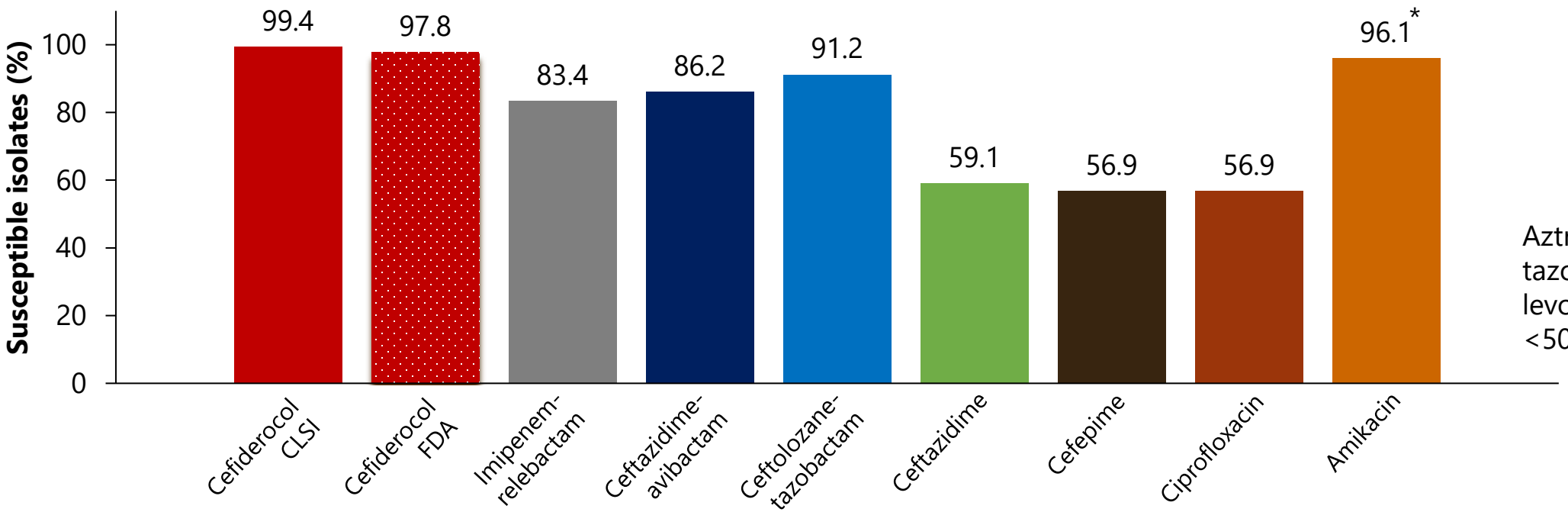
TMP-SMX, trimethoprim-sulfamethoxazole.

- Cefiderocol was the most active β-lactam, with 100% susceptibility.
- Newer β-lactam–β-lactamase inhibitor combinations showed susceptibility >90%.
- Tigecycline was the only non-β-lactam antibiotic with >90% susceptibility.

*All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species.
†Tigecycline does not have a CLSI breakpoint.

Activity of Cefiderocol and Comparator Agents Against 181 Carbapenem Non-Susceptible *Pseudomonas aeruginosa* Isolates

- 20.4% of *P. aeruginosa* (181/886) isolates were carbapenem non-susceptible.



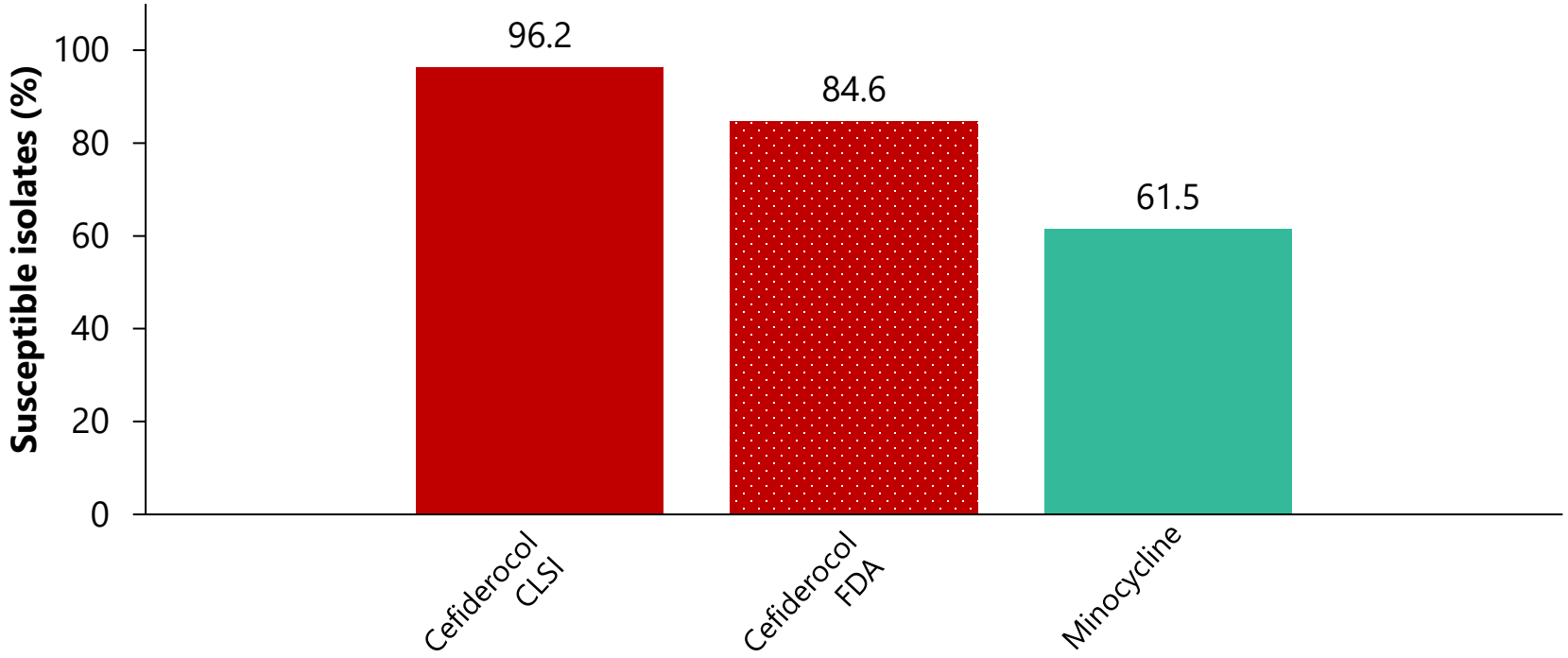
Aztreonam, piperacillin-tazobactam, and levofloxacin showed <50% susceptibility.

- Cefiderocol was the most active agent, with >97% of isolates testing as susceptible.
- Ceftolozane-tazobactam was the only other β-lactam showing >90% susceptibility.
- Amikacin was the only non-β-lactam antibiotic showing >90% susceptibility.

*Amikacin does not have a CLSI breakpoint.

Activity of Cefiderocol and Comparator Agents Against 52 Carbapenem Non-Susceptible *Acinetobacter baumannii-calcoaceticus* Complex Isolates

- 22.3% of *A. baumannii-calcoaceticus* (52/233) isolates were carbapenem non-susceptible.

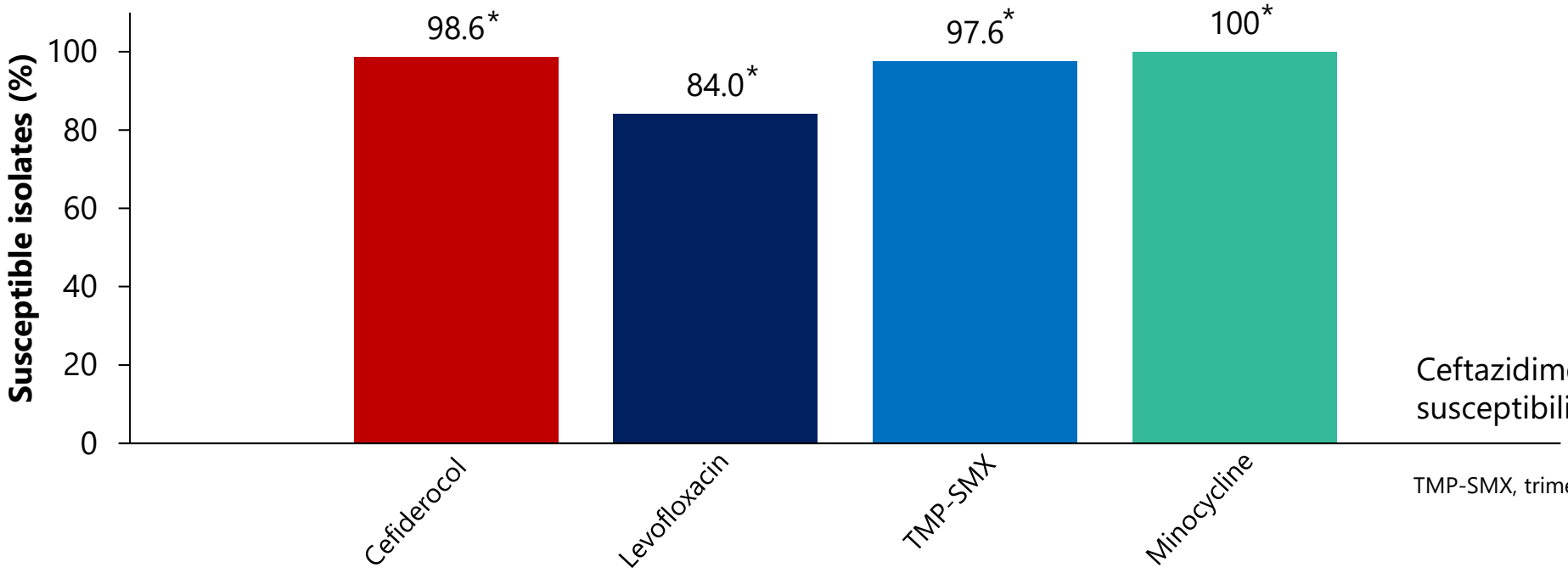


Imipenem-relebactam, ceftazidime, cefepime, piperacillin-tazobactam, ciprofloxacin, levofloxacin, amikacin, gentamicin, ampicillin-sulbactam, and trimethoprim-sulfamethoxazole all showed <50% susceptibility.

- Cefiderocol was the most active agent by both CLSI and FDA criteria.

Activity of Cefiderocol and Comparator Agents Against 293 *Stenotrophomonas maltophilia* Isolates

- *S. maltophilia* is intrinsically resistant to carbapenems.



Ceftazidime showed <50% susceptibility.

TMP-SMX, trimethoprim-sulfamethoxazole.

- Cefiderocol showed good activity, with >98% of isolates testing as susceptible by CLSI breakpoint.
- TMP-SMX and minocycline also showed >90% susceptibility.

*Only CLSI (2023) breakpoints apply.

Conclusions

- Carbapenem non-susceptibility is prevalent among Gram-negative bacteria isolated from patients with pneumonia in US intensive care units.
  - Prevalence of non-fermenters was over 20%.
- Treatment options against the carbapenem non-susceptible isolates are limited.
  - Only a few antibiotics show >90% susceptibility.
- Cefiderocol showed the highest susceptibility against these isolates.
  - Over 95% of isolates remain susceptible to cefiderocol (CLSI breakpoints).
- Cefiderocol could be considered as an empiric treatment option for the treatment of patients with pneumonia when carbapenem non-susceptible Gram-negative isolates are highly suspected or encountered in the intensive care unit.

Thank you for your time!

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