


Bleach, fire, and alcohol

When Enterobacteriales outclass cefiderocol


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Disclosure Statement



Dr. Gregory Tallman has no relevant financial relationships to disclose

Learning Objectives



1. Summarize current treatment recommendations for infections caused by carbapenem-resistant Enterobacteriales
2. Explain mechanisms of resistance to avibactam and cefiderocol among carbapenemase-producing Enterobacteriales
3. Select appropriate antimicrobial therapy for patients with infections due to carbapenem-resistant Enterobacteriales

Pre-Test Question #1



Based on guidance from the Infectious Diseases Society of America, which antibiotic would be preferred when treating a systemic infection due to carbapenemase-producing Enterobacterales?

- A. Ceftazidime-avibactam
- B. Ceftolozane-tazobactam
- C. Colistin
- D. Trimethoprim-sulfamethoxazole

Pre-Test Question #2



Which mechanism is mostly likely to explain cross-resistance to ceftazidime-avibactam and cefiderocol?

- A. Carbapenemase mutations
- B. Efflux pump upregulation
- C. Penicillin-binding protein mutations
- D. Porin mutations


Pre-Test Question #3



A 65-year-old man is admitted with *Klebsiella pneumoniae* bacteremia secondary to a central line infection. Molecular testing indicates the organism is a KPC producer. Microbiology testing reveals resistance to all antibiotics, including ceftazidime-avibactam, ceftiderocol, colistin, and imipenem-cilastatin-relebactam. It is susceptible to meropenem-vaborbactam and eravacycline. What agent is most appropriate to recommend to treat this patient's bacteremia?


- A. Colistin
- B. Eravacycline
- C. Imipenem-cilastatin-relebactam
- D. Meropenem-vaborbactam

Abbreviations



- **CP-CRE**: carbapenemase-producing carbapenem-resistant Enterobacterales
- **CRE**: carbapenem-resistant Enterobacterales
- **CZA**: ceftazidime-avibactam
- **I-R**: imipenem-cilastatin-relebactam
- **IMP**: imipenemase
- **KPC**: *Klebsiella pneumoniae* carbapenemase
- **MBL**: metallo-β-lactamase
- **MVB**: meropenem-vaborbactam
- **NDM**: New Delhi metallo-β-lactamase
- **OXA**: oxacillinase
- **PBP**: Penicillin-binding protein
- **TMP-SMX**: trimethoprim-sulfamethoxazole
- **VIM**: Verona integrin-mediated metallo-β-lactamase

4:30pm on a Friday




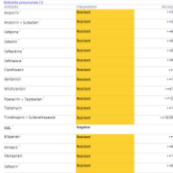
Miss director
Do you get notified about outpatient cultures?

Talman, Greg (Dr/Res/NH)
Not usually, what's up?


Miss director
Looks like we have a carbapenemase-producing *Klebsiella pneumoniae* from a urine culture.


Talman, Greg (Dr/Res/NH)





Case XH, D1: clinic visit





History of Present Illness:
70 y/o woman with 2-3 days pelvic pain. Prolonged hospitalization in China following surgical repair of spinal fracture, complicated by ICU admission and multiple IV antibiotics. Post-discharge UTI symptoms, not responsive to 3 courses of antibiotics. Arrived in USA 6 weeks ago.



Past Medical History

- Diabetes
- UTI (2 mo ago)
- Spinal fracture s/p repair (4 mo ago)

Allergies
NKDA

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Case XH, D1: clinic visit

Urinalysis

Color	Yellow
Clarity	Clear
Glucose	Negative
Blood	Trace
Protein	1+
Nitrite	Positive
Leuk. est.	3+



Urine Culture

pending

Rx: cephalexin 500mg PO BID x5 days

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 Urinalysis icon by SAM Designs

Case XH, D6: Initial micro results

Urinalysis

Color	Yellow
Clarity	Clear
Glucose	Negative
Blood	Trace
Protein	1+
Nitrite	Positive
Leuk. est.	3+


Urine Culture

Klebsiella pneumoniae

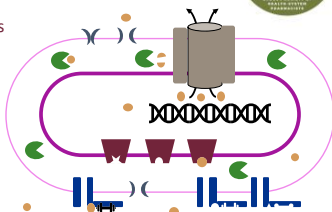
Amikacin	Resistant	≥ 64
Ciprofloxacin	Resistant	≥ 4
Mecopenem	Resistant	≥ 16
Nitrofurantoin	Resistant	≥ 512
TMP-SMX	Resistant	≥ 16/304
Tobramycin	Resistant	≥ 16
ESBL	Negative	

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 Urinalysis icon by SAM Designs

Enzymes & efflux & porins, oh my!




- Beta-lactamases
- Target site modifications
 - PBPs
 - Ribosome
 - Gyrase/topoisomerase
- ↓ Drug entry
 - Porin loss
 - Siderophore receptor
- ↑ Drug efflux



PBP: penicillin-binding protein
 Pelleg, AJ et al. N.Engl. J.Med. 2003.

Making a CRE



Carbapenem-resistant: non-susceptible to ≥ 1 carbapenem antibiotic or cOR produces a carbapenemase

Enterobacteriales: *E. coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Citrobacter* spp., etc.

Excludes: *Pseudomonas*, *Acinetobacter*, *Stenotrophomonas*


Carbapenem-resistant Enterobacteriales

- CP-CRE: 35-83% (USA), 75-90% (global)
 - KPC
 - OXA-48-like
 - NDM, IMP, VIM
- Non-CP CRE
 - Porin loss
 - Efflux pumps
 - Other β-lactamases

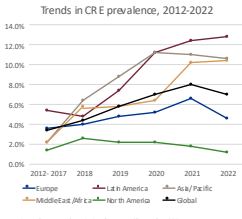
CP-CRE, carbapenemase-producing carbapenem-resistant Enterobacteriales; IMP, impenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; KPC, Klebsiella pneumoniae-mediated carbapenemase

Nordstrom P et al. Clin Infect Dis. 2018.
Van Duin D, et al. Lancet Inf Dis. 2020.
Kamareddin KM, et al. Antimicrob Agents Chemother. 2021.
Wu MH, et al. J Glob Antimicrob Resist. 2024.
Tamma PD, et al. Clin Infect Dis. 2024. Online ahead of print. doi: 10.1093/cid/ciaf003

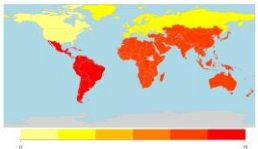
Resistance is futile inevitable



Trends in CRE prevalence, 2012-2022




Global CRE prevalence (%) 2022



Kamareddin KM, et al. Antimicrob Agents Chemother. 2021.
Wu MH, et al. J Glob Antimicrob Resist. 2024.

Treatment of CP-CRE



Clinical Infectious Diseases
IDSA GUIDELINES | AIDSA | hvma | CDC


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

Parsons B, Tenover J, Eady J, Holt J, Lavin A, Jones J, King J, Whittam J, Saffar J, Toffa S, and Robert A. Stevens*

<p>Uncomplicated cystitis</p> <ul style="list-style-type: none"> Fluoroquinolone Fosfomycin (<i>E. coli</i> only) Nitrofurantoin TMP-SMX 	<p>Pyelonephritis</p> <ul style="list-style-type: none"> Fluoroquinolone TMP-SMX See "systemic infection" 	<p>Systemic infection</p> <ul style="list-style-type: none"> Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-relebactam Cefiderocol
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Tamma PD, et al. Clin Infect Dis. 2024. Online ahead of print. doi: 10.1093/cid/ciaf003

Treatment of CP-CRE



Clinical Infectious Diseases
IDSA GUIDELINES
 Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections
Paolino D. Tarrero, Emily L. Hall, Julie Ann Jahn, Amy J. Whittam, Michael J. Sattis, and Robert K. Branson


Uncomplicated cystitis
 Fluoroquinolone
 Fosfomycin (E.coli only)
 Nitrofurantoin
 TMP-SMX

Pyelonephritis
 Fluoroquinolone
 TMP-SMX
 See "systemic infection"

Systemic infection
 Ceftazidime-avibactam
 Meropenem-vaborbactam
 Imipenem-relebactam
 Cefiderocol

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New(ish) β -lactams* for CRE





Antibiotic	Mechanism	KPC	OXA-48	MBL
Ceftazidime-avibactam	Existing β -lactams paired with novel β -lactamase inhibitors	✓	✓	✗
Imipenem-cilastatin-relebactam		✓	✗	✗
Meropenem-vaborbactam		✓	✗	✗
Cefiderocol		Novel siderophore cephalosporin	✓	✓

*Tetacycline derivatives (tigecycline, eravacycline) may have activity against KPC- and MBL-producing organisms, but are not recommended for UTI

Tarrero PD et al. Clin Infect Dis. 2024. Online ahead of print. doi: 10.1093/cid/ciaf003


Case XH, D7 – 10: more results





Urinalysis

Color: Yellow
 Clarity: Clear
 Glucose: Negative
 Blood: Trace
 Protein: 1+
 Nitrite: Positive
 Leuk. est.: 3+

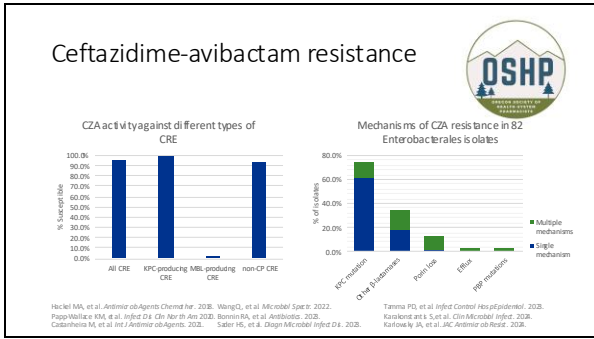


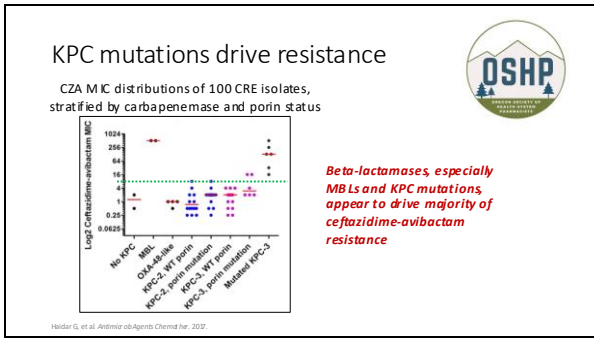
Urine Culture
Klebsiella pneumoniae

Antibiotic	Result	CFU
Meropenem	Resistant	≥ 16
Ceftazidime-avibactam	Resistant	16
Ceftolozane-tazobactam	Resistant	256
Cefiderocol	pending	
ESBL	Negative	

Call to patient (DB)
 Culture results shared, ED/hospital recommended. Patient reports symptom improvement, so deferred ED visit.

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Case XH, D10 – 17: more results

State Lab Report (D13)



- IMP: Undetected
- KPC: **Detected**
- NDM-1: Undetected
- OXA-48: Undetected
- VIM: Undetected

Urine Culture
Klebsiella pneumoniae

Meropenem	Resistant	≥ 16
Ceftazidime-avibactam	Resistant	16
Ceftiozone-taxidactam	Resistant	256
Ceftiderocol	pending	
ESBL	Negative	

Call to patient (D17)
Additional culture results shared, further care recommended. Patient reports no symptoms, so declined ER visit.

Case XH, D19: hospitalization





History of Present Illness:
New urinary frequency x1 day PTA. Pt reports she received letter from health dept. stating she needs tx with cefiderocol.

Past Medical History

- Diabetes
- UTI (2 mo ago)
- Spinal fracture s/p repair (4 mo ago)



Allergies
NKDA



138	105	17	203	8.2	15.0	295
4.1	26	0.94			43.3	

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MRI icon by fotomac/istock, PNH icon by serjov/istock

Case XH, D19: micro updates, again

Urinalysis (D19)

Color	Yellow
Clarity	Cloudy
Glucose	1+
Blood	Negative
Protein	Trace
Nitrite	Positive
Leuk. est.	3+

Urine Culture (D1)
Klebsiella pneumoniae

Meropenem	Resistant	≥ 16
Ceftazidime-avibactam	Resistant	16
Ceflozane-tazobactam	Resistant	256
Cefiderocol	Intermediate	8
ESBL	Negative	


Resulted D19

Urine Culture (D19)
pending

Rx: ????

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LA analysis icon by SAM Designs

Cefiderocol resistance




- Beta-lactamases**
 - Some MBLS
 - KPC, AmpC, ESBL mutants
 - Hyperexpression
- Target site modification**
 - PB P3 mutations
- Drug entry**
 - Porin mutations (*ompC, ompF, ompK*)
 - Siderophore receptor mutations (*citA, fit*)
- Drug efflux**
 - Heavy metal ion transporter (*chrA*)
 - Efflux pump (*SugE*)

Resistant Isolate Program
For non-susceptible isolates, manufacturer will:

- Confirm organism and susceptibility
- Whole genome sequencing for:
 - PB P3, PB P1a mutations
 - Porin mutations
 - Iron-transport gene mutations

Kazianka et al. J, et al. Antibiotics. 2022.
Personal communication with Jay Binyovsky, Director of Field Microbiology, Shionogi Inc. (Dec. 2023).

KPC mutations and cross-resistance




Cefiderocol activity against different types of CRE

CRE Type	% Susceptible
All CRE	~95%
KPC	~95%
MBL	~85%
non-KP CRE	~90%
CZA-SCRE	~95%
CZA-R CRE	~85%

Hobson CA, et al. Clin Microbiol Infect. 2023. Wang Q, et al. Microbiol Spectr. 2022. Biano G, et al. Eur J Clin Microbiol Infect Dis. 2023. Tamura PJ, et al. Infect Control Hosp Epidemiol. 2023. Karakent et al. S, et al. Clin Microbiol Infect. 2023.

KPC mutations and cross-resistance



Cefiderocol activity against different types of CRE

CRE Type	% Susceptible
All CRE	~95%
KPC	~95%
MBL	~85%
non-KP CRE	~90%
CZA-SCRE	~95%
CZA-R CRE	~85%


4x CZA-induced KPC mutations increase cefiderocol MICs 2-32x

CZA-resistant CRE less likely to be susceptible to cefiderocol

Ceftazidime-avibactam resistance in KPC-producers suggests possible cross-resistance due to KPC variants +/- presence of other resistance mechanisms.

Hobson CA, et al. Clin Microbiol Infect. 2023. Wang Q, et al. Microbiol Spectr. 2022. Biano G, et al. Eur J Clin Microbiol Infect Dis. 2023. Tamura PJ, et al. Infect Control Hosp Epidemiol. 2023. Karakent et al. S, et al. Clin Microbiol Infect. 2023.

Treatment of CP-CRE



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


Parsons B, Tenover J, Tenover J, et al. JAMA. 2024. doi:10.1001/jama.2024.11111

Uncomplicated cystitis	Pyelonephritis	Systemic infection
Fluoroquinolone	Fluoroquinolone	Ceftazidime-avibactam
Fosfomycin (E.coli only)	TMP-SMX	Meropenem-vaborbactam
Nitrofurantoin	See "systemic infection"	Impenem-relebactam
TMP-SMX		Cefiderocol

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Treatment of CR

Sooo... now what?



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

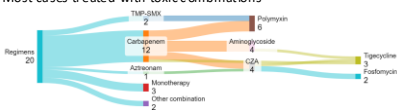
Aravind G. Tamma, Emily L. Hall, Julie Ann Jahn, Amy J. Whittam, Michael J. Saitis, and Robert K. Baxter

Uncomplicated cystitis	Pyelonephritis	Systemic infection
Fluoroquinolone	Fluoroquinolone	Ceftazidime-avibactam
Fosfomycin (F-co/only)	TMP-SMX	Meropenem-vaborbactam
Nitrofurantoin	See "systemic infection"	Impenem-relebactam
TMP-SMX		Cefiderocol

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Cytosion by Dan Khooon La
Tamma AG, et al. Clin Infect Dis. 2024. Online ahead of print. doi: 10.1093/cid/cia403

A dearth of data on treatment

Most cases treated with toxic combinations



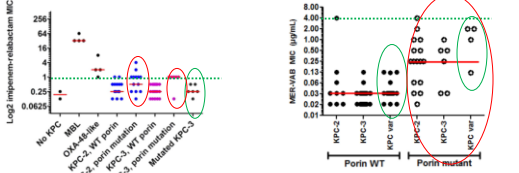
What about imipenem-relebactam and meropenem-vaborbactam?

Citation	Type	Clinical details	Tx	Outcome
Athans 2019	Case report	24 yo F, BSI + liver ats cess	MVB + tigecycline	Success @ ~2 mo
Tiseo 2021	Case report	68 yo M, BSI + UTI	MVB	Success @ 6 mo
Rezzonico 2021	Case report	59 yo M, meningitis	MVB + IT gent	Success @ 4 mo
Plazza 2024	Case series	3 patients, BSI + VAP	MVB	Not reported

Plazza V, et al. Antimicrob Agents Chemother. 2024; Tiseo G, et al. Open J Infect Dis. 2023; Athans V, et al. J Glob Antimicrob Resist. 2021; Rezzonico L, et al. J Microbiol Immunol Infect. 2021; Figure modified: SankuMATIC.com


Exploring our options

I-R (left) and MVB (right) MIC distributions of CRE isolates, stratified by carbapenemase and porin status



Heidar G, et al. Antimicrob Agents Chemother. 2022; Wilson WH, et al. Antimicrob Agents Chemother. 2019.

"Porin" over the data



I-R and MVB activity against CZA-R and non-CP CRE


Study	Imipenem-relebactam (%)	Meropenem-vaborbactam (%)
Castillo-Pérez 2022 (n=12)	~100	~100
Lorbaudo 2022 (n=10)	~65	~35
Wilson 2019 (n=19)	~100	~100
Surveillance non-CP CRE	~80	~80

"[Porin loss] plays a major role in [imipenem-relebactam] resistance ... selection of [imipenem-relebactam] resistance has a collateral effect on [meropenem-vaborbactam] susceptibility - indicative of shared resistance mechanisms..."

Susceptibility data crucial to selecting optimal therapy. Cannot reliably predict imipenem-relebactam and meropenem-vaborbactam activity.

Wilson WH, et al. Antimicrob Agents Chemother. 2019; Lorbaudo D, et al. Clin Microbiol Infect. 2022; Castillo-Pérez A, et al. J Antimicrob Chemother. 2023; Capenhorn M, et al. Int J Antimicrob Agents. 2023; Papp-Wallace KJA, et al. Antimicrob. 2020; Saller H, et al. Diagn Microbiol Infect Dis. 2020; Fredtjof A, et al. Antimicrob Agents Chemother. 2020; Bonaventura, et al. Antimicrob. 2020; Katsouli A, et al. J Antimicrob Chemother. 2020.


So... what do we do?



Metallo-β-lactamase suspected

- Ceftazidime-avibactam PLUS aztreonam
- Obtain susceptibility testing + genetic markers

So... what do we do?



Metallo-β-lactamase suspected

- Ceftazidime-avibactam PLUS aztreonam
- Obtain susceptibility testing + genetic markers


KPC variant suspected


- Imipenem-relebactam OR meropenem-vaborbactam
- Obtain susceptibility testing + genetic markers

KPC variant + other mutation(s) suspected


- Slight preference for meropenem-vaborbactam?
- Obtain susceptibility testing + genetic markers

Case XH, D19-32: conclusion







ID consulted:
Rec short course




Imi-rel x 3 days
Methenamine ppx



Not sent for sequencing
(cultures discarded) Resulted O32




Symptoms improved
Not seen since d/c



Urine Culture (D1)
Klebsiella pneumoniae

Meropenem	Resistant	≥ 16
Ceftazidime-avibactam	Resistant	16
Ceftolozane-tazobactam	Resistant	256
Cefiderocol	Intermediate	8
Imipenem-relebactam	Susceptible	1/4
Meropenem-vaborbactam	Susceptible	4/8
ESBL	Negative	

Key takeaways



Treatment of serious CRE infections

Preferred treatments for serious carbapenemase-producing CRE include ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam, and cefiderocol


Resistance to new agents rare, but complex

Ceftazidime-avibactam resistance often due to KPC mutation or MBL enzyme, may lead to cross resistance with cefiderocol, meropenem-vaborbactam, and/or imipenem-relebactam

Susceptibility and genetic markers crucial

Ideally, selection of optimal therapy for serious CRE infections will be guided by genetic data regarding type of beta-lactamase, as well as susceptibility testing

Post-Test Question #1



Based on guidance from the Infectious Diseases Society of America, which antibiotic would be preferred when treating a systemic infection due to carbapenemase-producing Enterobacterales?

A. Ceftazidime-avibactam

B. Ceftolozane-tazobactam

C. Colistin

D. Trimethoprim-sulfamethoxazole

Post-Test Question #2



Which resistance mechanism is mostly likely to explain cross-resistance to ceftazidime-avibactam and cefiderocol?

- A. Carbapenemase mutations
- B. Efflux pump upregulation
- C. Penicillin-binding protein mutations
- D. Porin mutations

Post-Test Question #3



A 65-year-old man is admitted with *Klebsiella pneumoniae* bacteremia secondary to a central line infection. Molecular testing indicates the organism is a KPC producer. Microbiology testing reveals resistance to all antibiotics, including ceftazidime-avibactam, cefiderocol, colistin, and imipenem-cilastatin-relebactam. It is susceptible to meropenem-vaborbactam and tigecycline. What agent is most appropriate to recommend to treat this patient's bacteremia?

- A. Colistin
- B. Eravacycline
- C. Imipenem-cilastatin-relebactam
- D. Meropenem-vaborbactam

Thank you!



QUESTIONS?



Gregory.taliman@provide.nce.org



503.216.0210

References



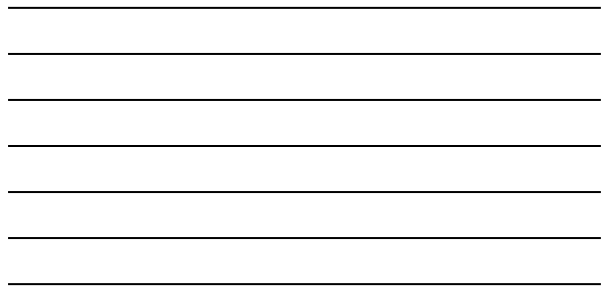
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