NYSCHP | New York State Council of Health-system Pharmacists

When Bacteria Fight Back:

A Review of Gram-negative Resistance

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Conflicts of Interest / Disclosure

- Both speakers have no conflicts of interest
- Speakers intend to reference unapproved / unlabeled uses of drugs or products in the presentation

Learning Objectives (Pharmacists):

1. Discuss the problem of drug-resistant infections in the United States and the importance of antimicrobial stewardship
2. Summarize mechanisms of resistance employed by Gram-negative organisms and the potential resistance genes present
3. Formulate appropriate empiric and directed antimicrobial treatment regimens to treat infections caused by drug-resistant Gram-negative organisms

Learning Objectives (Pharmacy Technicians):

1. Discuss the problem of drug-resistant infections in the United States and the importance of antimicrobial stewardship
2. Define different drug-resistant infections and why they can be difficult to treat
3. Describe the antimicrobial agents that are available for the treatment of infections caused by Gram-negative organisms

Antimicrobial Resistance is a Growing Problem

- An urgent global public health threat
- In the United States, **more than 2.8 million** antimicrobial-resistant infections occur each year
  - **More than 35,000 deaths per year**
- The CDC and WHO classify six highly virulent pathogens account for more than **$4.6 billion** in healthcare costs annually

Lancet 2022; 399: 629–55.
About Antimicrobial Resistance. Centers for Disease Control and Prevention. Oct 2022.

AT LEAST
1.7M
adults develop sepsis each year

MORE THAN
30M
people have diabetes

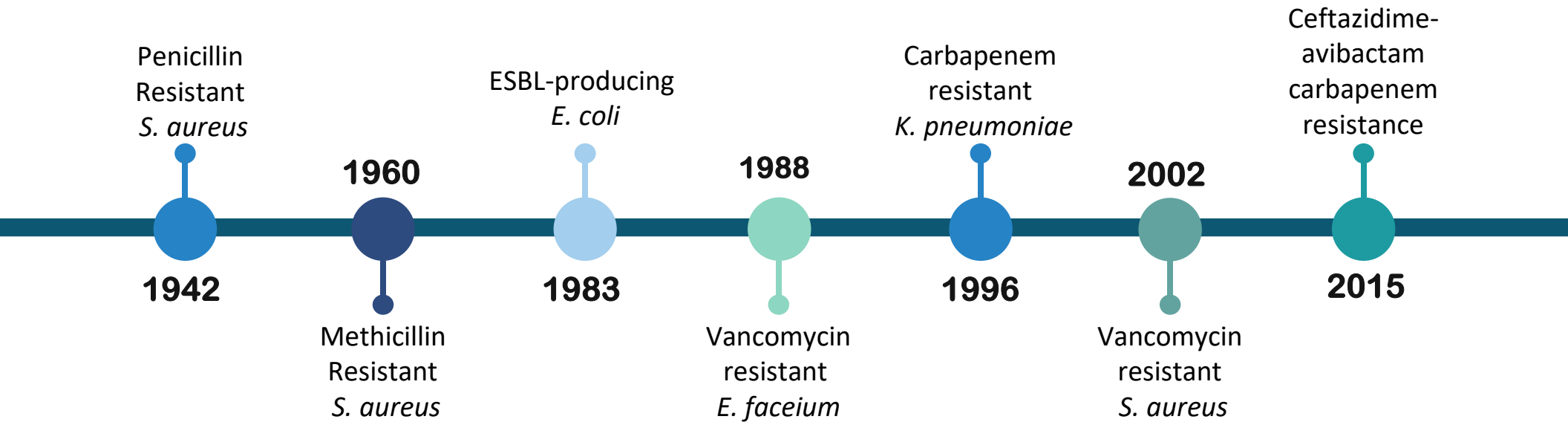
MORE THAN
33,000
organ transplants performed in 2016

MORE THAN
500,000
people received dialysis treatment in 2016

Antimicrobial Resistance Threat

Antibiotic-Resistant Infections Threaten Modern Medicine. Center for Disease Control and Prevention. 2022

Antimicrobial Resistance Over Time

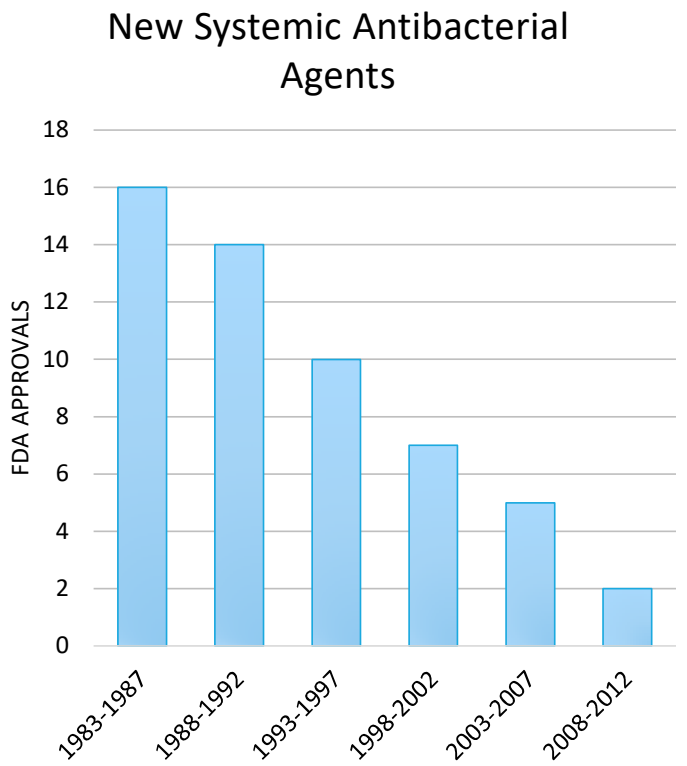


ESBL = extended-spectrum β-lactamase

Centers for Disease Control and Prevention. Revised Dec 2019.

New Antibiotic Development/Pipeline

- New antibiotic agents approved by the Food and Drug Administration (FDA) have been declining
- High failure rate during drug development
  - Prolonged process for approval
  - Inadequate compensation for these agents
- Many larger pharmaceutical manufacturers have lost interest in developing new antibiotics and left the market to smaller- and medium-sized companies



Chahine EB, et al. Ann Pharmacother. 2022 Apr;56(4):441-462.
Bush K, et al. ACS Infect. Dis. 2015, 1, 11, 509–511

Actions Against Antimicrobial Resistance

US National Strategy for Combating Antibiotic-Resistant Bacteria (CARB): 2015-2020 Five-year plan

Core Elements of Hospital Antibiotic Stewardship Programs published by the CDC

Antimicrobial Use and Resistance Module via National Healthcare Safety Network (NHSN)

US Action Plan 2020 – 2025

Centers for Disease Control and Prevention. Revised Dec 2019.

CDC Threat Report – 2019

Urgent

- **Carbapenem-resistant A*cinetobacter***, *C. auris, C. difficile,* **Carbapenem-resistant Enterobacterales**, N. gonorrhoeae

Serious

- **ESBL-producing Enterobacterales**, Vancomycin-resistant *Enterococci* (VRE), **Multi-drug resistant *Pseudomonas aeruginosa***, Methicillin-Resistant S. aureus, Drug-resistant *Campylobacter*, Drug-resistant *Candida*, Drug-resistant *Salmonella*, Drug-resistant *Shigella*, Drug-resistant *S. pneumoniae*, Drug-resistant TB

Concerning

- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

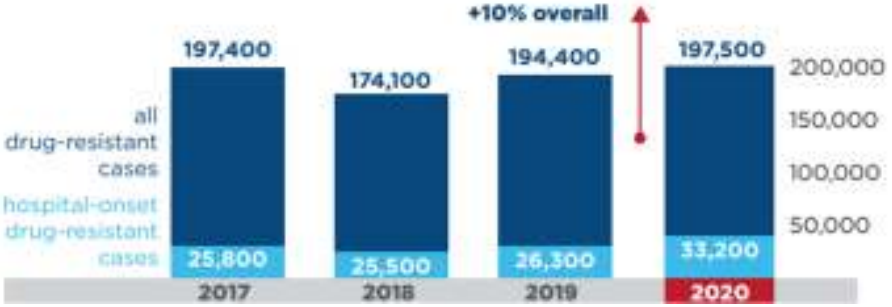
CDC. Antibiotic Resistance Threats in the United States, 2019

COVID-19 Impact on Antimicrobial Resistance

Carbapenem-Resistant Enterobacterales

March 2020 - October 2020, **~ 80%** of patients hospitalized with COVID-19 received an antibiotic

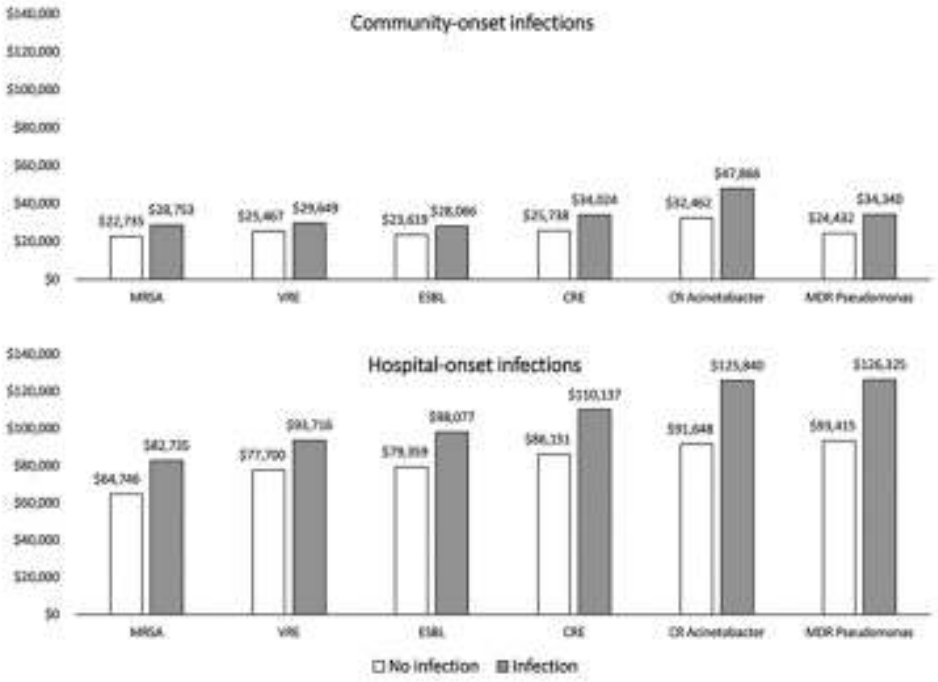
ESBL-producing Enterobacterales

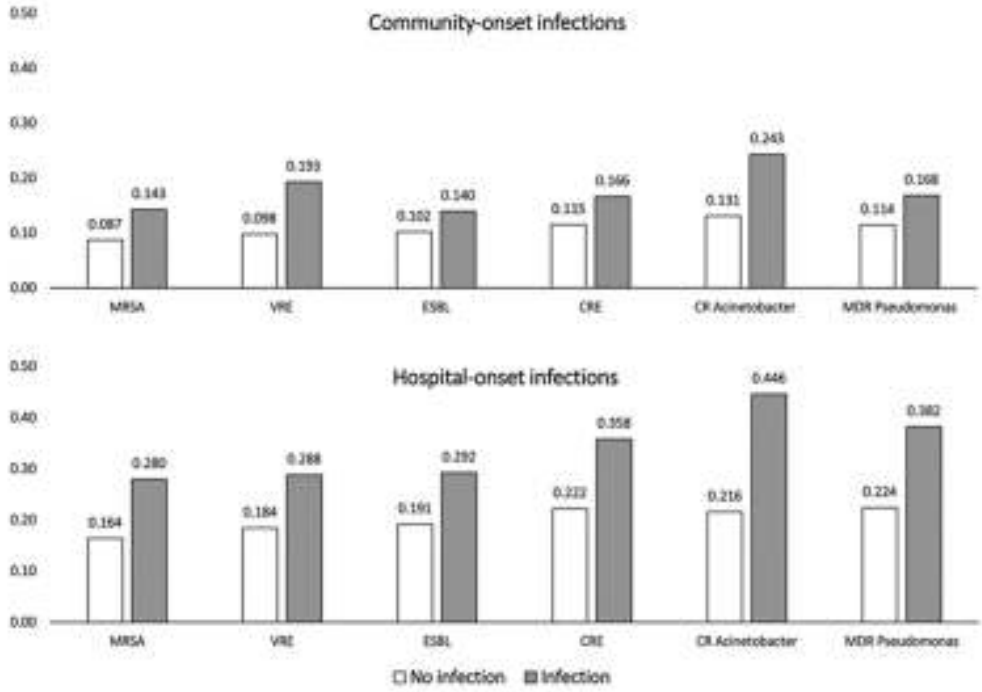


Multi-drug Resistant *Pseudomonas aeruginosa*

CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report. 2022.

Antimicrobial Resistance: Adults > 65





Nelson RE, et al. Clin Infect Dis. 2022;74(6):1070–80

Importance of Antimicrobial Stewardship

- Improved patient outcomes
- Reduced adverse events including *Clostridiodies difficile* infection (CDI)
- Improvement in antibiotic susceptibility rates to targeted antimicrobials
- Optimization of resource utilization across the continuum of care

Barlam TF, et al. Clin Infec Dis. 2016;62(10):e51–e77

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] & Cornelius J. Clancy[6]

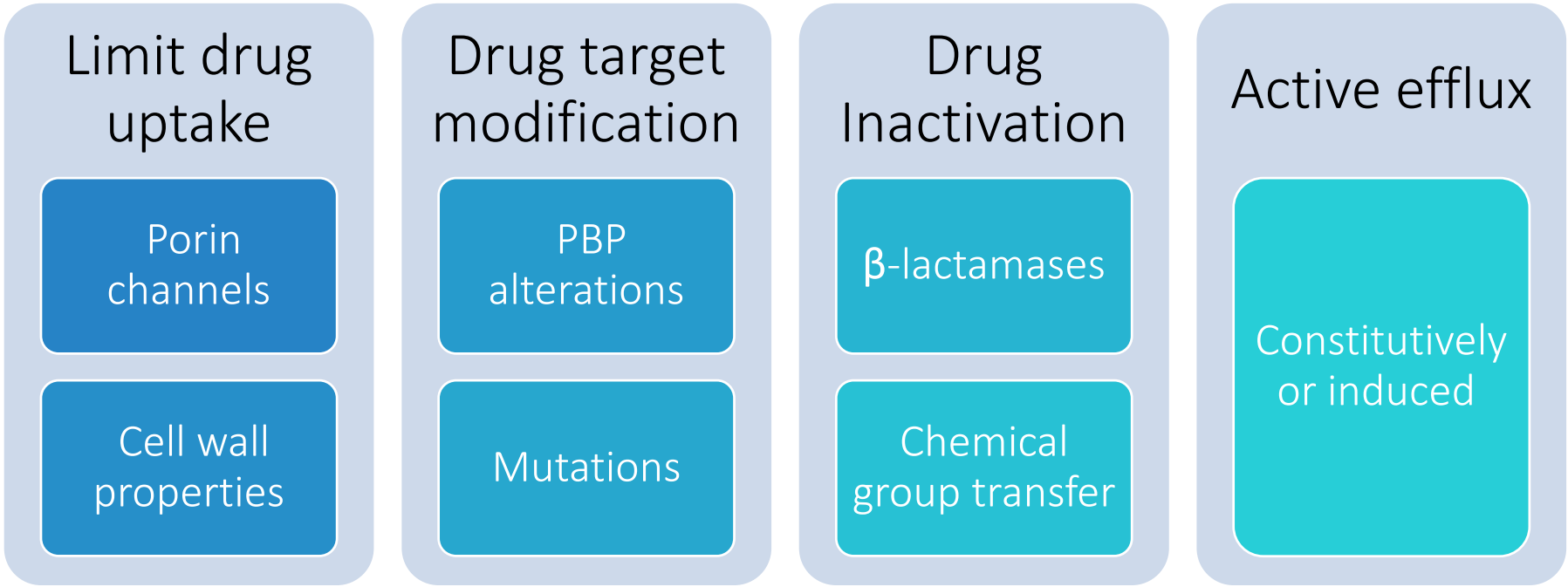
IDSA Treatment Guidance Document 2023

IDSA Treatment Guidance Outline

- Extended Spectrum Beta-lactamases (ESBLs)
- AmpC Beta-lactamases
- Carbapenem-Resistant Enterobacterales
- *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance
- Carbapenem-Resistant *Acinetobacter baumannii*
- *Stenotrophomonas maltophilia*

Tamma PD, et al. IDSA 2023; Version 3.0

Mechanisms of Antimicrobial Resistance



Reygaert WC. AIMS Microbiol. 2018; 4(3): 482–501.
Munita JM, et al. Microbiol Spectr. 2016 Apr; 4(2).

PBP = penicillin-binding proteins

Gram-negative Resistance: β-lactamases

- Most common cause of β-lactam resistance among the Enterobacterales group
- Enzymes are encoded on chromosomal genes or mobile genetic elements (i.e., plasmids)
  - Inactivation of the drug mechanism
- ≥ 1,000 β-lactamases have been described

Ruppé et al. Ann. Intensive Care (2015) 5:21

β-lactamases: Ambler Classification

Type	Class	Characteristic	Genes
Narrow-spectrum β-Lactamases	A	Hydrolyze penicillin	TEM SHV
Extended-Spectrum β-Lactamases (ESBLs)	A	Hydrolyze narrow and extended spectrum B-lactams	TEM SHV CTX-M
Serine Carbapenemases	A	Hydrolyze carbapenems	KPC IMI
Metallo-beta-lactamases	B	Hydrolyze carbapenems	VIM IMP NDM
Cephalosporinases	C	Hydrolyze cephamycins	AmpC
OXA-type enzymes	D	Hydrolyzes oxacillin, carbapenems	OXA

Ruppé et al. Ann. Intensive Care (2015) 5:21

Assessment Question #1:

Which of the following are impacted by the emergence of antimicrobial resistance?

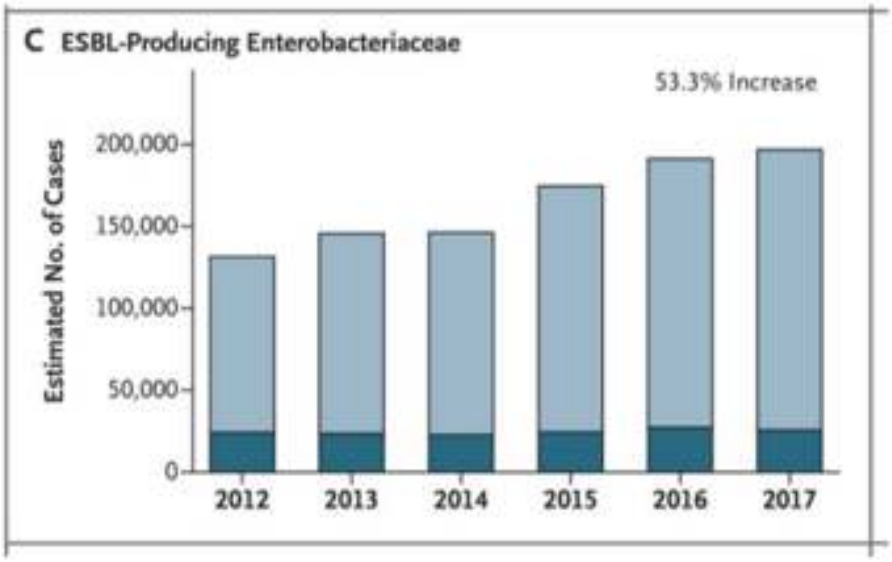
1. Financial costs
2. Treatment regimens
3. Patient outcomes
4. All of the above

Extended Spectrum β-lactamases (ESBLs)

Extended Spectrum β-lactamases (ESBLs)

- β-lactamases capable of conferring bacterial resistance to penicillins, first-, second-, and third-generation cephalosporins, and aztreonam

- The incidence of ESBL identified in bacterial cultures in the US increased by 53% from 2012 to 2017
  - **CTX-M** is the most common ESBL worldwide
  - Other variants include: SHV-1, TEM-1



Tamma PD, et al. IDSA 2023; Version 3.0
Ruppé et al. Ann. Intensive Care (2015) 5:21
Jernigan JA, et al. N Engl J Med 2020; 382:1309-1319

GU0

ESBL Treatment Options

- Non-susceptibility to ceftriaxone/ceftazidime is often utilized as a proxy for ESBL production
- <u>Treatment for uncomplicated cystitis:</u>
  - Nitrofurantoin
  - Trimethoprim/sulfamethoxazole
- <u>Treatment of complicated cystitis/pyelonephritis:</u>
  - Carbapenems
  - Levofloxacin/ciprofloxacin
  - Trimethoprim/sulfamethoxazole
- <u>Treatment of infections outside the urinary tract:</u>
  - Carbapenems

Piperacillin/tazobactam is not recommended for the treatment of infections outside of the urinary tract, even if susceptibility is demonstrated

Tamma PD, et al. IDSA 2023; Version 3.0

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MERINO Trial

Piperacillin/Tazobactam compared to meropenem did not result in a non-inferior 30-day mortality

Study Design

- Non-inferiority, parallel group, randomized clinical trial

Population

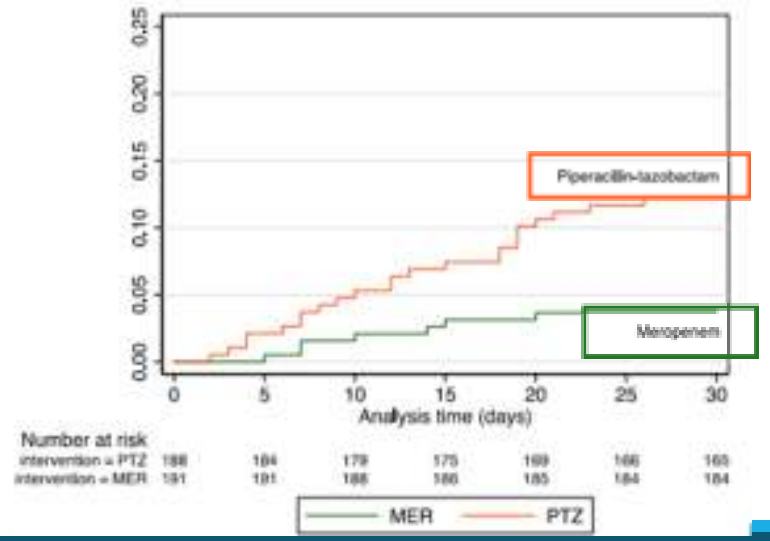
- Adult patients with ≥1 positive culture with ceftriaxone non-susceptible, pip/tazo susceptible *E. coli* or *K. pneumoniae*

Intervention

- Pip/tazo 4.5 g IV q6h administered over 30 minutes
- Meropenem 1 g IV q8h administered over 30 minutes

30-Day Mortality, No./Total No. (%)		P-value for non-inferiority
Piperacillin/Tazobactam	Meropenem	
23/187 (12.3)	7/191 (3.7)	0.90

eFigure 4: Kaplan-Meier Failure Estimates for Primary Outcome



Harris PN, et al. JAMA. 2018;320(10):984-994

Cefepime for ESBL UTI Treatment

Study Design

- Retrospective study with ESBL isolates obtained Jul 2014 – Jan 2017

Population

- Patients ≥ 18 years of age with a symptomatic UTI who received ≥ 48 hours of either cefepime or a carbapenem for treatment

Results

- No patients included experienced clinical or microbiologic failure
- Relapse:
  - Carbapenem: 7.0%
  - Cefepime: 0.0%

MIC Category	Cefepime (n=17)	Carbapenems (n=89)
≤ 2 mcg/mL	16 (94%)	50 (56%)
4-8 mcg/mL	1 (6)	17 (19)
≥ 16 mcg/mL	0 (0)	22 (35)

Cefepime may be a suitable, effective alternative in the treatment of ESBL-producing Enterobacterales-related UTI when MIC ≤ 2 mcg/mL

Kim SA, et al. Int. J. Antimicrob. Agents. 2018;51:155–158

Patient Case # 1:

You receive this page from a medical resident:

"Hi - can I change this patient to ceftriaxone or do you have any additional streamline recommendations? Thanks!"

Blood Culture	***Enterobacter cloacae***
Ampicillin	R
Cefepime	S
Ceftazidime	S
Ceftriaxone	S
Meropenem	S
Piperacillin-tazobactam	R

AmpC β-lactamases

AmpC β-lactamases

- AmpC is a type of β-lactamase that can rapidly hydrolyze penicillins, cephalosporins, and monobactams
  - Not significantly inhibited by β-lactamase inhibitors (Clavulanic acid, sulbactam, tazobactam, etc.)

Inducible chromosomal resistance	• Initially tests susceptible to ceftriaxone/ceftazidime → Can develop resistance while on treatment
Non-inducible chromosomal resistance due to mutations	• Non-susceptible to ceftriaxone/ceftazidime *in vitro*
Plasmid-mediated AmpC resistance	• Non-susceptible to ceftriaxone/ceftazidime *in vitro*

Tamma PD, et al. IDSA 2023; Version 3.0

SPACE / SPICE Organisms

These organisms **were <u>previously</u> thought** to demonstrate (harbor) inducible AmpC

S*erratia marcescens*

P*seudomonas aeruginosa*

Indole-positive *Proteus* / ***A****cinetobacter*

C*itrobacter* spp.

E*nterobacter* spp.

Are the "SPACE/SPICE" organisms all equal in AmpC production?

Macdougall C. J Pediatr Pharmacol Ther 2011;16(1):23–30

SPACE / SPICE Organisms

- The Infectious Diseases Society of America (IDSA) guidance document on the treatment of antimicrobial-resistant Gram-negative infections found the following:

  - ***Serratia marscescens, Morganella morganii,*** and ***Providencia*** species
    - **Unlikely** to overexpress AmpC based on *in vitro* and clinical reports **suggesting clinically significant AmpC production occurs in less than 5% of these organisms**

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Moderate-High Risk for Clinically Significant AmpC

- ***Enterobacter cloacae*, *Klebsiella aerogenes*,** and ***Citrobacter freudnii*** are at moderate to high risk for clinically significant AmpC production

- Organisms such as ***H. alvei*, *Citrobacter youngae***, and ***Yersinia enterocolitica*** carry chromosomal AmpC genes but are not reported in many clinical reports, limiting the ability to interpret the clinical relevance of inducible AmpC expression

Tamma PD, et al. IDSA 2023; Version 3.0

Moderate-High Risk for Clinically Significant AmpC

H*afnia alvei*

E*nterobacter cloacae*

C*itrobacter freundii*

K*lebsiella aerogenes*

Yer*sinia enterocolitica*

When these agents are recovered in cultures, the IDSA suggests avoiding treatment with ceftriaxone or ceftazidime, even if the isolate tests susceptible to the agents initially

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AmpC β-lactamases Treatment Options

- Third generation cephalosporins (ceftriaxone, ceftazidime) should be avoided due to the potential for resistance to develop while on therapy

Cefepime (when MIC ≤ 2 mcg/mL)

Carbapenems (when cefepime MIC ≥ 4 mcg/mL as ESBL co-production may be present)

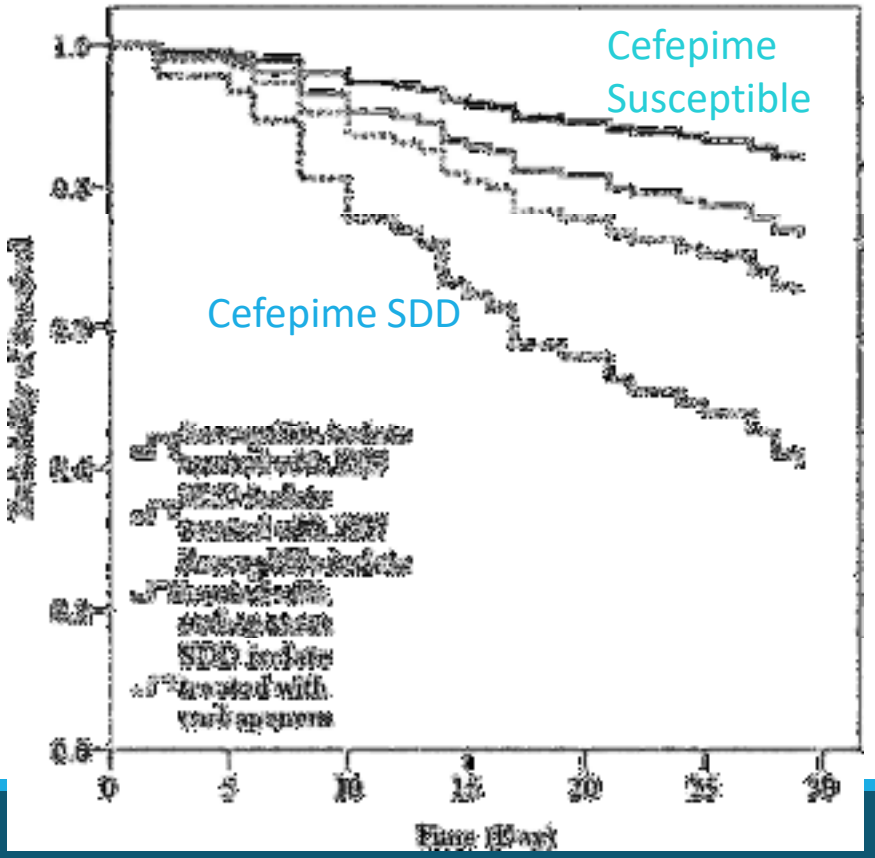
Fluoroquinolones

TMP/SMX

Tamma PD, et al. IDSA 2023; Version 3.0

Cefepime for AmpC-Producing Organisms

- Retrospective study
- 305 adult patients with *Enterobacter cloacae* bloodstream infections
- Cefepime was compared to a carbapenem



Outcomes varied by cefepime MIC values

→ **MIC ≤ 2 mcg/mL (Susceptible)**

= Cefepime (Dosed: 2 grams IV q8hrs)

→ **MIC ≥ 4 mcg/mL (SDD or Resistant)**

= Carbapenem

Lee et al. AAC 2015; 59(12).

Patient Case #2:

80 YO M with NKDA presents to your institution with complaints of abdominal pain, chills, and GI upset. Blood cultures are obtained, and the gram stain reveals gram-negative bacilli after 12 hours. The patient has been receiving piperacillin/tazobactam 3.375 grams IV every 6 hours. What recommendations would you make to his regimen?

A. Recommend cefepime 2 g IV q8hr
B. Keep the patient on piperacillin/tazobactam 3.375 g IV q6hr
C. Recommend increase to Piperacillin/tazobactam 4.5 g IV q6hr
D. Recommend switch to ertapenem 1 g IV q24
E. Recommend switch to meropenem 1g IV q8hr

	E. coli
Amikacan	<=16 Susceptible
Amp/sulbactam	>16 Resistant
Ampicillin	>16 Resistant
Aztreonam	>16 Resistant
Cefazolin	>16 Resistant
Cefepime	>16 Resistant
Ceftazidime-avibactam	<=4 Susceptible
Ceftolozone-tazobactam	<=2 Susceptible
Ceftriaxone	>32 Resistant
Ciprofloxacin	>2 Resistant
Ertapenem	<=0.5 Susceptible
Levofloxacin	>4 Resistant
Meropenem	<=1 Susceptible
Piperacillin-tazobactam	<=8 Susceptible
TMP/SMX	>2 Resistant

Assessment Question #2:

What is the best empiric antibiotic agent to treat the following rapid diagnostic result?

Gram stain: *Gram-negative bacilli in aerobic bottle after 8 hours of incubation*

Preliminary identification*: K. pneumoniae; Isolate is POSITIVE for KPC*

1. Ertapenem
2. Ceftazidime-avibactam
3. Cefiderocol
4. Ceftolozone-tazobactam

Carbapenem-Resistant Enterobacterales

Carbapenem-Resistant Enterobacterales (CRE)

Resistant to ≥1 carbapenem

Producing a carbapenemase enzyme (i.e. KPC)

- CRE account for > 13,000 nosocomial infections and contribute to > 1,000 deaths annually
- Carbapenemase-producing isolates account for approximately 35%-59% of CRE cases in the United States
  - Most common: *K. pneumoniae* carbapenemases (**KPCs**)
  - New Delhi metallo- β-lactamases (**NDMs**)
  - Verona integron-encoded metallo-β-lactamases (**VIMs**)
  - Imipenem-hydrolyzing metallo- β-lactamases (**IMPs**)
  - Oxacillinases (**OXA-48-like**)

Carbapenem-Resistant Enterobacterales (CRE)

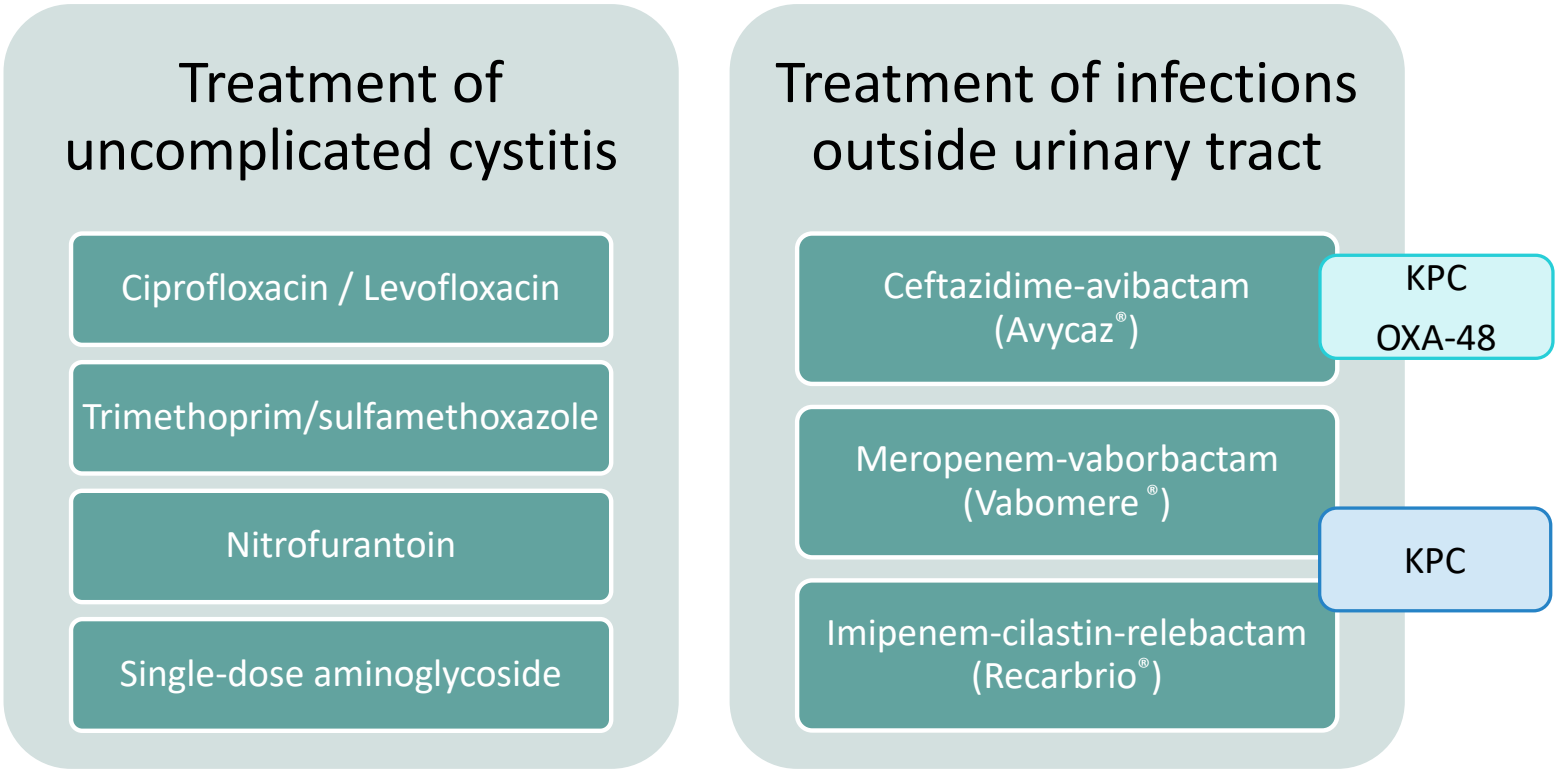
Ertapenem:	Meropenem:	Imipenem*:
MIC ≥ 2 mcg/mL	MIC ≥ 4 mcg/mL	MIC ≥ 4 mcg/mL

- There is the potential that the bacterial isolate is **resistant** to ertapenem but **susceptible** to meropenem
  - For uncomplicated cystitis → standard-infusion meropenem can be utilized
  - For complicated cystitis/pyelonephritis → extended-infusion meropenem
  - For infections outside the urinary tract → extended-infusion meropenem
    - Alternatives should be explored

*intrinsically not susceptible to imipenem (e.g., *Proteus spp., Morganella spp., Providencia spp*)

Tamma PD, et al. IDSA 2023; Version 3.0

CRE Treatment Options



Tamma PD, et al. IDSA 2023; Version 3.0

Metallo-β-lactamase (MBL) Producing Isolates

- Growing antimicrobial resistance threat
  - Renders all β-lactams, including carbapenems, ineffective
  - Aztreonam is not inactivated by MBLs

- MBLs comprise of the genes: **NDM**, **VIM**, and **IMP**

- Bacteremia due to carbapenem-resistant MBL-producing isolates is associated with > 30% mortality

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Combination Therapy for MBL-Producing Isolates

- Prospective observational study conducted at 3 hospitals in Greece and Italy from 2018 to 2019
- Objective:
  - Compare outcome of patients with MBL-producing Enterobacterales bloodstream infections with either ceftazidime-avibactam (CAZ-AVI) plus aztreonam (ATM) or other active antibiotics (OAAs)

CAZ-AVI 2.5 g IV every q8hr

PLUS

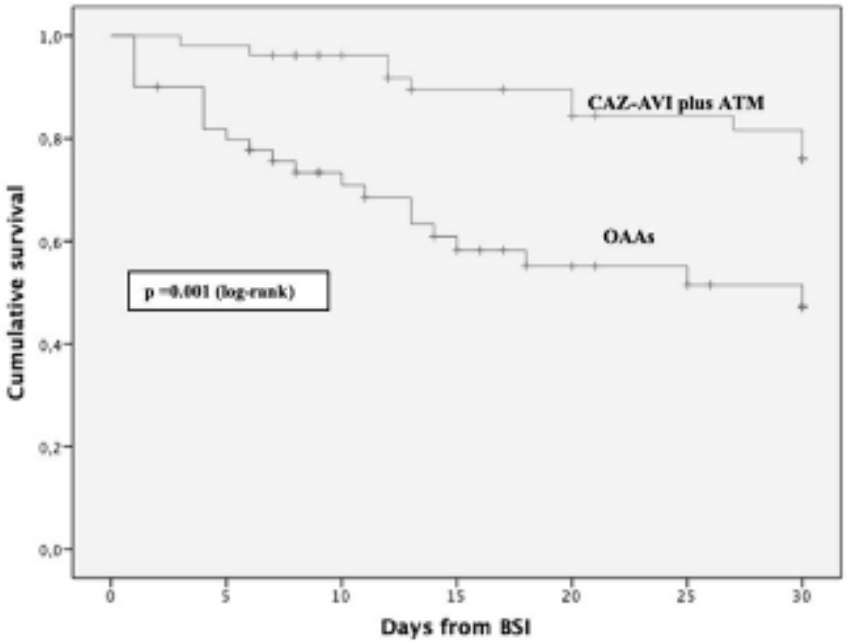
ATM 2 g IV q8hr

OR

- Colistin 9 million units IV, followed by 4.5 million units IV q 12hr
- Fosfomycin 4-6 mg IV every 6hr
- Tigecycline 100 mg IV q12hr
- Gentamicin 3-5 mg/kg IV q24hr
- Meropenem 2 g IV q8hr

Falcone M, et al. Clin Infect Dis. 2021 Jun 1;72(11):1871-1878.

Combination Therapy for MBL-Producing Isolates



Primary Outcome	CAZ-AVI + ATM (n=52)	OAAs (n=50)	p-value
30-day mortality	10 (19.2%)	22 (44%)	0.007
Secondary Outcomes			
Clinical failure at day 14	13 (25%)	26 (52%)	0.005
Drug-induced AKI	1 (1.9%)	10 (20%)	0.003

CAZ-AVI + ATM has a favorable impact on the outcome of patients with bloodstream infections caused by MBL-producing Enterobacterales

Falcone M, et al. Clin Infect Dis. 2021 Jun 1;72(11):1871-1878.

Patient Case #3:

57 YO M with end-stage renal disease s/p kidney transplant 2021 transferred from an outside hospital

- Presented with altered mental status, febrile (39.5°C), hypotension requiring vasopressors
- CTA/P: perinephric stranding; bladder wall thickening
- Empiric regimen from OSH: meropenem 1 g IV q12h

Microbiology:
Urine culture:
> 100,000 CFU/mL *Klebsiella pneumoniae*

Blood culture:
Klebsiella pneumoniae
Isolate positive for OXA-48

Primary team switches to meropenem-vaborbactam and calls for approval.
Is this appropriate?

Difficult-to-Treat Resistance: *Pseudomonas aeruginosa*

Difficult-to-Treat (DTR) *P. aeruginosa*

- 32,600 cases of MDR P. aeruginosa were identified in the US in 2017 per the CDC
  - ~ 2,700 deaths
- Resistance evolves through multiple complex resistance mechanisms

Multi-drug resistant (MDR) *P. aeruginosa*	Difficult-to-treat (DTR) *P. aeruginosa*
Non-susceptibility to at least one antibiotic in at least three antibiotic classes for which susceptibility is generally expected: ○ Penicillins ○ Cephalosporins ○ Fluoroquinolones ○ Aminoglycosides ○ Carbapenems	Non-susceptibility to ALL of the following: ○ Piperacillin-tazobactam ○ Ceftazidime ○ Cefepime ○ Aztreonam ○ Meropenem ○ Imipenem ○ Ciprofloxacin ○ Levofloxacin

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Carbapenem Resistance in *P. aeruginosa*

- β-lactamases
  - Derepression of chromosomal beta-lactamases (AmpC production)
  - Increased MICs can reflect increased beta-lactamase production
  - Carbapenemase production (less common in the U.S.)
    - Isolates are more likely to be multi-drug resistant
    - Metallo-beta-lactamases and KPC producers
- Reduced porin expression (OprD) = Imipenem resistance
  - Changes in OprD expression leading to reduced carbapenem influx
- Efflux pumps = reduced meropenem susceptibility (MexAB-OprM)

DTR *P. aeruginosa* Treatment

Treatment of Uncomplicated Cystitis

- Ceftolozane-tazobactam (Zerbaxa®)
- Ceftazidime-avibactam (Avycaz®)
- Imipenem-cilastatin relebectam (Recarbrio®)
- Cefiderocol (Fetroja®)
- Single-dose aminoglycoside

Treatment of Pyelonephritis & Infections Outside Urinary Tract

- Ceftolozane-tazobactam (Zerbaxa®) — NO CRE activity
- Ceftazidime-avibactam (Avycaz®)
- Imipenem-cilastatin relebectam (Recarbrio®)
- Cefiderocol (Fetroja®)

Tamma PD, et al. IDSA 2023; Version 3.0

DTR *P. aeruginosa* Treatment Regimens

Ceftazidime-avibactam (Avycaz®)	Ceftolozane-tazobactam (Zerbaxa®)	Imipenem-cilastatin relebectam (Recarbrio®)
FDA approval 2015 (cUTI, cIAI) ○ 2018: HAP/VAP indications Role in therapy = CRE infections (KPC and OXA-48 producers) • No activity against MBLs alone • No anaerobic coverage	FDA approval 2014 (cUTI, cIAI) Role in therapy = DTR Pseudomonas • No activity against CRE • No anaerobic coverage	FDA approval 2019 (cUTI, cIAI) Role in therapy = CRE infections (KPCs) • No activity against OXA-48 or MBLs

Avycaz (ceftazidime-avibactam) [prescribing information]. Madison (NJ): Allergan USA Inc.; Mar 2019.
Zerbaxa (ceftolozane-tazobactam) [prescribing information]. Lexington (MA): Cubist Pharmaceuticaals U.S. Dec 2014.
Recarbrio (imipenem-cilastatin relebectam) [prescribing informtation]. Rahway (NJ): Merck Sharp & Dohme LLC; May 2022.

Zerbaxa® for DTR *P. aeruginosa*

Study Design

- Retrospective, **multicenter, observational cohort study** with data from 2008-2010

Population

- Patients treated for an infection due to MDR **or** XDR *P. aeruginosa* for ≥48 hours
- Those with resistant isolates to study drugs were excluded

Intervention

- Cef/tazo 1.5-3 g IV q8h
- IV aminoglycoside OR IV polymyxin

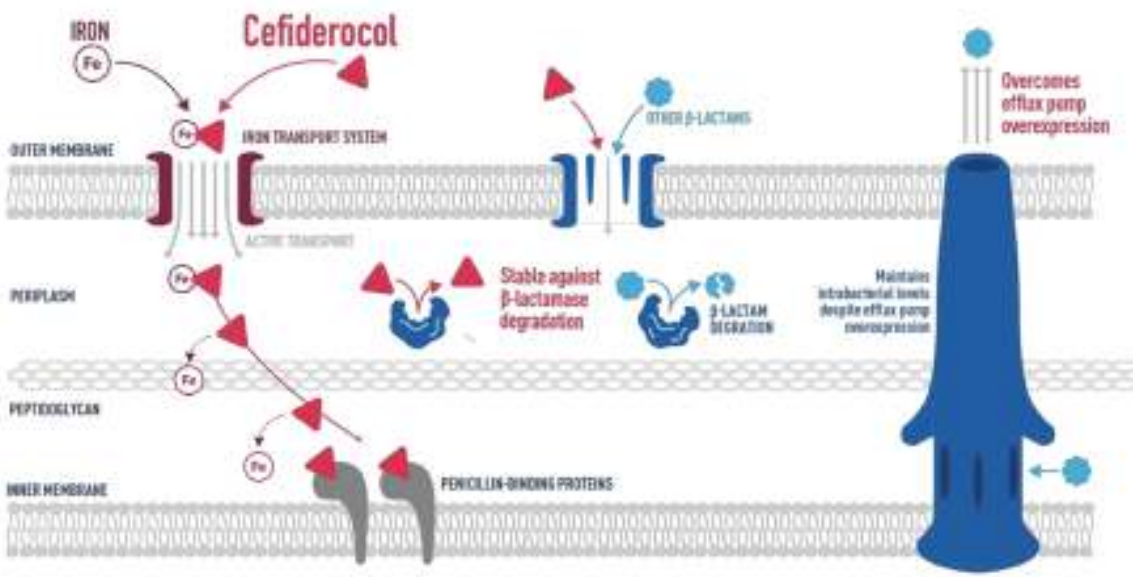
XDR = extensively drug-resistant

Outcome	Ceftol/Tazo (n=100)	AG or polymyxin (n=100)	P-value	OR 95% CI
Clinical cure	81	61	0.02	2.72 (1.43-5.17)
AKI	6	34	<0.001	0.12 (0.05-0.31)
In-hospital mortality	20	25	0.40	0.75 (0.38-1.46)

Ceftolozane/tazobactam demonstrated higher rates of clinical cure and lower rates of AKI. This agent should be given over AG or polymyxin based regimens

Cefiderocol (Fetroja®)

- Unique cephalosporin in that it functions as a siderophore
- Overcomes three main resistance mechanisms:
  - Enzymatic hydrolysis (Ambler class A, B, and C)
  - Porin channel mutations
  - Efflux overproduction
- Recommended to be reserved for non-fermenting Gram-negative pathogens
  - In vitro activity – CRE including MBLs, DTR *P. aeruginosa*, CRAB, *S. maltophilia*



Drugs. 2019;79(3):271-289.
Fetroja (cefiderocol) [prescribing information]. Florham Park (NJ): Shionogi Inc; 2020.

Cefiderocol Clinical Data

CREDIBLE-CR STUDY

- Randomized, open-label, phase 3 trial
- Adult patients with a serious carbapenem-resistant Gram-negative infection (n=152)
  - ~ 25% *P. aeruginosa*
  - ~ 45% CRAB
- Randomized to cefiderocol or best available therapy (up to 3 antibiotics)
- Overall similar clinical & microbiological efficacy
  - Clinical cure: 50% cefiderocol group vs. 53% best available group for HAP, VAP
  - Micro cure: 53% cefiderocol vs. 20% best available group

APEKS-NP STUDY

- Randomized, double-blind, non-inferiority study
- Adult patients with Gram-negative HAP/VAP (n=292)
  - ~ 1% CR-*P. aeruginosa*
  - ~10% CRAB
- Randomized to cefiderocol or meropenem 2 g IV q8h 3-hour infusion
- Cefiderocol was shown to be non-inferior: similar all-cause mortality at day 14
  - Similar mortality among those with CR-*P. aeruginosa* and CRAB infections

Bassetti M, et al. Lancet Infect Dis 2021; 21(2): 226-40.
Wunderink RG, et al. Lancet Infect Dis 2021; 21: 213-25.

Assessment Question #3:

True/False: Ceftolozone-tazobactam has activity against KPC-producing organisms.

True

False

Carbapenem-Resistant *Acinetobacter baumannii*

Carbapenem-Resistant *A. baumannii* (CRAB)

- Nearly all carbapenem-resistant *Acinetobacter* infections happen in patients who recently received care in a healthcare facility
  - Pose clinical challenge: Infection vs colonization
- *Acinetobacter* is resistant to many antibiotics
  - Resistance to carbapenems further reduces treatment options

Limits drug uptake	Drug target modification	Drug inactivation	Efflux
• Porin channels (CarO)	• PBP alterations	• Carbapenemases (OXA 23, OXA 58) • Aminoglycoside modifying enymes	• Overexpression

Tamma PD, et al. IDSA 2023. Version 3.0
Perez F, et al. AAC. 2007 Oct; 51(10):3471-84.
Watkins RR. Exp Rev Antiinfect Ther. 2018; 16(2):89-110.

CRAB Treatment

- There is no clear "standard of care" antibiotic treatment regimen for CRAB infections given the limited clinical data

- For the treatment of moderate to severe infections, combination therapy with **at least two active agents** is suggested until clinical improvement

High-dose ampicillin-sulbactam
(6-9 grams per day sulbactam component)

At least one other agent:
Polymyxin, tigecycline, minocycline, cefiderocol

Tamma PD, et al. IDSA 2023. Version 3.0

Sulbactam/Durlobactam (Xacduro®)

- Novel β-lactam / β-lactamase combination
- Activity against *Acinetobacter*
  - Sulbactam -> direct antibacterial activity
  - Durlobactam -> activity against β-lactamases, including OXA-type carbapenemases
    - Restores activity of sulbactam against multi-drug resistant *Acinetobacter* in-vitro
- Dosing:
  - 1 gram sulbactam + 1 gram durlobactam IV administered over 3 hours
  - Lower dosing of sulbactam component compared to ampicillin/sulbactam recommendation for CRAB treatment
    - Durlobactam inhibiting β-lactamases allows more sulbactam to reach PBPs

Xacduro (sulbactam-durlobactam) [prescribing information]. Waltham (MA): La Jolla Pharmaceutical Company; May 2023.

Sulbactam/Durlobactam Clinical Data

Study design:

- Phase 3, pathogen-specific, randomized, noninferiority clinical trial
- Non-inferiority margin: 20%

Population

- Part A: Adults with HAP, VAP, ventilated pneumonia or bloodstream infections caused by ABC
- Part B: Adults with ABC infections resistant, or clinical failure, or known intolerance to colistin or polymyxin B

Intervention

- Sulbactam-durlobactam vs. Colistin with imipenem-cilastatin as background therapy

	Sulbactam-durlobactam, n/N(%)	Colistin, n/N (%)	Treatment difference, %(95% CI)
28-day all-cause mortality	12/63 (19.0%)	20/62 (32.3%)	-13.2 (-30.0 to 3.5)
	Part A: sulbactam-durlobactam (n=63)	**Part A: colistin (n=62)**	**Part B: sulbactam-durlobactam (n=28)**
Clinical cure rates	39 (62%)	25 (40%)	20 (71%)
Nephrotoxicity	0	8 (9%)	1 (4%)
Any TEAE	80 (88%)	81 (94%)	24 (86%)

Kaye KS, et al. Lancet Infect Dis. 2023;23(9):1072-84.

Patient Case #4:

35 YO M with paraplegia secondary to gun shot wound (GSW) ~4 years ago presents from their long-term care facility with increased work of breathing requiring ventilator support, increased respiratory secretions, and fever (38.5°C). Patient with NKDA.

Based on the patient's respiratory culture, what regimen would you recommend for monotherapy?

Resp Cx:	Acinetobacter baumanni complex
Amp/sulbactam	Susceptible
Levofloxacin	Susceptible
Meropenem	Susceptible
Piperacillin/tazobactam	Resistant
Trimethoprim/Sulfamethoxazole	Resistant

A. Meropenem

B. Ampicillin-sulbactam

C. Minocycline

D. Cefiderocol

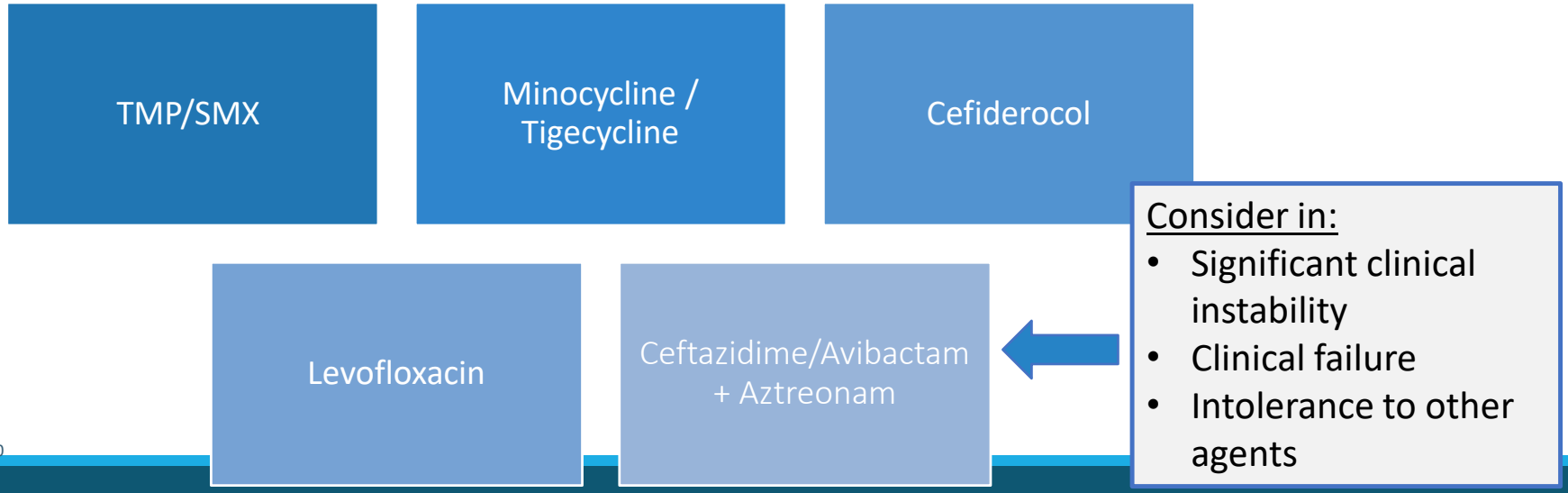
Stenotrophomonas maltophilia

S. maltophilia

- Infection rate has been increasing
  - Increased immunocompromised patients & wide use of antimicrobials
  - Pose clinical challenge similar to CRAB
- Estimated to be the most common carbapenem-resistant Gram-negative bacterial cause of bacteremia in the US
- Expresses multiple resistance mechanisms
  - Intrinsically resistant to β-lactams (intrinsic MBL (L1) and inducible β-lactamase (L2))
  - Intrinsically resistant to aminoglycosides
  - Efflux pumps
    - Decreased susceptibility to TMP/SMX, tetracyclines, and fluoroquinolones

S. maltophilia Treatment

- Combination therapy with **at least 2 active agents**, in cases of moderate-severe disease until at least clinical improvement is observed
- Sequential approach of initiating TMP/SMX and adding a second agent if an appropriate clinical response is not observed



Tamma PD, et al. IDSA 2023. Version 3.0

S. maltophilia Treatment Considerations

- TMP/SMX has been the drug of choice for *S. maltophilia* infections
  - Long-standing clinical experience

- Combination until clinical stability?
  - Meta-analysis:
    - Decreased mortality rates in HAP with monotherapy (HR 1.42) compared to combination therapy
    - No significant difference in mortality rates in bacteremia between monotherapy and combination therapy (HR 0.76)

- Levofloxacin monotherapy should be avoided?
  - Retrospective review of lab-confirmed *S. maltophilia* in blood & respiratory cultures
    - Similar mortality risk with levofloxacin monotherapy compared to TMP/SMX monotherapy (OR 0.76; 95% CI, 0.58-1.01; p=0.06)

Tamma PD, et al. IDSA 203. Version 3.0
Sarzynski SH, et al. Open Forum Infect Dis. 2022 Jan 17;9(2):ofab644
Prawang A, et al. Antibiotics (Basel). 2022 Dec 9;11(12):1788.

S. maltophilia Treatment Considerations

- Minocycline
  - Treatment limitations: rapid tissue distribution following administration
    - Limited concentrations in the urine/serum
  - Clinical data:
    - Compared to TMP/SMX, monotherapy minocycline treatment failure did not differ significantly (p=0.67)

- Other agents (Cefiderocol; Ceftazidime-Avibactam + Aztreonam)
  - Reserve for serious infections
  - Last-line agents

Tamma PD, et al. IDSA 2023. Version 3.0
Hand E, et al. J Antimicrob Chemother 2016; 71(4): 1071-5.

Patient Case #5:

31 YO M with PMH asthma, uncontrolled T2DM (A1C ~11%), and morbid obesity presented with flu-like symptom complaints & respiratory distress. He required in t cr

Blood Culture:
Gram stain: *Gram-negative bacilli in aerobic bottle after 8 hours of incubation.*

Pseudomonas aeruginosa
Preliminary identification *performed by ePLEX. Isolate is POSITIVE for VIM*

P tions re

A had increased WOB, and WBC 25.4

-> Initiated on meropenem 1 g IV q8hr & vancomycin 15 mg/kg IV q12h

Patient Case #5 Continued:

Blood Culture:
Pseudomonas aeruginosa
Preliminary identification *performed by ePLEX.*
Isolate is POSITIVE for VIM

Based on the preliminary identification and isolated resistance gene, how would you adjust this patient's antimicrobials?

A. Adjust to ceftazidime-avibactam
B. Adjust to ceftazidime-avibactam + aztreonam
C. Adjust to meropenem-vaborbactam
D. Adjust to piperacillin/tazobactam

Expected Activity Table

Agent	KPC	NDM	OXa-48	CR-*Pseudomonas*	CRAB	*S. maltophilia*
Aztreonam – avibactam						
Cefiderocol						
Ceftazidime – avibactam						
Ceftolozone – Tazobactam						
Imipenem – cilastatin relebactam						
Meropenem – vaborbactam						
Polymyxin B						
Sulbactam - durlobactam						

Tamma PD, et al. JPIDS. 2019;8(3):251–60.

Conclusion

Gram-negative resistance is a rapidly growing global health threat, where the need for novel antimicrobial agents to be developed continues

Organisms may exhibit multiple mechanisms of resistance through limiting drug uptake, modification of drug targets, drug inactivation, and creation of efflux pumps

The treatment of resistant Gram-negative infections depends on the specific organism isolated and the mechanisms of resistance (if detected)

Patient specific factors, clinical response to therapy, and antimicrobial susceptibility data, along with available clinical trial data should be utilized to help guide empiric and definitive therapies

NYSCHP | New York State Council of Health-system Pharmacists

When Bacteria Fight Back:

A Review of Gram-negative Resistance

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