Antimicrobial Resistant Infections III
Pseudomonas aeruginosa, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*

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Objectives

- Review the antibiotic treatment for infections caused by:
  - *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*)
  - Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
  - *Stenotrophomonas maltophilia*

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Disclosures

- I have no disclosures.

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Clinical Infectious Diseases
IDSA GUIDELINES

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Pranita D. Tamma,[1,a] Emily L. Heil,[2] Julie Ann Justo,[3] Amy J. Mathers,[4] Michael J. Satlin,[5] and Robert A. Bonomo[6]

Provides guidance on the treatment of:

- Extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E)
- AmpC beta-lactamase producing Enterobacterales (AmpC-E)
- Carbapenem-resistant Enterobacterales
- *Pseudomonas aeruginosa* with difficult-to-treat resistance
- Carbapenem-resistant *Acinetobacter baumannii* complex
- *Stenotrophomonas maltophilia* infections

www.idsociety.org/practice-guideline/amr-guidance/

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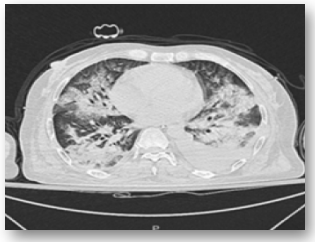
Clinical Case

- 12-year-old male with acute myelogenous leukemia
  - Absolute neutrophil count = 0 cells/mL
- Developed acute onset fevers and respiratory distress
  - Multifocal pneumonia
- *P. aeruginosa* recovered from bronchoalveolar lavage fluid



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Antibiotic	MIC	Interpretation
Amikacin	> 8 µg/mL	R
Aztreonam	> 16 µg/mL	R
Cefepime	> 16 µg/mL	R
Ceftazidime	> 16 µg/mL	R
Ciprofloxacin	> 2 µg/mL	R
Colistin	2 µg/mL	I
Gentamicin	> 8 µg/mL	R
Imipenem	8 µg/mL	R
Meropenem	8 µg/mL	R
Piperacillin/tazobactam	> 64/4 µg/mL	R
Tobramycin	> 8 µg/mL	R

Clinical and Laboratory Standards Institute (CLSI) has **no susceptible category** for polymyxins against *P. aeruginosa* (≤2 µg/mL = intermediate)

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Colistin is No Longer a Preferred Therapy

- Penetration into pulmonary epithelial lining fluid is suboptimal, even with dose optimization
- Colistin administered as inactive prodrug colistin methanesulfonate, which is slowly and incompletely converted to colistin **(<10%)**
  - Difficult to achieve adequate colistin plasma concentrations in patients with normal renal function
- Many reports of heteroresistance during polymyxin monotherapy
  - May be related to suboptimal polymyxin concentrations at site of infection
- Many new antibiotic trials use colistin as a comparator; almost all with inferior outcomes in the colistin arm
- Almost half of patients receiving colistin develop acute kidney injury

Landersdorfer CB, et al. J Antimicrob Chemother. 2018;73462-468. Cheah S, et al. J Antimicrob Chemother. 2015;70:3291-7. Sandi AM, et al. Clin Infect Dis. 2013;57:524-31. Li J, et al. Antimicrob Agents Chemother. 2006;9:2946–50. Rojas LJ, et al. Clin Infect Dis. 2016;64:711–718. Howard-Anderson J, J Antimicrob Chemother. 2022; 77:793-798.

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General Mechanisms	Examples	Antibiotics Typically Impacted
Reduced membrane permeability	Reduced production of OprD porin	Carbapenems (imipenem>meropenem)

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Active antibiotic extrusion	Increased expression of MexAB-OprM efflux pump	Piperacillin, cefepime, meropenem, fluoroquinolones, tazobactam, avibactam, relebactam

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Target site modification	Modification of PBP3 target	Ceftazidime, cefepime, aztreonam, cefiderocol, ceftolozane
	DNA gyrase (*gyrA*) and topoisomerase IV (*parC*)	Fluoroquinolones
	Modifications in the outer membrane (e.g., PhoPQ, PmrAB)	Polymyxins

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	DNA gyrase (*gyrA*) and topoisomerase IV (*parC*)	Fluoroquinolones
	Modifications in the outer membrane (e.g., PhoPQ, PmrAB)	Polymyxins
Enzymatic modification	*Pseudomonas*-derived cephalosporinases (i.e., PDC)	Piperacillin, ceftazidime, aztreonam
	Carbapenemases (e.g., KPC, NDM, VIM)	Penicillins, cephalosporins, carbapenems, sometimes aztreonam
	Aminoglycoside-modifying enzymes (e.g., AAC, ANT, APH)	Aminoglycosides

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Ciprofloxacin	>2 µg/mL	R
Colistin	2 µg/mL	I
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Imipenem	8 µg/mL	R
Meropenem	8 µg/mL	R
Piperacillin-tazobactam	>64/4 µg/mL	R
Tobramycin	>8 µg/mL	R

Difficult-to-treat resistance (**DTR**) defined as resistance to all traditional β-lactam and fluoroquinolone antibiotics

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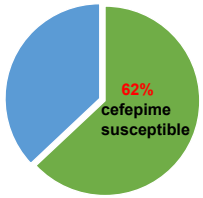
P. aeruginosa with Difficult-to-Treat Resistance: Definition

- *P. aeruginosa* exhibiting in vitro resistance to all the following:
  - Piperacillin-tazobactam
  - Ceftazidime
  - Cefepime
  - Aztreonam
  - Meropenem
  - Imipenem-cilastatin
  - Ciprofloxacin
  - Levofloxacin

Carbapenem-resistant *P. aeruginosa* isolates from 12 countries (n=542)



Kadri SS, et al. Clin Infect Dis 2018; 67: 1803-14. Gill CM, et al. Antimicrob Ag Chemother 2021;65:e0120421. Khalili Y, et al. Acta Microbiol Immunol Hung. 2019;66:529-540. Campana EH, et al. Braz J Infect Dis. 2017;21:57-62. Zeng ZR, et al. Diagn Microbiol Infect Dis. 2014;78:268-270.

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β-Lactam Landscape for DTR Infections

Agents	Carbapenem-Resistant Enterobacterales			*Pseudomonas aeruginosa* with difficult-to-treat resistance	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
	KPCs	MBLs (NDM, VIM, IMP)	OXA-48-like			
Ceftolozane-tazobactam	R	R	R	S	R	R
Ceftazidime-avibactam	S	R	S	S	R	R
Meropenem-vaborbactam	S	R	R	R	R	R
Cefiderocol	S	S	S	S	S	S
Imipenem-cilastatin-relebactam	S	R	R	S	R	R
Sulbactam-durlobactam	R	R	R	R	S	R
Aztreonam-Avibactam	S	S	S	R	R	S

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Contemporary Susceptibility Data for DTR *P. aeruginosa*

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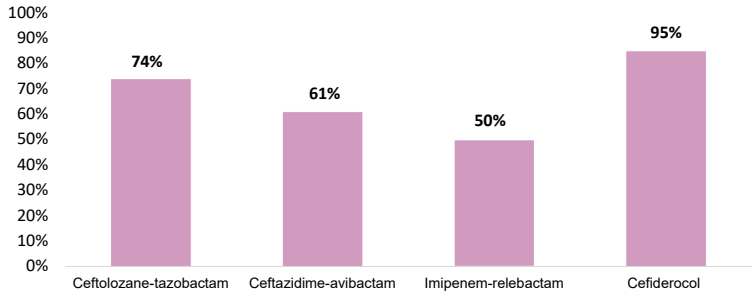
Contemporary Susceptibility Data for DTR *P. aeruginosa*



Data from Antibacterial Resistance Leadership Group

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Cefiderocol

- Innate immune system minimizes available free iron in response to bacterial infections
  - Most iron in humans bound to hemoglobin, myoglobin, or the iron binding proteins
- Bacteria upregulate the production of their siderophores
  - Iron-chelating compounds that scavenge the human body for free iron
- Cefiderocol is a siderophore conjugated to a cephalosporin
- "Trojan Horse" approach to enter bacteria through iron transport channels
- Once across outer membrane it dissociates from iron molecule and binds to primarily to PBP3, disrupting cell wall synthesis

McCreary EK, et al. Antimicrob Agents Chemother. 2021;65:e0217120.

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Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

Antibiotic	Empiric activity for index infection
Ceftolozane-tazobactam	
Ceftazidime-avibactam	
Cefiderocol	
Imipenem-cilastatin-relebactam	

Green = very favorable, Yellow = more likely to be favorable than not, Purple = proceed with caution

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Comparing Clinical Outcomes Across Agents

Agent	~Day 30 Survival	Study Type	Notes
Ceftolozane-tazobactam	~80%	Observational data (n=427)	Performed **better** than polymyxin
Ceftazidime-avibactam	~80%	Observational data (n=374)	Performed **better** than polymyxin
Imipenem-relebactam	90%	Subgroup of clinical trial (n=16)	Performed **better** than polymyxin
Cefiderocol	75%	Subgroup of clinical trials (n=38)	Performed **same** as polymyxin

Pogue JM, et al. Clin Infect Dis. 2020; 11;71:304-310. Hareza DA, et al. Antimicrob Ag Chemother. 2024;68:e0090724. Motsch J, et al. Clin Infect Dis. 2020;70:1799-1808. Bassetti M, et al. Lancet Infect Dis. 2021;21:226-240. Shields RK, et al. Lancet Infect Dis. 2025;25:574-584. Lodise TP, J Antimicrob Chemother. 2024;79:2954-2964. Bassetti M, et al. Lancet Infect Dis. 2021;21(2):226-240. Paterson DL, et al. Lancet Infect Dis. 2026;26(2):148-159.

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Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

Antibiotic	Empiric activity for index infection	Optimal clinical outcomes
Ceftolozane-tazobactam		
Ceftazidime-avibactam		
Cefiderocol		
Imipenem-cilastatin-relebactam		

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Emergence of Resistance

- 28 consecutive patients with DTR *P. aeruginosa* isolates susceptible to ceftolozane-tazobactam and treated with ≥72 hours of ceftolozane-tazobactam
  - *P. aeruginosa* isolates before and after ceftolozane-tazobactam exposure evaluated by broth microdilution testing and sequencing (confirmation of genetic relatedness)
- **50%** of isolates developed **ceftolozane-tazobactam** resistance
- **86%** of isolates initially susceptible to ceftazidime-avibactam developed resistance to **ceftazidime-avibactam**
- **25%** of isolates initially susceptible to cefiderocol developed ≥4-fold increases in **cefiderocol** MICs

Tamma PD, et al. Clin Infect Dis 2021;73:e4599-e4606. Simner PJ, et al. Open Forum Infect Dis. 2021;8:ofab311.

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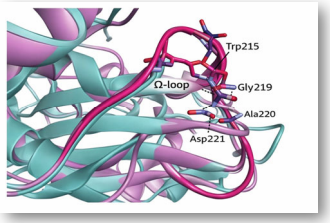
Acquired Resistance to Cephalosporin-Based Agents

- Resistant mutants commonly emerge because of amino acid changes in the catalytic center of *Pseudomonas*-derived cephalosporinases [**PDCs**]
- Enabling better accommodation of β-lactams with bulky R2 side chains
  - Ceftolozane, ceftazidime, cefepime, cefiderocol



Barnes M, et al. mBio. 2018 Dec 11;9(6):e02085-18.

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Acquired Resistance to Imipenem-Relebactam

- Typically result of a combination of the following:
  - **Loss of porins** (OprD reducing imipenem entry)
  - **PBP2 mutations** (target of imipenem)
  - **Increased production of efflux pumps** (MexAB-OprM and/or MexEF-OprN may efflux a portion of relebactam)
- Emergence of resistance to imipenem-relebactam while on therapy **~24%**

Gomis-Font MA, et al. J Antimicrob Chemother. 2020;75:2508-2515. Shields RK, et al. Clin Infect Dis. 2022;75(4):710-714.

23

Acquired Resistance to Cefiderocol

- About **13%** of isolates had ≥4-fold increase in cefiderocol MICs in trials
- Mechanisms described:
  - Mutations in the iron transport system (e.g., *piu*, *pir*)
  - Increased expression of bla_{VIM} or other carbapenemases due to increased copy numbers
  - Upregulation of PDCs or amino acid substitutions in catalytic center of PDCs
  - Upregulation of MexAB-OprM and other RND efflux systems
  - PBP3 mutations
  - OXA-2/OXA-10 ESBL mutations

Oliver A, et al. Clin Microbiol Infect. 2025:S1198-743X(25)00131-4. Karakonstantis S, et al. Antibiotics (Basel). 2022;11(6):723.

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Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

Antibiotic	Empiric activity for index infection	Optimal clinical outcomes	Likelihood of sustained activity for subsequent infection
Ceftolozane-tazobactam			
Ceftazidime-avibactam			
Cefiderocol			
Imipenem-cilastatin-relebactam			

Using denominator of index isolates (and not subsequent *P. aeruginosa* isolates) to calculate emergence of resistance on therapy:

- **Ceftolozane-tazobactam: ~24%**
- **Ceftazidime-avibactam: ~24%**
- **Cefiderocol: ~10%**
- **Imipenem-relebactam: ~24%**

Green = very favorable, **Yellow** = more likely to be favorable than not, **Purple** = proceed with caution

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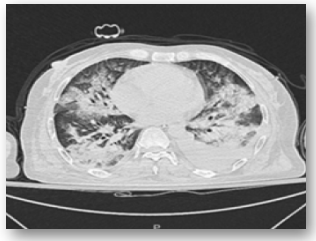
Clinical Case: *P. aeruginosa*

- 12-year-old male with acute myelogenous leukemia
  - Absolute neutrophil count = 0 cells/mL
- Developed acute onset fevers and respiratory distress
  - Multifocal pneumonia
- DTR *P. aeruginosa* recovered from bronchoalveolar lavage fluid



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Antibiotic	MIC	Interpretation
Amikacin	>8 µg/mL	R
Aztreonam	>16 µg/mL	R
Cefepime	>16 µg/mL	R
Cefiderocol	0.25 µg/mL	S
Ceftazidime	>16 µg/mL	R
Ceftazidime-avibactam	256 µg/mL	R
Ceftolozane-tazobactam	256 µg/mL	R
Ciprofloxacin	>2 µg/mL	R
Colistin	2 µg/mL	I
Gentamicin	>8 µg/mL	R
Imipenem-relebactam	>8 µg/mL	R
Meropenem	8 µg/mL	R
Piperacillin-tazobactam	>64/4 µg/mL	R
Tobramycin	>8 µg/mL	R

- Isolate contained a ***bla*$_{\text{VIM-2}}$** gene, a type of metallo-beta-lactamase **(MBL)** carbapenemase gene
- MBL-producing *P. aeruginosa* are **always resistant** to ceftolozane-tazobactam, ceftazidime-avibactam, & imipenem-relebactam

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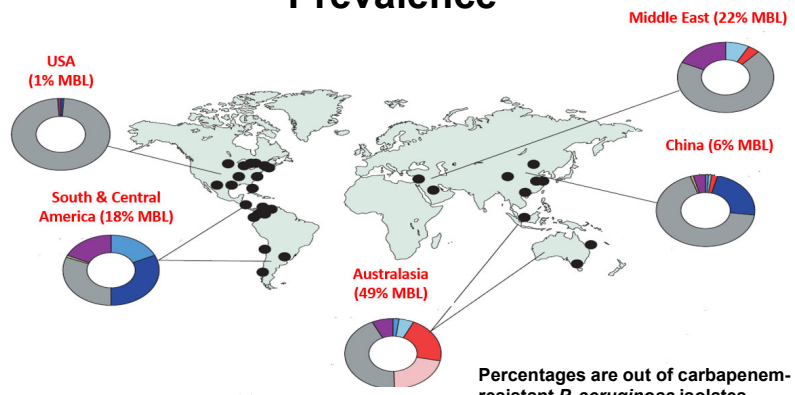
MBL-Producing *P. aeruginosa* Prevalence



Reyes G, et al Lancet Microbe. 2023;4(3):e159-e170.

Percentages are out of carbapenem-resistant *P. aeruginosa* isolates

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Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

Antibiotic	Empiric activity for index infection	Optimal clinical outcomes	Likelihood of sustained activity for subsequent infection	Known VIM-producing carbapenemase
Ceftolozane-tazobactam				
Ceftazidime-avibactam				
Cefiderocol				
Imipenem-cilastatin-relebactam				

Green = very favorable, Yellow = more likely to be favorable than not, Purple = proceed with caution/unlikely to be active

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Take Home Points

- Pros and cons to all β-lactams with activity against DTR *P. aeruginosa*
  - Select a susceptible agent (**ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam** > **cefiderocol**)
  - Retest subsequent DTR *P. aeruginosa* isolates
- VIM-producing *P. aeruginosa* isolates
  - Hint: Resistance to all available β-lactam-β-lactamase inhibitor combinations
  - **Cefiderocol** preferred

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Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) Infections

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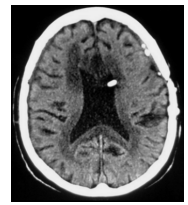
Clinical Case

- 42-year-old women with ventriculoperitoneal (VP) shunt dependency for congenital hydrocephalus
- VP shunt removal and external ventricular drain (EVD) placement scheduled after elective intra-abdominal surgery
- 6 days after EVD placement presents with fevers, headache, and generally ill appearance
- Culture of the cerebrospinal fluid growing CRAB



Tamma PD, et al. Clin Infect Dis. 2024; doi: 10.1093/cid/ciae210.

32

Antibiotic	MIC	Interpretation
Amikacin	>32 µg/mL	R
Ampicillin-sulbactam	>16/8 µg/mL	R
Ceftazidime	>16 µg/mL	R
Ciprofloxacin	>2 µg/mL	R
Colistin	≤1 µg/mL	I
Cefepime	>16 µg/mL	R
Gentamicin	>8 µg/mL	R
Meropenem	>8 µg/mL	R
Tobramycin	>8 µg/mL	R
Trimethoprim/sulfamethoxazole	>2/38 µg/mL	R

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Benefits of Sulbactam

- Ability to function as a β-lactam and can saturate **PBP1a/1b** and **PBP3** of *A. baumannii* isolates
- Unique activity against *A. baumannii* isolates demonstrated through in vitro studies, animal models, and clinical outcomes data

Lenhard JR, et al. Antimicrob Agents Chemother. 2017;61:e01268-01216. Beganovic M, et al. Antimicrob Agents Chemother.2021;65:e01680-01620. Abdul-Mutakabbir JC, et al. Antibiotics (Basel). 2021;10. Rodriguez-Hernandez MJ, et al. J Antimicrob Chemoth er. 2001;47:479-482. Makris D, et al. Indian J Crit Care Med. 2018;22:67-77. Betrosian AP, et al. Scand J Infect Dis. 2007;39:38-43. Assimakopoulos Sfet al. Infez Med. 2019;27:11-16. Liu J, et al. J Glob Antimicrob Resist. 2021;24:136-147. Jung SY, et al. Crit Care. 2017;21:319.

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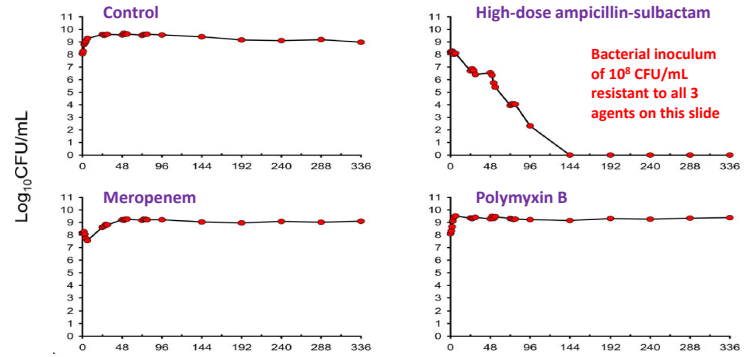
Hollow Fiber Infection Model



Lenhard JR, et al. Antimicrob Ag Chemother. 2017;61:e01268-16.

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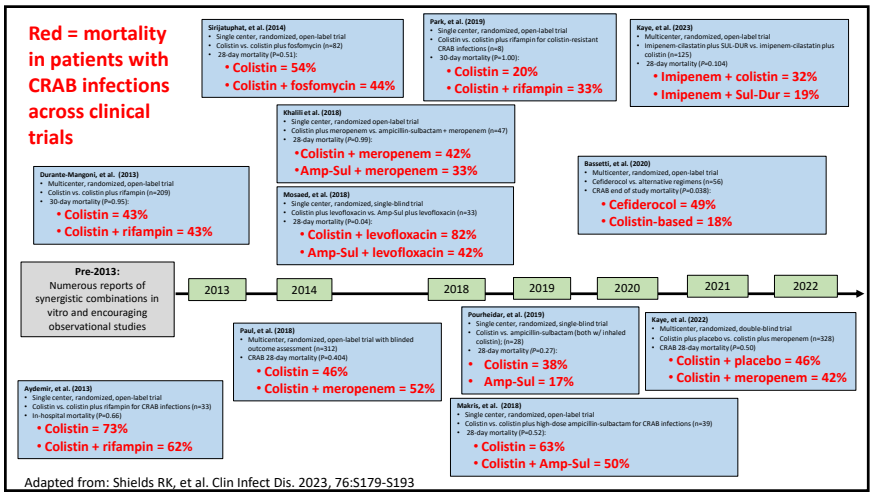

Adapted from: Shields RK, et al. Clin Infect Dis. 2023, 76:S179-S193

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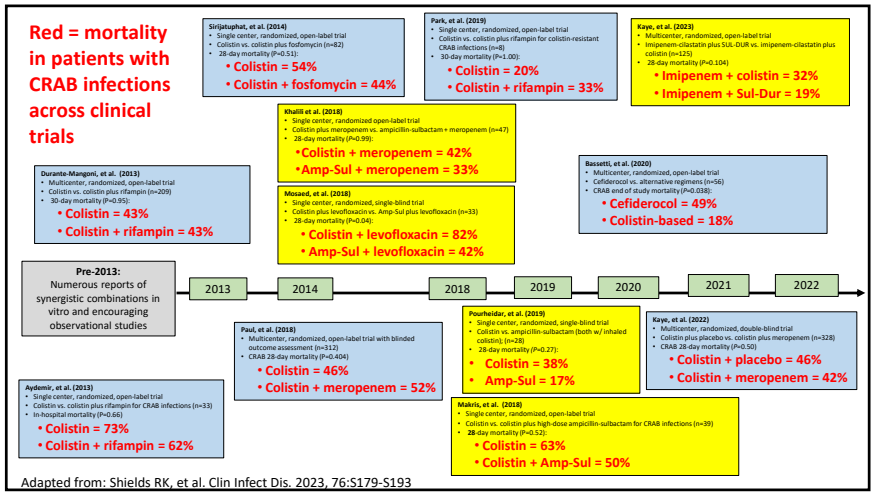

Adapted from: Shields RK, et al. Clin Infect Dis. 2023, 76:S179-S193

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Sulbactam-Durlobactam (Sul-Dur)

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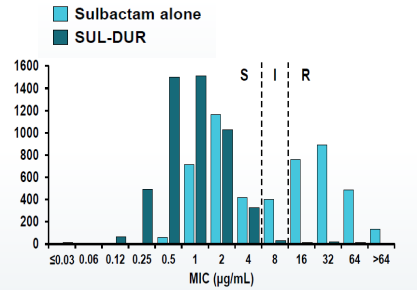
Sulbactam-Durlobactam (Sul-Dur)

- Durlobactam is β-lactamase inhibitor that inhibits class D β-lactamases (e.g., OXA-23)
- Does **NOT** inhibit class B β-lactamases (e.g., NDM)
- 98% of isolates with MIC of ≤4/4 µg/mL (i.e., susceptible) against 5,032 *A. baumannii* isolates



Karlowsky JA, et al. Antimicrob Ag Chemother. 2022;e007812.

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THE LANCET

Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

Keith S Kaye, Andrew F Shorr, Richard G Wunderink, Bin Du, Gabrielle E Poirier, Khurram Rana, Alita Miller, Drew Lewis, John O'Donnell, Lan Chen, Harald Reinhart, Subasree Srinivasan, Robin Isaacs, David Altarac

Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

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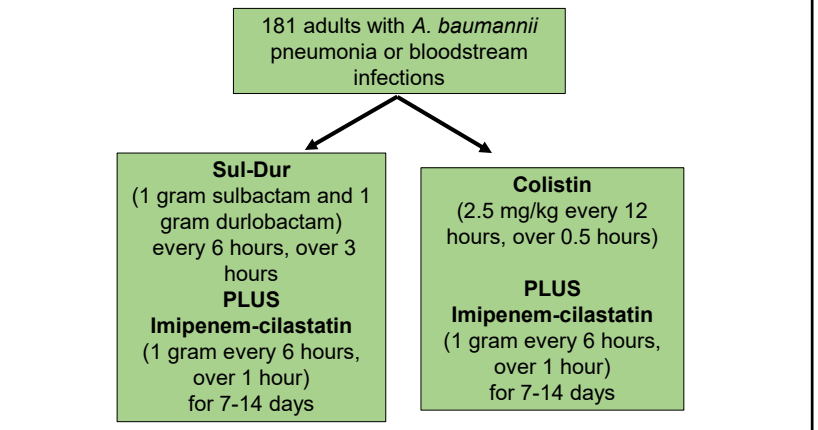

Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

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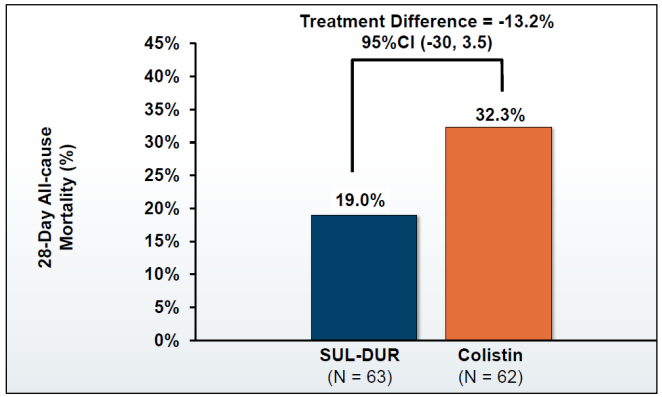

Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

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Do We Need the Carbapenem?

- Studies suggest the combination of sulbactam-durlobactam and imipenem-cilastatin lowers the sulbactam-durlobactam MIC by ~1-2-fold
  - For example, 4/4 µg/mL to 2/4 µg/mL or 1/4 µg/mL
  - Similar impact with meropenem
- Hypotheses
  - Targeting of multiple PBPs; sulbactam binds to PBP1 and PBP3; carbapenem binds to PBP2, both under protection of durlobactam

O'Donnell J, et al. Antimicrob Agents Chemother 2024;68:e0031223. Iovleva A, et al. mBio 2022;13:e0275921. Choi JY, et al. Clin Microbiol Infect 2004;10:1098-101.

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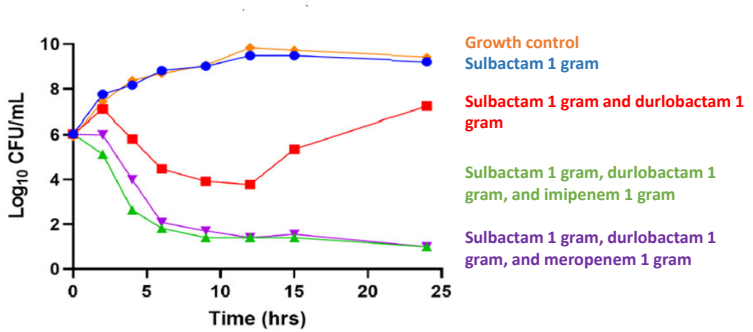

O'Donnell J, et al. Antimicrob Agents Chemother 2024;68:e0031223.

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THE LANCET

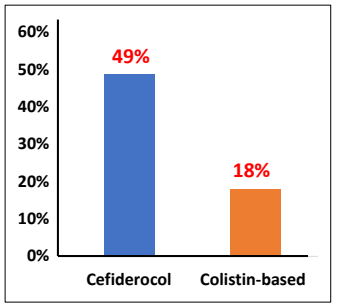
Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

Matteo Bassetti, Roger Echols, Yuko Matsunaga, Mari Ariyasu, Yohei Doi, Ricard Ferrer, Thomas P Lodise, Thierry Naas, Yoshihito Niki, David L Paterson, Simon Portsmouth, Julian Torre-Cisneros, Kiichiro Toyoizumi, Richard G Wunderink, Tsutae D Nagata

Bassetti M, et al. Lancet Infect Dis. 2021;21:226-240.

45

End of Study Mortality for 54 Patients with CRAB infections



Bassetti M, et al. Lancet Infect Dis. Lancet Infect Dis. 2021;21:226-240.

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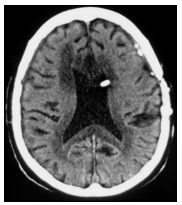
Clinical Case

- 42-year-old women with ventriculoperitoneal (VP) shunt dependency for congenital hydrocephalus
- VP shunt removal and external ventricular drain (EVD) placement scheduled after elective intra-abdominal surgery
- 6 days after EVD placement presents with fevers, headache, and generally ill appearance
- Culture of the cerebrospinal fluid growing CRAB



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- **Day 1-10:** EVD replaced; received cefiderocol and high-dose Amp-Sul (CSF cultures remained positive)
- **Day 11:** Sul-Dur and meropenem initiated and continued for 14 days; no further positive cultures after this regimen began; remains clinically well 6 months out

Antibiotic	MIC	Interpretation
Amikacin	>32 µg/mL	R
Ampicillin-sulbactam	>16/8 µg/mL	R
Cefiderocol	0.25 µg/mL	S
Ceftazidime	>16 µg/mL	R
Ciprofloxacin	>2 µg/mL	R
Colistin	≤1 µg/mL	I
Cefepime	>16 µg/mL	R
Gentamicin	>8 µg/mL	R
Meropenem	>8 µg/mL	R
Sulbactam-durlobactam	--	S
Tobramycin	>8 µg/mL	R
Trimethoprim-sulfamethoxazole	>2/38 µg/mL	R

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Take-Home Points: CRAB

- Identification of CRAB in a clinical specimen does not always mean antibiotic therapy is indicated
- Sulbactam-based regimens remain the cornerstone of treatment
  - Preferred choice: **Sul-Dur** (with imipenem or meropenem)
  - Alternative choice: **High-dose Amp-Sul** (with an additional agent)
- Potential "additional agents" include **polymyxin B** or **minocycline** or **cefiderocol**

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Stenotrophomonas maltophilia Infections

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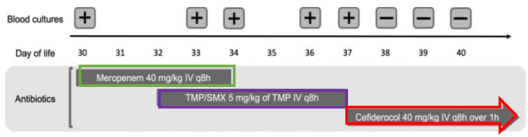
Clinical Case: *S. maltophilia*

- 30-day-old with transposition of great arteries
- Arterial switch operation on day 5, ECMO post-operatively, awaiting cardiac transplant
- Persistent *S. maltophilia* bacteremia
- Trimethoprim-sulfamethoxazole (TMP-SMX) susceptibility confirmed with broth microdilution (i.e., all isolates with MIC ≤2/38 µg/mL)



Hsu AJ, et al. Open Forum Infect Dis. 2023; 10: ofad174.

51

Brief Overview of *S. maltophilia*

- Present extensively in the environment (e.g., water sources, plant, soil)
- Opportunistic pathogen that colonizes or infects vulnerable hosts usually with underlying dysbiosis (e.g., cystic fibrosis, intensive care unit patients)
- Can cause hemorrhagic pneumonia in patients with hematologic malignancies
  - Attributable mortality over **80%**
  - Each additional day of meropenem increases the risk of *S. maltophilia* infection by **17%** in this population

Mojica MF, et al. JAC Antimicrob Resist. 2022;4:dlac040. Brooke JS. Clin Microbiol Rev. 2012;25:2-41. Paez JI, et al. J Hosp Infect 2008;70:101-8. Karaba SM, et al. Antimicrob Agents Chemother 2021; 65:e0079321. Kim SH, et al. Eur J Clin Microbiol Infect Dis 2019; 38:285–95. Aitken SL, et al. Clin Infect Dis. 2021;72:1507-1513.

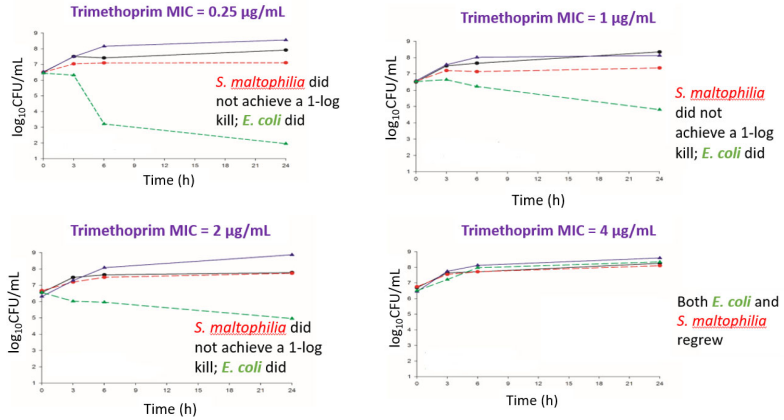
52

TMP-SMX: Maybe Not as Reliable for *S. maltophilia* as We Once Believed?

- >10,000 isolates from 2000-2022: remains active against **~90%** of isolates
  - No clinical trials investigating the role of TMP-SMX for *S. maltophilia* infections
- Difficult to interpret clinical outcomes data of TMP-SMX for *S. maltophilia*
  - Small sample sizes, heterogeneity of sources of infection, unclear if colonization or infection, MIC data missing, delays in initiation of active therapy, etc.
- We are left deriving TMP-SMX efficacy against *S. maltophilia* from pharmacokinetic-pharmacodynamic and animal models

Fischer JJ. J Infect Dis 1973;128:Suppl:771-3. Dadashi M, et al. J Glob Antimicrob Resist 2023;34:253-67. Mendes ET, et al. Rev Inst Med Trop Sao Paulo 2020; 62: e96. Hu LF, et al. J Chemother 2018;30: 25–30.

53

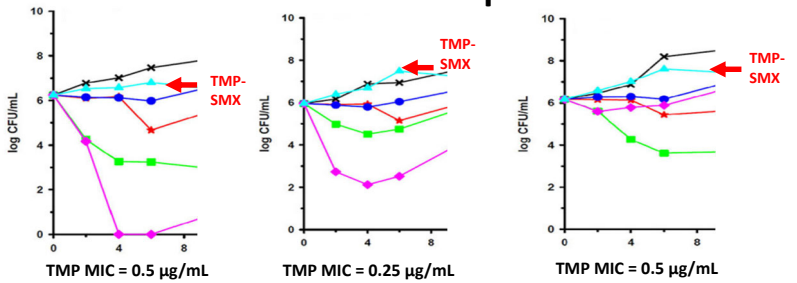


TMP-SMX human simulated dosages equivalent to 20 mg/kg/day

Lasko MJ, et al. Antimicrob Agents Chemother. 2022; 66:e0216721.

54

Additional Time-Kill Experiments



TMP-SMX concentration was 4 times the TMP MIC for 3 TMP-susceptible isolates with no bactericidal activity observed.

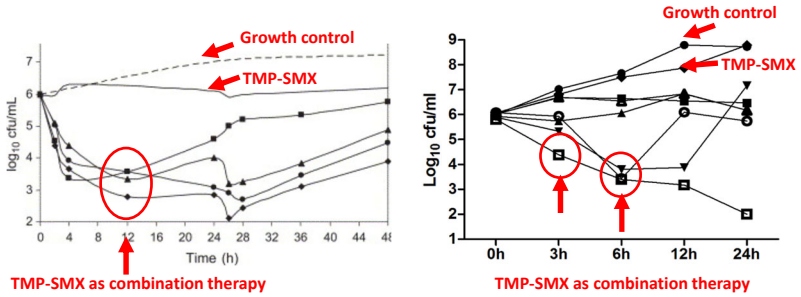
Biagi M, et al. Antimicrob Agents Chemother. 2020;64:e00559-20.

55

Can Combination Therapy Improve the Activity of TMP-SMX?

56

Can Combination Therapy Improve the Activity of TMP-SMX? (Maybe)



Zelenitsky SA, et al. Diagn Microbiol Infect Dis. 2005;51:39-43. Wei C, et al. PLoS One. 2016;11:e0152132.

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Results from Monte Carlo Simulations

TMP-SMX 10 mg/kg/day	*S. maltophilia* stasis	*E. coli* stasis
TMP MIC 0.5 µg/mL	**96%**	100%
TMP MIC 1 µg/mL	12%	84%
TMP MIC 2 µg/mL	0%	2.5%
TMP-SMX 15 mg/kg/day	***S. maltophilia* stasis**	***E. coli* stasis**
TMP MIC 0.5 µg/mL	**100%**	100%
TMP MIC 1 µg/mL	71.1%	99.6%
TMP MIC 2 µg/mL	0.8%	39.8%

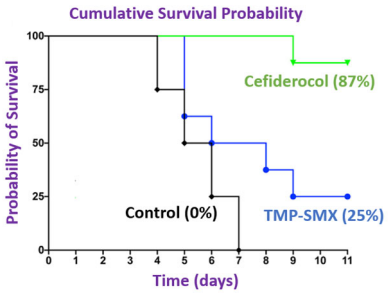
Derived from Cheng AC, et al. Antimicrob Agents Chemother. 2009;53:4193-9. Chin TW, et al. Antimicrob Agents Chemother.1995;39:28-33.

58

TMP-SMX & *S. maltophilia* in a Rabbit Model

Response of *S. maltophilia* pneumonia in neutropenic rabbits treated with:

- **No antibiotics** (n=8)
- **TMP-SMX** (n=8)
- **Cefiderocol** (n=8)



Note: Due to high natural thymidine levels in mice, murine models not suitable for TMP-SMX evaluations. Serine thymidine levels in rabbits comparable to humans.

Petraitis V, et al. Antimicrob Agents Chemother. 2022;66:e0061822.

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Cefiderocol Clinical Data

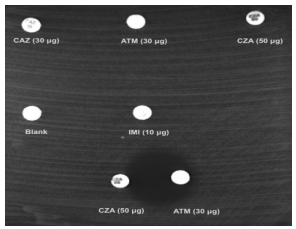
- Clinical trial comparing cefiderocol versus colistin-based regimens
  - All 5 patients with *S. maltophilia* infections randomized to cefiderocol arm
  - Treatment response for the 5 cases categorized as "indeterminant" with 4 of the 5 patients not surviving
- Several case reports suggest clinical success associated with use of cefiderocol for refractory *S. maltophilia* infections

Bassetti M, et al. Lancet Infect Dis 2021;21:226–40. Hsu AJ, et al. Open Forum Infect Dis. 2023; 10: ofad174. Frantoni AJ, et al. Int J Antimicrob Agents. 2021;58:106395. Falcone M, et al. Clin Infect Dis. 2021;72:2021-2024. Zappulo E, et al. Ann Hematol. 2022;101:2805-2806. Koirala A, et al. Pediatr Infect Dis J. 2023;42:1012-1016.

60

Aztreonam-Avibactam

- *S. maltophilia* is intrinsically resistant to most β-lactams because of two chromosomally encoded inducible β-lactamases
  - LI metallo-β-lactamase **(Aztreonam)**
  - L2 cephalosporinase **(Avibactam)**



Evidence of synergy between aztreonam & avibactam

Mojica MF, et al. Antimicrob Agents Chemother 2016; 60:5130-5134. Mojica MF, et al. Antimicrob Agents Chemother. 2017;61:e00777-17. Poeylaut-Palena AA, Bioorg Med Chem Lett. 2007;17:5171-4.

61

Activity of Aztreonam-Avibactam Against *S. maltophilia*

- Aztreonam-avibactam active against **~90%** of *S. maltophilia* isolates
- Reduced aztreonam-avibactam susceptibility associated with increased expression of genes encoding LI metallo-β-lactamase and efflux pumps

Biagi M, et al. Antimicrob Agents Chemother 2020; 64:e00297-20. Mojica M, et al. Antimicrob Agents Chemother 2017; 61:e00777-17. Lin Q, et al. BMC Microbiology 2021; 21:60. Sader HS, et al. Antimicrob Agents Chemother 64:e01433-20.

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Aztreonam-Avibactam Clinical Data

- Clinical trial to compare efficacy of aztreonam-avibactam versus alternative therapy for invasive MBL-producing infections
  - Only 3 patients with *S. maltophilia* infections
  - All randomized to aztreonam-avibactam
  - Outcomes: 1 favorable, 1 indeterminate, 1 unfavorable
- Several case reports suggest clinical success associated with use of aztreonam-avibactam for refractory *S. maltophilia* infections

ClinicalTrials.gov Identifier: NCT03580044. Mojica MF, et al. Antimicrob Agents Chemother 2016; 60:5130-5134. Diarra A, et al. Infect Dis Now. 2021 Oct:637-638. Torres ND, et al. J Infect Dev Citries. 2023;17:881-885.

63

Minocycline

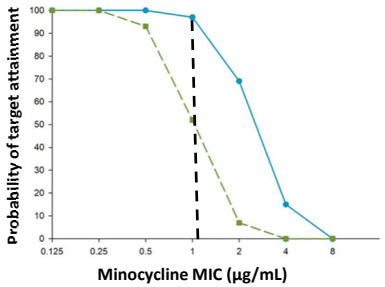
- Minocycline breakpoint against *S. maltophilia* is ≤1 µg/mL
- *S. maltophilia* susceptibility to minocycline ranges from ~35% to 90%
- *S. maltophilia* resistance to minocycline generally mediated by upregulation of several intrinsic multidrug-resistant efflux pumps

Mojica MF, et al. JAC Antimicrob Resist 2022;4:dlac040. Bakthavatchalam YD, et al. Eur J Clin Microbiol Infect Dis 2024;43:2453-7. Crowley PD, et al. Eur J Clin Microbiol Infect Dis. 2025;44:459-460. Wei C, et al. PLoS One 2016; 11: e0152132

64

Minocycline PK-PD Data

- Monte Carlo simulations indicate minocycline dosages of 200 mg IV every 12 hours have a **>90%** probability of achieving PK/PD targets associated with **bacterial stasis** in a neutropenic mouse thigh model for organisms with **MICs of 1 µg/mL**
  - **50%** probability of achieving targets associated with **1-log kill**



Frantoni AJ, et al. J Antimicrob Chemother. 2022;77:1052-1060.

65

Levofloxacin

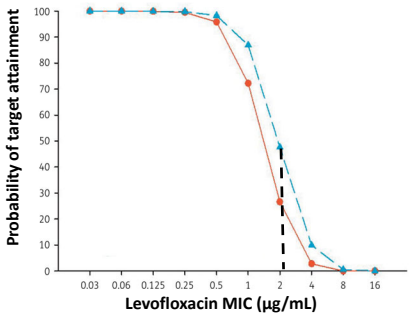
- Levofloxacin breakpoint against *S. maltophilia* ≤2 µg/mL
- Susceptibility against approximately 80% of *S. maltophilia* isolates
- Resistance associated with overexpression of efflux pumps & a chromosomally encoded Sm*qnr* gene that protects gyrase and topoisomerase from levofloxacin
  - Upon exposure to levofloxacin, Sm*qnr* gene upregulated
- Observational studies indicate emergence of resistance to levofloxacin during therapy generally ranges between 20-50%

Cho SY, et al. Antimicrob Agents Chemother 2014;58:581-3. Nys C, et al. Antimicrob Agents Chemother 2019;63. Sánchez MB, et al. Antimicrob Agents Chemother 2010; 54: 580–1. García-León G, et al. Environ Microbiol 2014;16:1282–96. García-León G, Clin Microbiol Infect 2015;21:464–7.

66

Levofloxacin PK-PD Data

- Monte Carlo simulations indicate levofloxacin dosages of 750 mg IV every 24 hours has a **87%** probability of achieving PK/PD targets associated with **bacterial stasis** in a neutropenic mouse thigh model for organisms with **MICs of 1 µg/mL**
  - **72%** probability of achieving targets associated with **1-log kill**



Frantoni AJ, et al. J Antimicrob Chemother. 2021;77:164-168.

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Take-Home Points: *S. maltophilia*

- Identification of *S. maltophilia* in a clinical specimen does not always indicate antibiotic therapy is necessary
  - *S. maltophilia* infections in hematologic malignancy patients should be taken seriously
- For severe infections IDSA AMR Guidance suggests **cefiderocol** as preferred therapy
- For non-severe infections combinations of **aztreonam-avibactam**, **TMP-SMX**, **minocycline**, or **levofloxacin** are suggested

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