Resistance is Rising: Overview of Updated Guidance on Resistant Gram-negative Infections

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Objectives – Pharmacists & Nurses

- Recall characteristics of resistant gram-negative organisms
- Identify key changes in the 2024 updated guidance document from the Infectious Disease Society of America (IDSA) for the treatment resistant gram-negative infections
- Recognize an evidence-based treatment regimen for a resistant gram-negative infection that aligns with the 2024 updated guidance from IDSA

Objectives – Pharmacy Technicians

- Recall factors that contribute to antibiotic resistance
- Identify resistance mechanisms that gram-negative organisms can develop
- Recognize an antibiotic used for the treatment of resistant gram-negative infections

Abbreviations

ADCs	*Acinetobacter baumannii*-derived cephalosporinases	**IV / PO**	Intravenous / By mouth
AmpC-E	AmpC β-lactamase producing Enterobacterales	**KPCs**	*Klebsiella pneumoniae* carbapenemases
AMP	Antimicrobial management program	**MBLs**	Metallo-β-lactamases
AMR	Antimicrobial-resistant	**MDR**	Multidrug resistant
CLSI	Clinical and Laboratory Standards Institute	**NDMs**	New Delhi metallo-β-lactamases
CRAB	Carbapenem-resistant *Acinetobacter baumannii*	**NF / NFR**	Non-formulary / Non-formulary restricted
CRE	Carbapenem-resistant Enterobacterales	**OXA**	Oxacillinases
cUTI	Complicated urinary tract infections	**PBPs**	Penicillin-binding proteins
DTR	Difficult-to-treat resistance	**PD / PK**	Pharmacodynamic / Pharmacokinetic
ESBL-E	Extended-spectrum β-lactamase producing Enterobacterales	**Q _ H**	Every _ Hours
FR	Formulary restricted	**R / I / S**	Resistant / Intermediate / Sensitive
FDA	Food and Drug Administration	**rRNA**	Ribosomal ribonucleic acid
IDSA	Infectious Diseases Society of America	**TMP-SMX**	Trimethoprim-sulfamethoxazole
IMPs	Imipenem-hydrolyzing metallo-β-lactamases	**VIMs**	Verona integron-encoded metallo-β-lactamases

Background

- Antimicrobial-resistant (AMR) infections are a global crisis:
  - Worldwide in 2019: ~1.3 million deaths estimated to be from AMR pathogens
  - In the U.S. from 2012-2017: >2.8 million infections and >35,000 deaths annually from AMR pathogens
- The Infectious Diseases Society of America (IDSA) published an updated guidance document on the treatment of antimicrobial resistant gram-negative infections in July 2024
  - New treatment recommendations / guidance
  - Newly Food and Drug Administration (FDA)-approved medications

This presentation will focus on HCA Healthcare formulary agents

Overview of Infections

- Extended-spectrum β-lactamase producing Enterobacterales (ESBL-E)
- AmpC β-lactamase producing Enterobacterales (AmpC-E)
- **Carbapenem-resistant Enterobacterales (CRE)**
- ***Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*)**
- **Carbapenem-resistant *Acinetobacter baumannii* (CRAB)**
- ***Stenotrophomonas maltophilia***

For these infections, an Infectious Diseases consult is recommended

CRE Infections

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CRE Infections

- CRE definition:
  - Resistance to at least 1 carbapenem (i.e., ertapenem, meropenem, imipenem, doripenem) or producing a carbapenemase enzyme
  - Resistance to at least 1 carbapenem other than imipenem is required for bacteria intrinsically less susceptible to imipenem (i.e., *Proteus* spp., *Morganella* spp., *Providencia* spp.)
- Carbapenemases:
  - *K. pneumoniae* carbapenemases (KPCs) – most common in the U.S.
  - Oxacillinases (i.e., OXA-48-like)
  - Metallo-β-lactamases (MBLs)
    - New Delhi metallo-β-lactamases (NDMs)
    - Verona integron-encoded metallo-β-lactamases (VIMs)
    - Imipenem-hydrolyzing metallo-β-lactamases (IMPs)

CRE Infections – Guidance Updates

MBLs

Acknowledges ↑ prevalence in the U.S.

Discusses CLSI's endorsed method (broth disk elution method) to test for activity of the combination of ceftazidime-avibactam + aztreonam

Dosing suggestion for ceftazidime-avibactam + aztreonam for MBL:

ceftazidime-avibactam	PLUS	aztreonam
2.5 g IV Q8H, infused over 3 hours	*administer simultaneously via Y-site administration*	2 g IV Q8H, infused over 3 hours

CRE Infections – Uncomplicated Cystitis & Pyelonephritis or cUTI

- Preferred antibiotics*:
  - **Nitrofurantoin^**
  - **Trimethoprim-sulfamethoxazole (TMP-SMX)**
  - **Ciprofloxacin**
  - **Levofloxacin**
- Alternative antibiotics:
  - Aminoglycoside
    - Single dose^
    - Once daily dosing
  - Meropenem-vaborbactam
  - Ceftazidime-avibactam
  - Imipenem-cilastatin-relebactam [NF]
  - Cefiderocol [NFR]
  - Oral fosfomycin (for *E. coli* only)^

^uncomplicated cystitis only

*if susceptibility is demonstrated

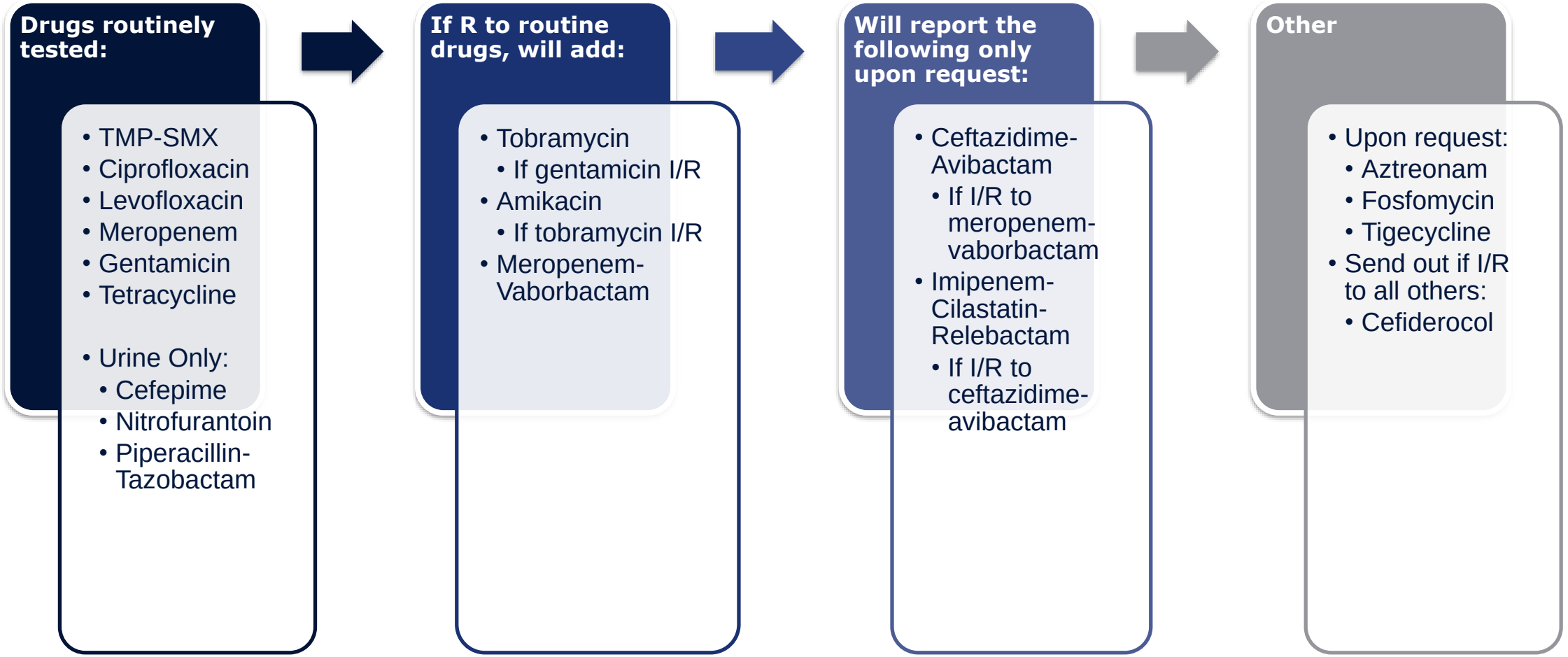
CRE Infections – Outside of the Urinary Tract

NOT Carbapenemase-Producing	
R to ONLY ertapenem	**R to ALL carbapenems**
• **Extended-infusion meropenem** • Extended-infusion imipenem-cilastatin	• **Meropenem-vaborbactam** • Ceftazidime-avibactam • Imipenem-cilastatin-relebactam

CRE Infections – Outside of the Urinary Tract

Carbapenemase-Producing	
KPC-producing	
Preferred antibiotics: • **Meropenem-vaborbactam** • Ceftazidime-avibactam • Imipenem-cilastatin-relebactam	**Alternative antibiotic:** • Cefiderocol
OXA-48-like-producing	
Preferred antibiotic: • **Ceftazidime-avibactam**	**Alternative antibiotic:** • Cefiderocol
NDM or other MBL-producing	
Preferred antibiotics: • **Ceftazidime-avibactam + aztreonam** • Cefiderocol	

HCA Healthcare Standardized Cascade for Carbapenem-Resistant Enterobacterales (CRE)



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Dosing of Antimicrobials

Nitrofurantoin	**Cystitis:** 100 mg PO Q12H
TMP-SMX	**Cystitis:** 160 mg (TMP component) IV/PO Q12H **All other infections:** 8-12 mg/kg/day (TMP component) IV/PO divided Q8-12H (consider max: 960 mg TMP per day)
Levofloxacin	750 mg IV/PO Q24H
Ciprofloxacin	**Cystitis:** 400 mg IV Q12H or 500 mg PO Q12H **All other infections:** 400 mg IV Q8H or 750 mg PO Q12H
Amikacin	For dosing, refer to the AMP Aminoglycoside PK/PD Guidance
Tobramycin	For dosing, refer to the AMP Aminoglycoside PK/PD Guidance
Gentamicin	For dosing, refer to the AMP Aminoglycoside PK/PD Guidance
Fosfomycin	**Cystitis:** 3 g PO as a single dose
Meropenem	For extended-infusion dosing, refer to the AMP Meropenem PK/PD Guidance

AMP: antimicrobial management program; IV: intravenous; PD: pharmacodynamic; PK: pharmacokinetic; PO: by mouth; Q _ H: every _ hour

Meropenem-Vaborbactam

- Formulary status: Non-formulary restricted (NFR) or formulary restricted (FR)
- Carbapenem + β-lactamase inhibitor
- Time-dependent, bactericidal
- Dosing: 4 g IV Q8H, infused over 3 hours

Adverse events	Contraindications/Precautions	Monitoring
• Headache (9%)	• Hypersensitivity to drug components or anaphylaxis with other β-lactams	• Renal function

Ceftazidime-Avibactam

- Formulary status: Formulary restricted (FR)
- Cephalosporin + β-lactamase inhibitor
- Time-dependent, bactericidal
- Dosing: 2.5 g IV Q8H, infused over 3 hours

Adverse events	Contraindications/Precautions	Monitoring
• Constipation (2-10%) • Diarrhea (3-8%) • Nausea (3-7%)	• Hypersensitivity to drug components and other cephalosporins	• Renal function • Blood urea nitrogen • Complete blood count

Resistant *Pseudomonas aeruginosa* Infections

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Resistant *P. aeruginosa* Infections

- Multidrug resistant (MDR) *P. aeruginosa* definition:
  - Resistance to at least 1 antibiotic in at least 3 antibiotic classes for which susceptibility is generally expected (i.e., penicillins, cephalosporins, fluoroquinolones, aminoglycosides and carbapenems)
- Difficult-to-treat resistance (DTR) *P. aeruginosa* definition:
  - Resistance to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin
- Resistance mechanisms:
  - ↓ expression of membrane porins
  - ↑ production of or amino acid substitutions within pseudomonal AmpC enzymes
  - Upregulation of efflux pumps
  - PBP target mutations
  - Presence of ESBLs (i.e., *bla*OXA-10)

DTR *P. aeruginosa* Infections – Guidance Updates

P. aeruginosa that is carbapenem-R but susceptible to traditional β-lactams (i.e., cefepime):

- Administer β-lactams as high-dose extended-infusions
- **NEW:** repeat susceptibility testing of traditional β-lactams is <u>not</u> needed to confirm susceptibility

Alternative treatment options for pyelonephritis or cUTI:

- **NEW:** once-daily amikacin or tobramycin

DTR *P. aeruginosa* Infections – Uncomplicated Cystitis & Pyelonephritis or cUTI

- Preferred antibiotics:
  - **Ceftolozane-tazobactam**
  - Ceftazidime-avibactam
  - Imipenem-cilastatin-relebactam
  - Cefiderocol
- Alternative antibiotics:
  - **Amikacin**
    - Single dose^
    - Once daily dosing
  - Tobramycin
    - Single dose^
    - Once daily dosing

^uncomplicated cystitis only

DTR *P. aeruginosa* Infections – Outside of the Urinary Tract

- Preferred antibiotics:
  - **Ceftolozane-tazobactam**
  - Ceftazidime-avibactam
  - Imipenem-cilastatin-relebactam
- Alternative antibiotics:
  - Cefiderocol (preferred if MBL present)

HCA Healthcare Standardized Cascade for *Pseudomonas aeruginosa*

Drugs routinely tested:

- Cefepime
- Ciprofloxacin
- Levofloxacin
- Piperacillin-Tazobactam

If R to routine drugs, will add:

- Meropenem
  - If I/R to cefepime or piperacillin-tazobactam
- Tobramycin
  - If I/R to cefepime or piperacillin-tazobactam
- Amikacin
  - If tobramycin I/R (urine)
- Aztreonam
  - If meropenem I/R
- Ceftazidime
  - If I/R to meropenem
- Ceftolozane-Tazobactam
  - If I/R to ceftazidime
- Ceftazidime-Avibactam
  - If I/R to ceftolozane-tazobactam
- Imipenem-Cilastatin-Relebactam
  - If I/R to ceftazidime-avibactam

If applicable, will send out to reference lab:

- Cefiderocol
  - If I/R to ceftolozane-tazobactam & ceftazidime-avibactam

Dosing of Antimicrobials

Ceftolozane-Tazobactam	**Uncomplicated Cystitis:** 1.5 g IV Q8H, infused over 1 hours **All other infections:** 3 g IV Q8H, infused over 3 hours
Ceftazidime-Avibactam	2.5 g IV Q8H, infused over 3 hours
Imipenem-Cilastatin-Relebactam	1.25 g IV Q6H, infused over 30 minutes
Cefiderocol	2 g IV Q8H, infused over 3 hours
Amikacin	For dosing, refer to the AMP Aminoglycoside PK/PD Guidance
Tobramycin	For dosing, refer to the AMP Aminoglycoside PK/PD Guidance

AMP: antimicrobial management program; IV: intravenous; PD: pharmacodynamic; PK: pharmacokinetic; Q _ H: every _ hour

Ceftolozane-Tazobactam

- Formulary status: Non-formulary restricted (NFR) or formulary restricted (FR)
- Cephalosporin + β-lactamase inhibitor
- Time-dependent, bactericidal
- Dosing:
  - Uncomplicated cystitis – 1.5 g IV Q8H, infused over 1 hour
  - Other infections – 3 g IV Q8H, infused over 3 hours

Adverse events	Contraindications/Precautions	Monitoring
• Diarrhea (6-17%) • Leukopenia (4-8%) • Nausea (3-8%) • Headache (3-6%)	• Hypersensitivity to components or other β-lactams	• Renal function • Blood urea nitrogen

Imipenem-Cilastatin-Relebactam

- Formulary status: Non-formulary restricted (NFR)
- Carbapenem + β-lactamase inhibitor
- Time-dependent, bactericidal
- Dosing: 1.25 mg IV Q6H, infused over 30 minutes

Adverse events	Contraindications/Precautions	Monitoring
• Elevated hepatic enzymes (10-12%) • Anemia (11%) • Hypokalemia (8%) • Diarrhea (8%) • Hyponatremia (6%)	• Hypersensitivity to drug components	• Renal function

Cefiderocol

- Formulary status: Non-formulary restricted (NFR)
- Cephalosporin
- Time-dependent, bactericidal
- Dosing: 2 g IV Q8H, infused over 3 hours

Adverse events	Contraindications/Precautions	Monitoring
• Elevated hepatic enzymes (2-16%) • Hypokalemia (2-11%) • Diarrhea (4-9%) • Hypomagnesemia (5%)	• Hypersensitivity to other β-lactams	• Renal function • Blood urea nitrogen

Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) Infections

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CRAB Infections

- Resistance mechanisms:
  - β-lactam resistance (including carbapenems):
    - Presence of OXA carbapenemases
    - Presence of serine β-lactamases [*A. baumannii*-derived cephalosporinases (ADCs)]
  - Sulbactam resistance:
    - Presence of OXA carbapenemases
    - Presence of serine β-lactamases [*A. baumannii*-derived cephalosporinases (ADCs)]
    - Presence of mutations targeting PBPs (PBP1a/1b and PBP3)
  - Aminoglycoside resistance:
    - Presence of aminoglycoside modifying enzymes or 16S rRNA methyltransferases
  - Fluoroquinolone resistance:
    - Presence of mutations in the chromosomally-encoded quinolone resistance determining regions

CRAB Infections – Guidance Updates

Preferred agent for the treatment of CRAB infections

- **NEW:** sulbactam-durlobactam + a carbapenem

Alternative regimen

- High-dose ampicillin-sulbactam + at least 1 other agent

CRAB Infections

Preferred antibiotics:

Moderate-Severe Infections

Sulbactam-durlobactam + meropenem

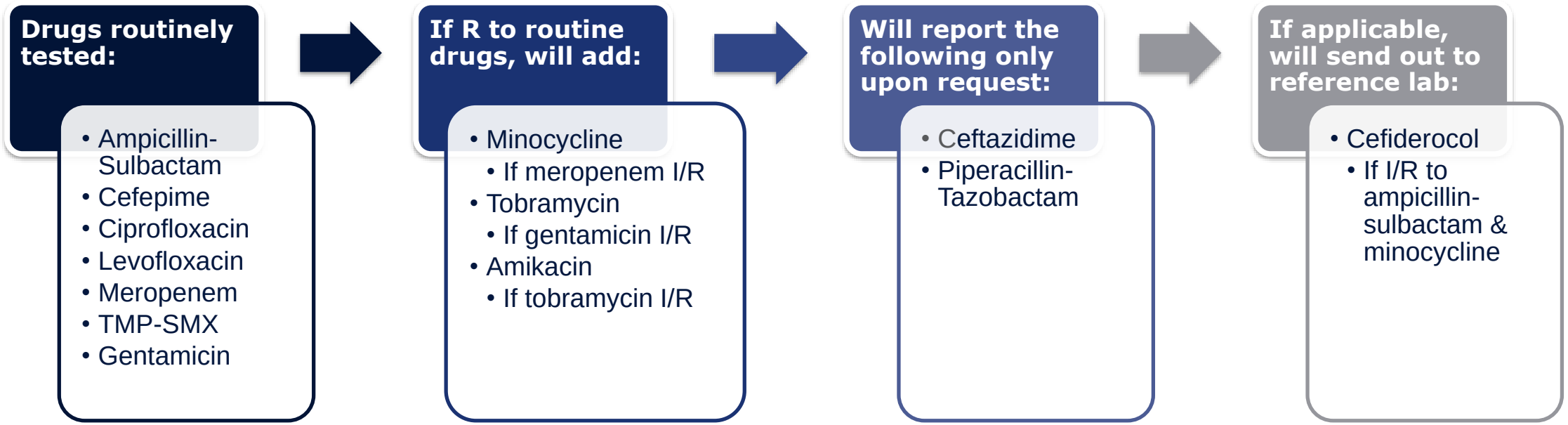
Alternative antibiotics:

Mild-Moderate Infections

High-dose ampicillin-sulbactam + at least one of the following:

- **Minocycline (oral preferred)**
- Cefiderocol
- Polymyxin B
- Tigecycline [NF]

HCA Healthcare Standardized Cascade for *Acinetobacter baumannii*



Dosing of Antimicrobials

Meropenem	For dosing, refer to the AMP Meropenem PK/PD Guidance
High-Dose Ampicillin-Sulbactam	**Total daily dose of 6-9 g of sulbactam** • 9 g (6 g ampicillin, 3 g sulbactam) IV Q8H, infused over 4 hours • 27 g (18 g ampicillin, 9 g sulbactam) IV as a continuous infusion • 3 g (2 g ampicillin, 1 g sulbactam) IV Q4H, infused over 30 minutes
Minocycline	200 mg IV/PO Q12H
Cefiderocol	2 g IV Q8H, infused over 3 hours
Tigecycline [NF]	200 mg IV as a single dose, then 100 mg IV Q12H
Polymyxin B [FR]	Refer to International Consensus Guidelines for the Optimal Use of the Polymyxins

AMP: antimicrobial management program; IV: intravenous; PD: pharmacodynamic; PK: pharmacokinetic; PO: by mouth; Q _ H: every _ hours

Sulbactam-Durlobactam

- Formulary status: Non-formulary restricted (NFR)
- β-lactamase inhibitor (antibacterial) + β-lactamase inhibitor
- Time-dependent, bactericidal
- Dosing: 2 g (total) IV Q6H, infused over 3 hours

Adverse events	Contraindications/Precautions	Monitoring
• Elevated hepatic enzymes (19%) • Diarrhea (17%) • Anemia (13%) • Hypokalemia (12%)	• Hypersensitivity to drug components or other β-lactams	• Renal function

Stenotrophomonas maltophilia Infections

Resistance is Rising

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Stenotrophomonas maltophilia Infections

- Aerobic, glucose non-fermenting, gram-negative bacillus that is ubiquitous in water environments
- β-lactam resistance:
  - L1 MBL and L2 serine β-lactamases
    - L1 hydrolyzes penicillins, cephalosporins, and carbapenems (but not aztreonam)
    - L2 hydrolyzes extended-spectrum cephalosporins and aztreonam
- Aminoglycoside resistance:
  - Intrinsic resistance via chromosomal aminoglycoside acetyl transferase enzymes
- TMP-SMX, tetracyclines, and fluoroquinolone resistance:
  - Can accumulate multidrug efflux pumps
  - Chromosomal Sm*qnr* genes (further reduces fluoroquinolone effectiveness)

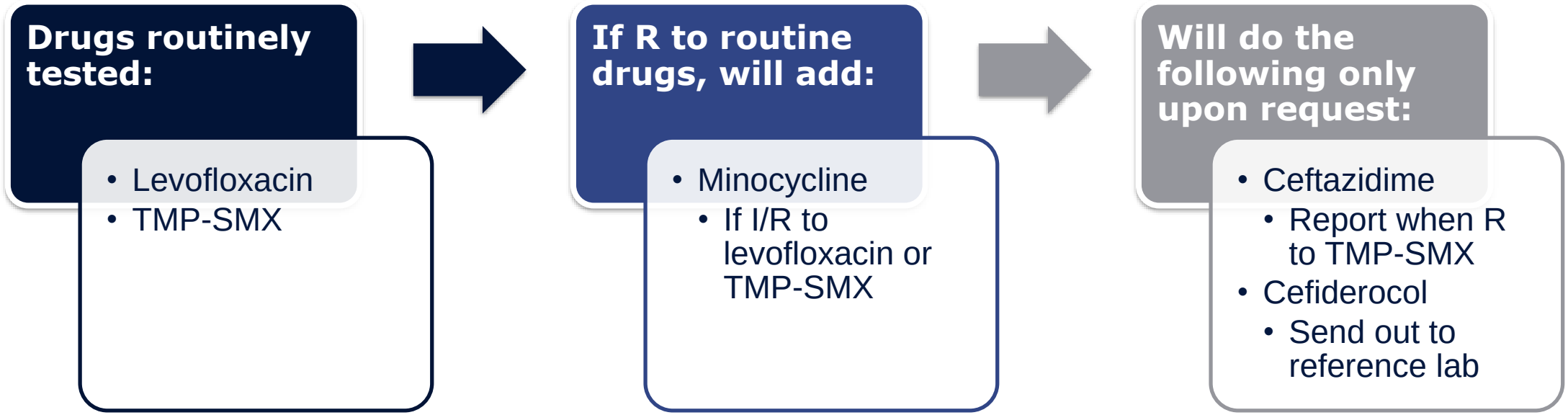
Stenotrophomonas maltophilia Infections – Guidance Updates

Agents listed in order of preference	Cefiderocol + a second agent
	Ceftazidime-avibactam + aztreonam
	Minocycline + a second agent
	TMP-SMX + a second agent
	Levofloxacin + a second agent
Discusses CLSI's endorsed method (broth disk elution method) to test for activity of the combination of ceftazidime-avibactam + aztreonam	
Tigecycline – removed as a component of combination therapy	
CLSI advises against testing ceftazidime for *maltophilia* infections	

Stenotrophomonas maltophilia Infections

Preferred antibiotics:	
Use of 2 of the following: • **Levofloxacin** • **TMP-SMX** • Minocycline (oral preferred) • Cefiderocol	Ceftazidime-avibactam + aztreonam

HCA Healthcare Standardized Cascade for *Stenotrophomonas maltophilia*



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Dosing of Antimicrobials

Levofloxacin	750 mg IV/PO Q24H
TMP-SMX	**Cystitis:** 160 mg (TMP component) IV/PO Q12H **All other infections:** 8-12 mg/kg/day (TMP component) IV/PO divided Q8-12H (consider max: 960 mg TMP per day)
Minocycline	200 mg IV/PO Q12H
Cefiderocol	2 g IV Q8H, infused over 3 hours
Ceftazidime-Avibactam	2.5 g IV Q8H, infused over 3 hours
Aztreonam	2 g IV Q6-8H (Q6H dosing preferred if possible), infused over 3 hours

AMP: antimicrobial management program; IV: intravenous; PD: pharmacodynamic; PK: pharmacokinetic; PO: by mouth; Q _ H: every _ hour

Summary

Antimicrobial Spectrum of Activity
Extended-Spectrum Antibiotics

	Ceftolozane-Tazobactam	Ceftazidime-Avibactam	Meropenem-Vaborbactam	Imipenem-Cilastatin-Relebactam	Cefiderocol	Sulbactam-Durlobactam
CRE	✘	✓	✓	✓	✓	✘
KPC	✘	✓	✓	✓	✓	✘
OXA-48	±	✓	✘	✘	✓	✘
MBL	✘	✓ (+) aztreonam	✘	✘	✓	✘
P. aeruginosa	✓	✓	✓	✓	✓	✘
DTR	✓	✓	✘	✓	✓	✘
A. baumannii	✘	±	✓	✓	✓	✓
CRAB	✘	✘	✘	✘	✓	✓
S. maltophilia	✘	✓ (+) aztreonam	✘	✘	✓	✘

■ HCA Preferred ✘ Resistant ± Variable activity ✓ Susceptible

Conclusion

- Resistant gram-negative infections are becoming more prevalent
- Refer to the most updated IDSA guidance document for an outline of general treatment recommendations
- Recommend making patient-specific treatment plans based on susceptibility results and formulary and/or insurance coverage

Question 1

Which of the following is TRUE regarding how antibiotic resistance can be developed?

a) Using the narrowest spectrum agent that is susceptible to treat an infection

b) Appropriately treating and completing a course of antibiotics

c) Using a broad-spectrum antibiotic unnecessarily for an extended duration of time

d) Using guideline-directed treatment protocols to ensure appropriate and effective use of antibiotics

Question 2

Which of the following is a resistant gram-negative organism?

a) Methicillin-resistant *Staphylococcus aureus* (MRSA)

b) Vancomycin-resistant *Enterococcus faecium* (VRE)

c) Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

d) Methicillin-resistant *Staphylococcus epidermidis* (MRSE)

Question 3

Which of the following is the HCA Healthcare PREFERRED treatment for a patient determined to have an infection caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB)?

a) Sulbactam-durlobactam 2 g IV Q6H + ampicillin-sulbactam 9 g IV Q8H

b) Sulbactam-durlobactam 2 g IV Q6H + meropenem 500 mg IV Q6H

c) Ampicillin-sulbactam 9 g IV Q8H + meropenem 2 g IV Q8H

d) Meropenem 2 g IV Q8H + cefiderocol 2 g IV Q8H

Question 4

Which of the following is NOT an example of a carbapenemase that may be produced by CRE infections?

a) KPC

b) AmpC

c) OXA-48

d) MBL

Question 5

Assuming all antimicrobials are susceptible, which of the following is preferred for treatment of DTR *P. aeruginosa* isolated outside of the urinary tract?

a) Sulbactam-durlobactam
b) Ceftolozane-tazobactam
c) Levofloxacin
d) Ampicillin-sulbactam

Question 6

Assuming all antimicrobials are susceptible, which of the following is preferred for treatment of *Stenotrophomonas maltophilia*?

a) Cefiderocol
b) TMP-SMX
c) Levofloxacin + TMP-SMX
d) Meropenem-vaborbactam + amikacin

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Thank you!!

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