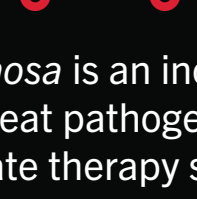


Cefiderocol Maintains Activity Against DTR *P. aeruginosa*, Including Isolates Non-susceptible to IDSA-Suggested β -Lactam/ β -Lactamase Inhibitor Combinations

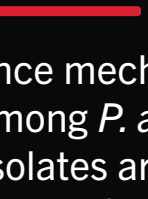
Summary of: Kimbrough JH, et al. *Microbiol Spectr.* 2025;13(11):e02079-25.

- KEY POINTS¹
- In a large collection of *P. aeruginosa* isolates from the SENTRY Antimicrobial Surveillance Program, IDSA-suggested β -lactam– β -lactamase inhibitor (BL-BLI) combinations showed limited activity against difficult-to-treat resistant (DTR) isolates (52.3%–56.0% susceptibility according to CLSI breakpoints), with considerable cross-resistance observed across agents
 - Cefiderocol maintained high activity against these DTR *P. aeruginosa* isolates (>95% susceptibility according to CLSI breakpoints) regardless of BL-BLI cross-resistance status
 - These findings support consideration of cefiderocol as a first treatment option for DTR *P. aeruginosa*

WHY WAS THIS STUDY DONE?



P. aeruginosa is an increasingly difficult-to-treat pathogen, with initial inappropriate therapy significantly increasing mortality risk^{2,3}



New resistance mechanisms are emerging among *P. aeruginosa*; increasingly isolates are resistant to first-line therapies (β -lactams and fluoroquinolones)—so-called DTR isolates⁴⁻⁶



IDSA guidance for treating DTR *P. aeruginosa* suggests any of three BL-BLI combinations—ceftolozane-tazobactam (TOL-TAZ), ceftazidime-avibactam (CAZ-AVI), and imipenem-relebactam (IMI-REL)—as the preferred options, with cefiderocol as an alternative option when these combinations are ineffective⁷



This study assessed the activity of cefiderocol and IDSA-suggested BL-BLI combinations against DTR *P. aeruginosa* collected as part of the SENTRY Antimicrobial Surveillance Program during 2020–2023¹

Background Information



What is DTR *P. aeruginosa*?
P. aeruginosa non-susceptible (NS) to all frontline β -lactams and fluoroquinolones⁷

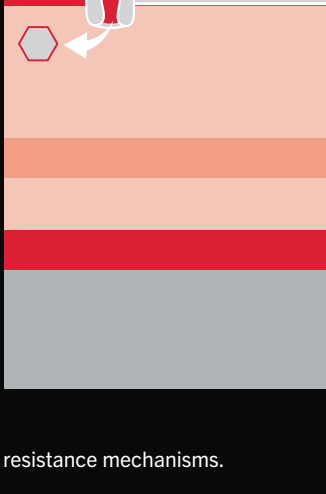


What is cross-resistance?
Shared vulnerability to bacterial resistance mechanisms among certain antimicrobials^{8,9}

Common β -lactam Resistance Mechanisms^{8,9}

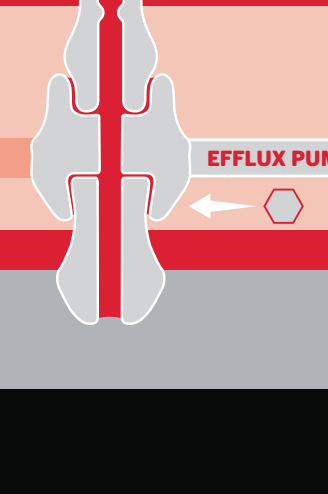
1

Porin Channel Changes*
Limit β -lactam access



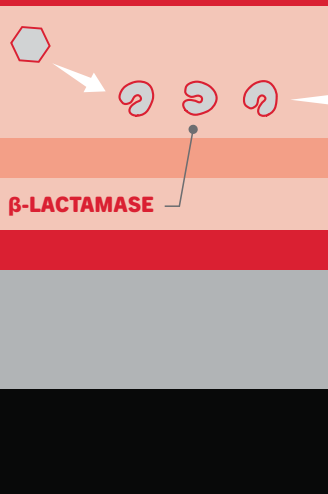
2

Efflux Pump Upregulation*
Increased expulsion of β -lactam



3

β -lactamase Expression (eg, MBLs, such as VIM)
Inactivate β -lactam



*Non-carbapenemase resistance mechanisms.

THE DATA SOURCE: THE SENTRY ANTIMICROBIAL SURVEILLANCE PROGRAM¹

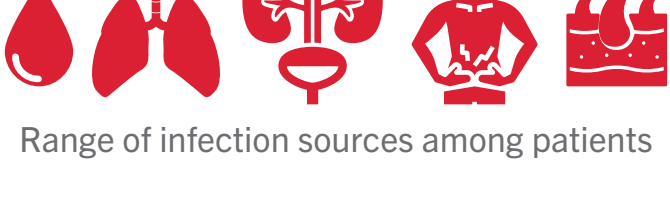
- The SENTRY Antimicrobial Surveillance Program is an ongoing, international surveillance program that monitors the activity of cefiderocol and comparators against Gram-negative isolates
- The analysis presented here reflects a recent data subset focused on more than 9500 *P. aeruginosa* isolates
- DTR isolates underwent DNA sequencing to identify the presence of β -lactamase genes

Dates: 2020–2023

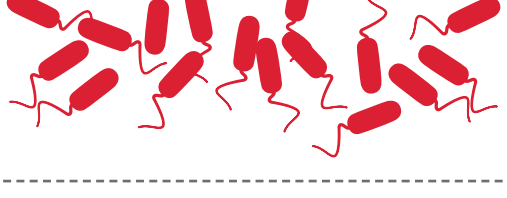


79

US and European sites



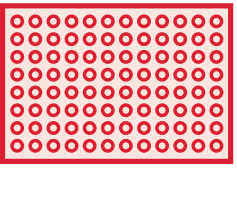
Range of infection sources among patients



9572

P. aeruginosa isolates

Susceptibility testing



Cefiderocol and comparators by broth microdilution; cefiderocol tested in iron-depleted, cation-adjusted Mueller Hinton Broth



Interpreted according to CLSI, FDA, and EUCAST 2025 breakpoints

WHAT THE DATA SHOWED¹

- Three IDSA-suggested BL-BLI combinations—TOL-TAZ, CAZ-AVI, and IMI-REL—demonstrated limited activity against DTR *P. aeruginosa* isolates, with substantial cross-resistance observed across agents
- Cefiderocol maintained high activity against DTR *P. aeruginosa* regardless of BL-BLI NS phenotype, suggesting that its activity is not compromised by the cross-resistance mechanisms affecting BL-BLI combinations

Susceptibility results by resistance subsets

	FDC (FDA BP)	FDC (CLSI BP)	CAZ-AVI	IMI-REL	TOL-TAZ	% Susceptible ^a
DTR ^b (n=377)	88.9	98.1	52.3	56.0	54.4	100%
BL-BLI NS ^c (n=238)	85.7	97.5	24.4	30.3	27.7	
CAZ-AVI NS (n=180)	83.9	97.2	0	29.4	25.0	75%
IMI-REL NS (n=166)	86.7	97.0	23.5	0	22.9	
TOL-TAZ NS (n=172)	82.0	96.5	21.5	25.6	0	50%
CAZ-AVI and IMI-REL NS (n=127)	84.3	96.1	0	0	13.4	
CAZ-AVI and TOL-TAZ NS (n=135)	79.3	96.3	0	18.5	0	20%
IMI-REL and TOL-TAZ NS (n=128)	84.4	96.1	14.1	0	0	
CAZ-AVI and IMI-REL and TOL-TAZ NS (n=110)	81.8	95.5	0	0	0	0%

Note: In vitro activity does not necessarily correlate with clinical efficacy.

- The majority of DTR *P. aeruginosa* did not express a β -lactamase, yet many of those isolates were not susceptible to the BL-BLI combinations. In addition, almost none of the DTR *P. aeruginosa* isolates that expressed a carbapenemase (mainly MBL) were susceptible to the BL-BLI combinations
- Cefiderocol maintained activity against DTR *P. aeruginosa* whether or not isolates expressed a β -lactamase

Susceptibility results by genotype

	FDC (FDA BP)	FDC (CLSI BP)	CAZ-AVI	IMI-REL	TOL-TAZ	% Susceptible ^a
Non-carbapenemase ^d (n=303)	90.1	98.3	63.7	69.6	67.7	100%
Carbapenemase ^e (n=74)	83.8	97.3	5.4	0	0	75%
• MBL (n=69)	82.6	97.1	0	0	0	50%
• VIM (n=53)	88.7	100	0	0	0	20%

Note: In vitro activity does not necessarily correlate with clinical efficacy.

- Author conclusions: The SENTRY findings support cefiderocol as a first treatment option for infections caused by DTR *P. aeruginosa* based on its high activity and lack of cross-resistance observed with other available treatment options¹

^aCLSI (2025), EUCAST (2025), and the FDA breakpoints for cefiderocol applied (≤ 4 , ≤ 2 , and ≤ 1 , respectively). CLSI (2025) breakpoints applied for comparator agents. ^bIsolates exhibiting NS CLSI results (CLSI) to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin. ^cIsolates NS to ≥ 1 of the following BL-BLI combination agent: ceftazidime-avibactam, imipenem-relebactam, and/or ceftolozane-tazobactam. ^dIncludes isolates where acquired carbapenemases were not detected. ^eIncludes isolates with *bla*_{GES-4} (1), *bla*_{GES-5} (1), *bla*_{GES-6} (3), *bla*_{IMP-1} (2), *bla*_{IMP-7} (5), *bla*_{IMP-8} (1), *bla*_{IMP-13} (1), *bla*_{NDM-1} (7), *bla*_{VIM-1} (6), *bla*_{VIM-1} + *bla*_{HMB-1} (1), *bla*_{VIM-2} (41), *bla*_{VIM-2} + *bla*_{GES-5} (1), *bla*_{VIM-4} (3), and *bla*_{VIM-5} (1). ^fIncludes isolates NS (CLSI) to the 3 suggested BL-BLI combinations and carrying acquired carbapenemases, as follows: *bla*_{GES-4} (1), *bla*_{IMP-1} (2), *bla*_{IMP-7} (5), *bla*_{IMP-8} (1), *bla*_{IMP-13} (1), *bla*_{NDM-1} (7), *bla*_{VIM-1} (6), *bla*_{VIM-1} + *bla*_{HMB-1} (1), *bla*_{VIM-2} (41), *bla*_{VIM-2} + *bla*_{GES-5} (1), *bla*_{VIM-4} (3), and *bla*_{VIM-5} (1).

BL-BLI= β -lactam– β -lactamase inhibitor; BP=breakpoint; CAZ-AVI=ceftazidime-avibactam; CLSI=Clinical and Laboratory Standards Institute; DTR=difficult-to-treat resistance; EUCAST=European Committee on Antimicrobial Susceptibility Testing; FDA=US Food and Drug Administration; FDC=cefiderocol; IDSA= Infectious Diseases Society of America; IMI-REL=imipenem-relebactam; MBL=metallo- β -lactamase; MIC=minimum inhibitory concentration; NS=non-susceptible; TOL-TAZ=ceftolozane-tazobactam; VIM=Verona integron-mediated metallo- β -lactamase.

References
1. Kimbrough JH, et al. *Microbiol Spectr.* 2025;13(11):e02079-25. 2. Itani R, et al. *PLoS One.* 2025;20(5):e0321935. 3. Kollef MH, et al. *Crit Care.* 2021;25(1):360. 4. Pang Z, et al. *Biotechnol Adv.* 2019;37(1):177-192. 5. Glen KA, et al. *Pathogens.* 2021;10(12):1638. 6. Reyes J, et al. *Lancet Microbe.* 2023;4(3):e159-e170. 7. Tamma PD, et al. *Clin Infect Dis.* 2024;ciae403. 8. Fernández L, Hancock REW. *Clin Microbiol Rev.* 2012;25(4):661-681. 9. Bush K. *Antimicrob Agents Chemother.* 2018;62:e01076-18.

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