IDSA Antimicrobial Resistance Guidelines

Madison Riojas, PharmD, BCIDP
Robbie Savely, PharmD, BCPS, BCIDP

OKLAHOMA
State Department of Health

Objectives

- Review the updated recommendations added to the antimicrobial resistance guidelines.
- Highlight Oklahoma reportable resistance mutations and tier levels.
- Identify treatment strategies for multi-drug-resistant pathogens.

Threat of Antimicrobial Resistance

2013

- 2 million antimicrobial resistant infections per year
- 23,000 associated deaths

2019

- 2.8 million antimicrobial resistant infections per year
- 35,000 associated deaths

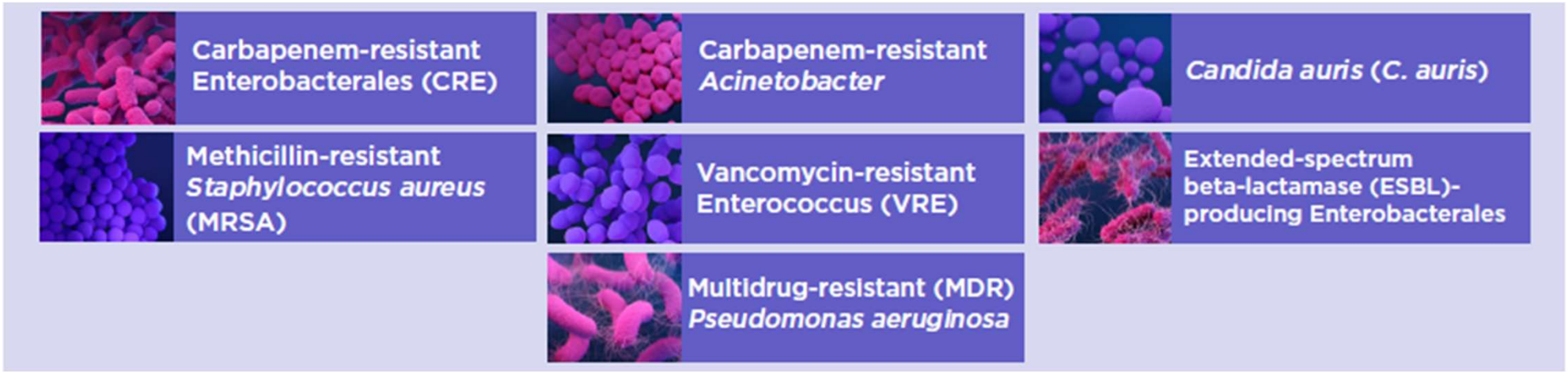
2021-2022

- Combined 20% increase in targeted antimicrobial resistant pathogens during the COVID-19 pandemic
- Rates of 5/6 targeted pathogens remained above pre-pandemic levels in 2022

CDC. Antibiotic Resistance Threats in the United States, 2019 and 2021-2022

Antimicrobial Resistance

Targeted pathogens in CDC Threat Report



State Reporting

Tier 1 No cases

- Never or very rarely identified in the US

Tier 2 Limited Spread

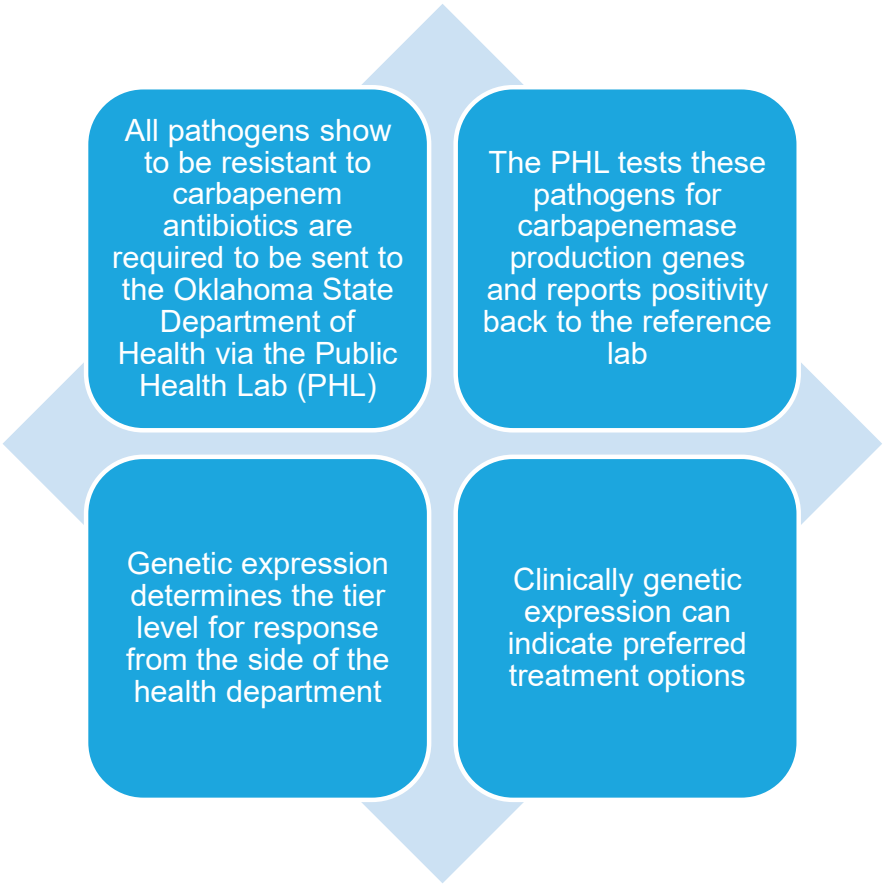
- Never or rarely isolated in a public health jurisdiction (state) but may be common in other parts of the US

Tier 3 Moderate Spread

- Somewhat commonly isolated but not considered an endemic pathogen to the jurisdiction

Tier 4 Endemic

- Commonly isolated in a particular jurisdiction



Antimicrobial Stewardship

Indication	• Colonization vs Infection • Abstaining from treatment of colonizing organisms reduces the pressure on the organism and contributes to preventing further resistance development.
Antimicrobial Selection	• Utilize the narrowest spectrum antimicrobial that will effectively treat the causative pathogen. • There is nothing wrong with broad-spectrum empiric therapy if de-escalation follows.
Duration of Therapy	• Prolonged antimicrobial courses have been linked to increased risk of resistance development.
Clinical Response	• Lack of clinical response does not always indicate a resistant pathogen, before escalating therapy assess for source control and antibiotic dosing.

Extended Spectrum Beta-Lactamase (ESBL)

Extended Spectrum Beta-Lactamases (ESBLs)

Enterobacterales producing ESBLs are generally resistant to all B-Lactams, with the exception of carbapenems.

Often these organisms have other mutations or genes that are resistant to fluoroquinolones, aminoglycosides, tetracyclines, and Bactrim (TMP/SMX).

The selection of an antibiotic needs to take these factors into account, as organisms may appear susceptible but result in clinical failures.

The length of therapy should be guided by the infection site (ESBLs do not generally warrant a longer LOT).

Uncomplicated ESBL Urinary Tract Infection Treatment

1st Line

- Nitrofurantoin
  - IF susceptible:
    - Bactrim (TMP/SMX)

Alternative 1st Line Options

- Ciprofloxacin
- Levofloxacin
- Gentamicin/amikacin/tobramycin
- Meropenem

NOT Recommended

- Augmentin (AMOX/CLAV)
- Doxycycline

Alternative Options With Less Support

Fosfomycin

- Exclusively for *E. Coli*.
- Not routinely tested on susceptibility panels
- Expensive, sometimes to find
- *Likely* requires 2-3 doses

Zosyn (PIP/TAZO)

- May be considered for non-severe uncomplicated UTIs
- Unanswered questions
  - Efficacy of extended interval and continuous infusion dosing strategies
  - Place for therapeutic dose monitoring (TDM)
  - Dosing ratio of TAZO to PIP

Cefepime

- Continue IF already in use while an ESBL was identified, and patient is improving

Pyelonephritis and Complicated ESBL Urinary Tract Infection Treatment

1st Line IF susceptible

- Bactrim (TMP/SMX)
- Ciprofloxacin
- Levofloxacin

Second Line

- Meropenem

Alternative Options

- Gentamicin

Zosyn (PIP/TAZO)

- Is less favorable to use in this patient population than with uncomplicated infections.

NOT Recommended

- Fosfomycin
- Cefepime
- Augmentin (AMOX/CLAV)
- Doxycycline

ESBL Infections Outside of the Urinary Tract

1st Line

- Carbapenems
  - Meropenem extended infusion

IV to PO Conversion

- Highly bioavailable oral options may be considered for de-escalation (Bactrim (TMP/SMX) or ciprofloxacin or levofloxacin).

AmpC

AmpC Beta-Lactamses

AmpC Beta-Lactamase is an enzyme that can hydrolyze most B-Lactams.

The clinical significance is that basal production levels are low enough to allow in-vitro susceptibility testing to show “susceptible,” yet resulting in clinical failures due to increased production of the enzyme.

Increased production occurs from exposure to 1st-3rd generation cephalosporins (primarily 3rd), but can occur with Zosyn (PIP/TAZO), aminopenicillins, or aztreonam as well.

AmpC Beta-Lactamase Producing Organisms

Moderate to High-risk organisms for inducible AmpC production	• *Enterobacter cloacae, Citrobacter freundii, Klebsiella aerogenes*
Organisms that are likely moderate-risk but lack data	• *Hafnia alvei* and *Yersinia enterocolitica*
Organisms that are likely low-risk, but may consider similar treatment guidelines in severe infections	• *S. marcescens, M. morgannii*, and *Providencia* spp

IDSA Antimicrobial Resistance Guideline Update

AmpC Producing Organism Infections: Isolated to the Urinary Tract – Uncomplicated UTI

1st Line

- Nitrofurantoin
- Bactrim (TMP/SMX)

Alternative Options

- Ciprofloxacin
- Levofloxacin
- Tobramycin
- Cefepime
- Meropenem (last resort)

Continuation of Ceftriaxone or Zosyn (PIP/TAZO)

Empiric regimens containing Ceftriaxone or Zosyn (PIP/TAZO) may be considered for continuation if using for moderate-high risk AmpC producing uncomplicated UTIs, the organism is susceptible, and the patient is clinically improving.

AmpC Producing Organism Infections: Isolated to the Urinary Tract – Pyelonephritis or Complicated UTI

1st Line IF susceptible

- Bactrim (TMP/SMX)
- Ciprofloxacin
- Levofloxacin

Alternative 2nd Line Options

- Cefepime extended infusion

Other Alternatives

- Tobramycin
- Meropenem extended infusion

AmpC Producing Organism Infections: Outside the Urinary Tract

1st Line

- Cefepime
  - *Although carbapenems should be considered for critically ill infections*

Step Down Therapy

- Ceftriaxone or Zosyn (PIP/TAZO) can be considered as step down therapy in uncomplicated infections if other options are not reasonable, the patient is clinically stable, and infectious signs/symptoms have resolved.

Carbapenem Resistant *Enterobacterales* (CRE)

Carbapenem Resistant Enterobacterales (CREs)

Enterobacterales resistant to at least one carbapenem

Carbapenemase producing CRE isolates are state reportable and the isolates with a KPC mutation are tier 4 (indicating that it is endemic to Oklahoma) and any other mutation is tier 2 (meaning it is never or very rarely isolated in Oklahoma).

The most common carbapenemases in the United States are *K. pneumoniae* carbapenemases (KPCs).

Other carbapenemases include:

- Oxacillinases (OXAs)
- Metallo-β-lactamases (MBLs)
  - New Delhi metallo-β-lactamases (NDMs)
  - Verona integron-encoded metallo-β-lactamases (VIMs)
  - Imipenem-hydrolyzing metallo-β-lactamases (IMPs)

Knowing the type of carbapenemase present helps guide treatment.

Carbapenem Resistant Enterobacterales (CREs) Treatment - General Principles

Although the newer β-Lactam-β-Lactamase inhibitor combinations are also preferred therapy for UTIs, similar ESBL/AmpC treatment options are possible for resistant infections not exhibiting carbapenemases.

For infections outside of the urinary tract, newer β-Lactam-β-Lactamase inhibitor combinations or cefiderocol are primary treatment options.

For carbapenem resistant infections not exhibiting carbapenemases, standard carbapenems can be used if shown susceptible.

Emergence of resistance is still a concern with the newer β-Lactam-β-Lactamase inhibitor combinations. Consider using a different agent if the patient presents with an infection, despite recent use.

Polymyxin B and colistin are not suggested for the treatment of infections caused by CRE (with the exception of colistin as an alternative for UTIs).

To date, there is no data to suggest double coverage offers any additional benefit.

Uncomplicated CRE Urinary Tract Infection Treatment

1st Line

- Nitrofurantoin
- Bactrim (TMP/SMX)
- Ciprofloxacin
- Levofloxacin

Alternative 2nd Line Options

- Gentamicin
- Meropenem
  - IF susceptible to meropenem and/or imipenem-cilastatin and not expressing a carbapenemase
- Ceftazidime-avibactam (Avycaz)

Other Alternatives

- Meropenem-vaborbactam (Vabomere)
- Imipenem-cilastatin-relebactam (Recarbrio)
- Cefiderocol (Fetroja)
- Colistin
- Gentamicin
- Fosfomycin (refer to ESBL section for potential issues)

Pyelonephritis or Complicated CRE Urinary Tract Infection Treatment

1st Line

- Bactrim (TMP/SMX)
- Ciprofloxacin
- Levofloxacin

Alternative 2nd Line Options

- Meropenem extended infusion
  - IF susceptible to meropenem and imipenem-cilastatin and not expressing a carbapenemase
- Ceftazidime-avibactam (Avycaz)

Other Alternatives

- Meropenem-vaborbactam (Vabomere)
- Imipenem-cilastatin-relebactam (Recarbrio)
- Cefiderocol (Fetroja)
- Gentamicin

CRE Infections Outside of the Urinary Tract - Non Carbapenemase Producing

For susceptibility to meropenem and imipenem-cilastatin

1st Line

- Meropenem extended infusion
  - *Monotherapy is recommended with either option.*

If no carbapenem is susceptible

1st Line

- Ceftazidime-avibactam (Avycaz)

Alternative 1st Line Options

- Meropenem-vaborbactam (Vabomere)
- Imipenem-cilastatin-relebactam (Recarbrio)

Other Alternatives

- Cefiderocol (Fetroja)
- Tigecycline or Eravacycline (for non urinary or blood source infections)

CRE Infections Outside of the Urinary Tract - KPC Producing

1st Line

- Ceftazidime-vibactam (Avycaz)

Alternative 1st Line Options

- Meropenem-vaborbactam (Vabomere)
- Imipenem-cilastatin-relebactam (Recarbrio)

Other Alternatives

- Cefiderocol (Fetroja)
- Tigecycline or Eravacycline (for non urinary or blood source infections)

IDSA Antimicrobial Resistance Guideline Update

CRE Infections Outside of the Urinary Tract - MBL Producing

1st Line

- Ceftazidime-avibactam (Avycaz)

Alternative Options

- Cefiderocol (Fetroja)
- Tigecycline or Eravacycline (for non urinary or blood source infections)

CRE Infections Outside of the Urinary Tract - OXA Producing

1st Line

- Ceftazidime-avibactam (Avycaz) PLUS Aztreonam (simultaneously at Y-Site)

Alternative 1st Line Options

- Cefiderocol (Fetroja)

Other Alternatives

- Tigecycline or Eravacycline (for non urinary or blood source infections)

Pseudomonas aeruginosa

Pseudomonas with Difficult to Treat Resistance (DTR)

Multi-drug-resistant (MDR) *Pseudomonas* – not susceptible to at least once antibiotic in at least three antibiotic classes

DTR *Pseudomonas* – not susceptible to **all** the following: piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem/cilastatin, ciprofloxacin, and levofloxacin

Pseudomonas resistance is mediated by a variety of resistance mechanisms, with many isolates demonstrating multiple mechanisms at once.

- Carbapenemase-producing *Pseudomonas* is rare in the U.S. but is gaining prevalence in other places throughout the world.
- This is significant to note, as a *Pseudomonas* isolate resistant to carbapenems via a carbapenemase is a state-reportable pathogen considered a Tier 2 organism in Oklahoma.
  - Tier 2: organism never or very rarely identified in a public health jurisdiction (state) but more common in other parts of the U.S.

MDR *Pseudomonas* Treatment

Unlike many other gram-negative pathogens, Pseudomonas can exhibit carbapenem resistance through mechanisms that do not impact the susceptibility of non-carbapenem antibiotics (ex. Cefepime, piperacillin/tazobactam, ciprofloxacin, etc.).

Non-carbapenem/ carbapenem susceptible

- Utilize non-carbapenem therapies preferentially

Carbapenem resistant/ Non-carbapenem susceptible

- Do not avoid non-carbapenem therapies.
  - There is a possible place in therapy here for new beta lactams in critically ill patients, but this is not preferred ~~in order~~ to preserve their activity.
- High-dose extended-infusion therapy is recommended.

Pseudomonas with Difficult to Treat Resistance (DTR)

When selecting antimicrobial therapy for a DTR *Pseudomonas* infection ensure testing of all new beta lactam agents with extended spectrum of activity, susceptibility can vary throughout the country based on pockets of resistance mechanisms.

Ceftolozone/tazobactam (Zerbaxa)

Ceftazidime/avibactam (Avycaz)

Imipenem/cilastatin/relebactam (Recarbrio)

Cefiderocol (Fetroja)

- For known metallo-beta-lactamase producing Pseudomonas, cefiderocol (Fetroja) is the preferred therapy.
- Meropenem/vaborbactam (Vabomere) – guidelines recommend against testing or empirically treating DTR *Pseudomonas* with Vabomere as it does not sufficiently extend the activity of meropenem for *Pseudomonas.*

DTR *Pseudomonas* Source Specific Treatment Preferences

Uncomplicated Cystitis

- Zerbaxa, Avycaz, Recarbrio, or Fetroja
- Alternative: single dose of tobramycin or amikacin

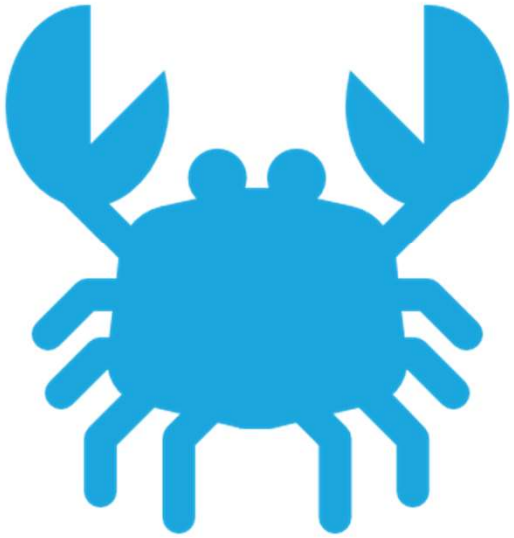
Pyelonephritis/Complicated Cystitis

- Zerbaxa, Avycaz, Recarbrio, or Fetroja
- Alternative: once-daily dosing amikacin or tobramycin

Non-Urinary Sources

- Zerbaxa, Avycaz, Recarbrio
- Alternative: Fetroja (recommendation limited by small sample sizes in trials)
  - ❖ The exception to this recommendation is in the case of a known metallo-beta-lactamase mechanism, Fetroja is recommended first line in this scenario.

Carbapenem Resistant *Acinetobacter Baumannii* (CRAB)



Carbapenem Resistant *Acinetobacter baumanii* (CRAB)

- In Oklahoma, carbapenemase producing CRAB is a state-reportable pathogen.
  - The tier level depends on the specific genetic mutation.
  - Most isolates are tier 3 (indicating moderate spread in the state).
- Traditionally, wild type *Acinetobacter* species are frequently susceptible to sulbactam, and ampicillin/sulbactam is commonly used as the empiric drug of choice.
- Once the isolate exhibits carbapenem resistance it generally has resistance to most other antibiotics.

CRAB Treatment Recommendations

Empiric therapy – combination therapy recommended (sulbactam-containing regimen and another therapy)

- Durlobactam/sulbactam (Xacduro) combined with a carbapenem
- Alternative: ampicillin/sulbactam (high dose) and another agent (polymyxin B, minocycline, cefiderocol)

Additional therapies – agents appropriate to use with sulbactam agent empirically

- Polymixin B – never utilize as monotherapy due to the concentrations needed for bactericidal activity and the narrow therapeutic window.
- Tetracyclines – high-dose minocycline is preferred over high-dose tigecycline due to tolerability and CLSI breakpoint availability.
- Cefiderocol (Fetroja) – limit to CRAB isolates refractory to other therapies or patient intolerance.

Stenotrophomonas

Stenotrophomonas species

Frequently isolated as a colonizing organism in patients with underlying lung disease, IV drug use history, and other comorbidities.

When isolated as a true pathogen *Stenotrophomonas* possesses many virulence factors that make it an aggressive pathogen with elevated morbidity and mortality.

Conventional beta lactams are unlikely to have activity, and it has intrinsic resistance to the aminoglycoside class of antibiotics.

Stenotrophomonas Treatment Recommendations

Empiric therapy

Combination of any two of the following agents

- Cefiderocol (Fetroja)
- Minocycline – high dose
- TMP/SMX
- Levofloxacin

OR

Ceftazidime/avibactam (Avycaz) and aztreonam

- Note that there is limited clinical data for this regimen.

Ceftazidime without avibactam is no longer a recommend option for treatment, and CLSI no longer provides breakpoints.

Combination therapy is indicated until clinical improvement is noted, then de-escalation to monotherapy is an option.

Summary

- There are an extensive number of antimicrobial resistance patterns, each with their own nuance to treatment.
- One of the key points to remember is to practice antimicrobial stewardship in all antibiotic selections to prevent development of further resistant organisms.

Questions?

Madison Riojas, PharmD, BCIDP

Madison.riojas@health.ok.gov

OKLAHOMA State Department of Health