Updates on Gram Negative Resistance

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Disclosures

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- Jorge Mera, MD, FACP, faculty for this educational event, is a Principal Investigator in COVID-19 and Acute HCV clinical trials for Merck and Abbvie.

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There is no commercial interest support for this educational activity.

Disclosures

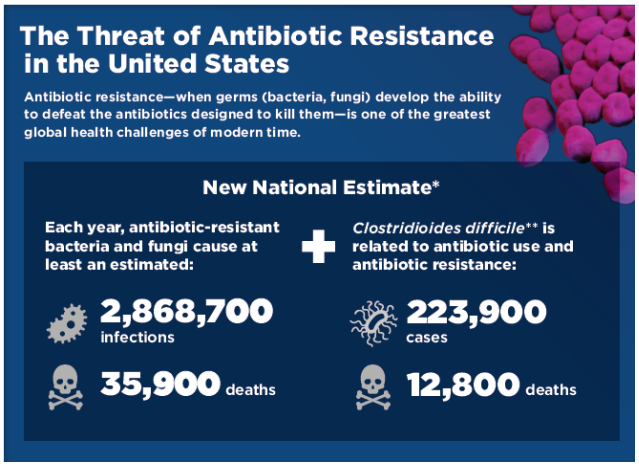
- I will be discussing “off-label” uses of the following medications:
  - Meropenem/vaborbactam is indicated for complicated UTI and pyelonephritis
    - The IDSA recommends this antibiotic as a treatment option for non-urinary indications

Objectives

Examine	The impact of gram-negative antibiotic resistance and mechanisms of resistance for gram-negative bacteria.
Identify	The therapeutic role of recent broad-spectrum antibiotics.
Incorporate	Into practice recent IDSA guidelines for treatment of gram-negative infections.

CDC Threat Levels

- **Urgent Threats**
  - **Carbapenem-resistant *Acinetobacter***
  - *Candida auris*
  - *Clostridioides difficile*
  - **Carbapenem-resistant Enterobacteriaceae**
  - **Drug-resistant *Neisseria gonorrhoeae***
- **Serious Threats**
  - **Drug-resistant *Campylobacter***
  - Drug-resistant *Candida*
  - **ESBL-producing Enterobacteriaceae**
  - Vancomycin-resistant *Enterococci*
  - **Multidrug-resistant *Pseudomonas aeruginosa***
  - **Drug-resistant nontyphoidal *Salmonella***
  - **Drug-resistant *Salmonella* serotype Typhi**
  - **Drug-resistant *Shigella***
  - Methicillin-resistant *Staphylococcus aureus*
  - Drug-resistant *Streptococcus pneumoniae*
  - Drug-resistant Tuberculosis

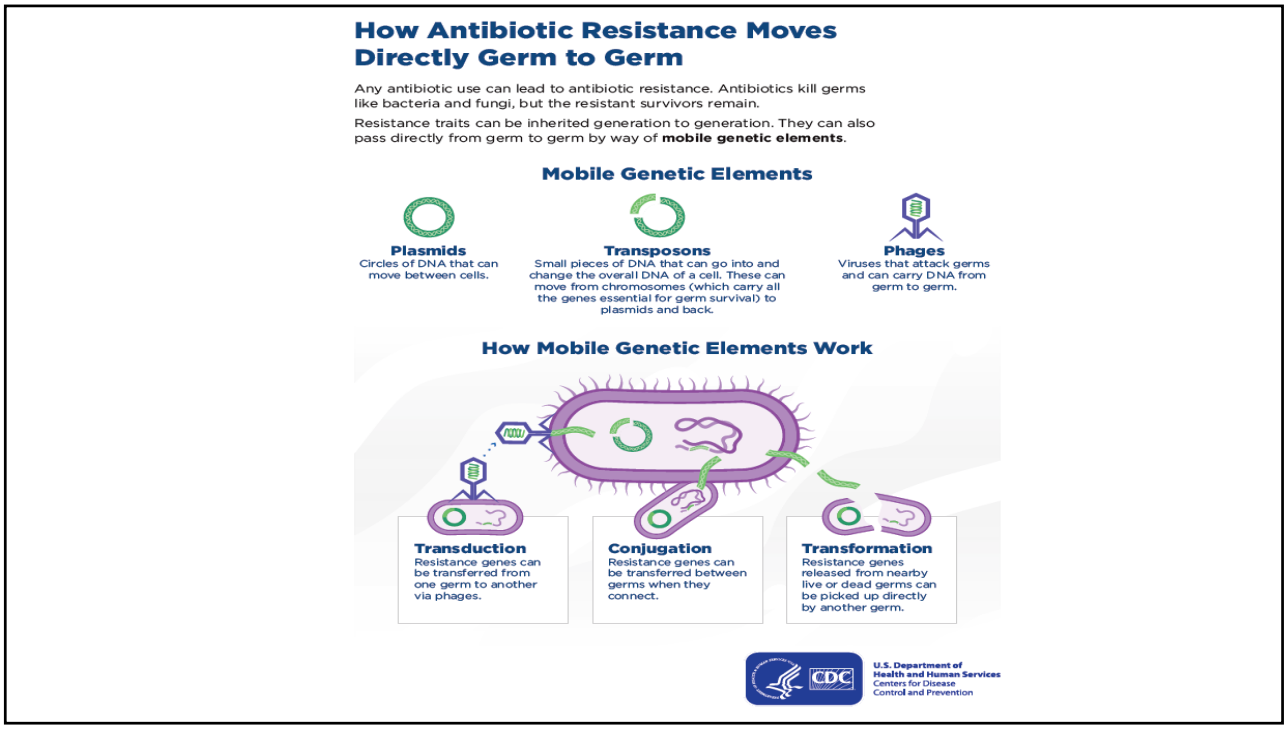


www.cdc.gov/DrugResistance/Biggest-Threats.html

Major Gene-Expressed Mechanisms of Resistance to Antibacterial Agents

- Enzymatic inactivation
  - Common
- Target site absent: Intrinsic Resistance
- Target site modification or protection (high level of resistance)
- Excessive binding sites
- Altered cell wall permeability
  - Porin mutations
- Drug efflux
  - Low level resistance

- Expression of chromosomal resistance genes
  - Constitutive (always expressed)
  - Inducible (In response to a substrate)
- Plasmids
  - Circular extrachromosomal DNA
  - Expression is almost always constitutive
  - Can be acquired through conjugation
- Some bacteria have a combination of resistance mechanism
  - These can be either acquired (plasmids or transposons) or mutational or a combination of both



Major Gene-Expressed Mechanisms of Resistance to Antibacterial Agents

More than 1500 beta lactamases reported

Conjugation is the main mechanism of acquisition

Less common

- Target modification
- Efflux pumps
- Decrease permeability

Phenotypic testing is routinely used but it does not detect the mechanism

Germs Develop Antibiotic Resistance

Select Germs Showing Resistance Over Time

Since the discovery of penicillin more than 90 years ago, germs have continued to develop new types of resistance against even our most powerful drugs. While antibiotic development has slowed, antibiotic resistance has not. This table demonstrates how rapidly important types of resistance developed after approval and release of new antibiotics, including antifungals.

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant *Staphylococcus aureus*[1, 2]	1942
		Penicillin-resistant *Streptococcus pneumoniae*[3,4]	1967
		Penicillinase-producing *Neisseria gonorrhoeae*[5]	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant *Enterococcus faecium*[6,7,8]	1988
		Vancomycin-resistant *Staphylococcus aureus*[9]	2002
Amphotericin B	1959	Amphotericin B-resistant *Candida auris*[10]	2016
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*[11]	1960
Extended-spectrum cephalosporin	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing *Escherichia coli*[12]	1983
Azithromycin	1980	Azithromycin-resistant *Neisseria gonorrhoeae*[13]	2011
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*[14]	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*[15]	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant *Candida*[16]	1988
Caspofungin	2001	Caspofungin-resistant *Candida*[17]	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*[18]	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*[19]	2015

www.cdc.gov/DrugResistance/Biggest-Threats.html

Beta-Lactams

Classes

- Penicillin's
- Cephalosporins
- Carbapenems
- Monobactams

Characteristics

- They all have a beta-lactam ring
- They all decrease the seizure threshold to different degrees
- All have the potential of allergies

Cephalosporins

Generation	Spectrum	Comments
First (Cefazolin)	MSSA, E. coli, Klebsiella sp.	No Enterococci activity
Second (Cefoxitin, Cefotetan)	Adds B. fragilis coverage	B Fragilis resistance increasing
Third (Ceftriaxone)	Most aerobic Enterobacterales	
Third (Ceftazidime)	Adds Pseudomonas sp	
Fourth (Cefepime)	MSSA, Enterobacterales and Pseudomonas sp	
Fifth (Ceftaroline)	MRSA and Enterobacterales	No Enterococci activity
(Ceftolazone/Tazobactam)	ESBL producing GNB including Pseudomonas	No B fragilis activity
(Ceftazidime/Avibactam)	ESBL producing GNB and KPCs	Inconsistent B fragilis activity
(Cefiderocol)	Serine/Metallo carbapenemase producing Enterobacterales and Non-fermenters	No GPC or anaerobic bacteria activity

Beta Lactamses Resistance

B-Lactam Group	Example	Penicillinases	ESBLs	AmpCs	Carbapenemases
Penicillin	Penicillin Ampicillin	X	X	X	X
Cephalosporin	Cefazolin Ceftriaxone Ceftazidime		X	X	X
Monobactam	Aztreonam		X	X	X
Carbapenem	Ertapenem Imipenem Meropenem Doripenem				X

Ambler Classification of β-LactamasesAdapted from Jacoby GA, Munoz-Price LS. The new β-lactamases. *N Engl J Med*. 2005;352:380-391

Class	Active Site	Enzyme Type	Substrates	Examples
A	Serine	**Penicillinases**		
		Broad-spectrum	Benzylpenicillin, aminopenicillins, carboxypenicillins, ureidopenicillins, narrow-spectrum cephalosporins	PC1 in *Staphylococcus aureus* TEM-1, SHV-1 in *Escherichia coli, Klebsiella pneumoniae*, and other gram-negative bacteria
		Extended-spectrum (ESBL)	Substrates of broad-spectrum plus oxymino-β-lactams (cefotaxime, ceftazidime, ceftriaxone) and aztreonam	In Enterobacteriaceae: TEM-derived, SHV-derived, CTX-M–derived; PER-1, VEB-1, VEB-2, GES-1, GES-2, IBC-2 in *Pseudomonas aeruginosa*
		Carbapenemases	Substrates of extended-spectrum plus cephamycins and carbapenems	KPC-1, KPC-2, KPC-3 in *K. pneumoniae*; NMC/IMI, SME family
B	Metallo-β-lactamases (Zn^{2+})	**Carbapenemases**	Substrates of extended-spectrum plus cephamycins and carbapenems	IMP, VIM, GIM, SPM, SIM lineages in *P. aeruginosa, Acinetobacter* spp.
C	Serine	**Cephalosporinases**	Substrates of extended-spectrum plus cephamycins	AmpC-type enzymes in Enterobacteriaceae, *Acinetobacter baumannii*
D	Serine	**Oxacillinases**		
		Broad-spectrum	Aminopenicillins, ureidopenicillins, cloxacillin, methicillin, oxacillin, and some narrow-spectrum cephalosporins	OXA-family in *P. aeruginosa*
		Extended-spectrum	Substrates of broad-spectrum plus oxymino-β-lactams and monobactam	OXA-derived in *P. aeruginosa*
		Carbapenemases	Substrates of extended-spectrum plus cephamycins and carbapenems	OXA-derived in *Acinetobacter* spp.

Talk to your microbiologist and understand the scope and limitations of what they can offer

Laboratory Detection of Betalactamases

Pneumonia and Blood Multiplex PCR Panel
Antimicrobial Resistance Genes

Carbapenemases:
- KPC
- NDM
- Oxa-48-like
- VIM
- IMP

ESBL:
- CTX-M

Newer Antibiotic Agents to Treat Gram-Negative Resistant Infections

Ceftolozane/tazobactam (Zerbaxa®)– FDA approved 2014;

- Anti-pseudomonal cephalosporin with beta-lactamase inhibitor
- Indications: **cUTI, CIAI, HAP/VAP**; AE: nausea, diarrhea.

Ceftazidime/avibactam (Avycaz®)– FDA approved 2015

- Antipseudomonal cephalosporin with beta-lactamase inhibitor—avibactam protects ceftazidime from ESBL, AmpC, KPC, and OXA-48
- It more effective against *P. aeruginosa* and *E. coli*;
- Indications: **cUTI, HAP/VAP**; AE: nausea, diarrhea, and positive Coombs test.

Meropenem/vaborbactam (Vabomere®) – FDA approved 2017

- Carbapenem with beta-lactamase inhibitor—vaborbactam
- Improves activity of carbapenem-susceptible Enterobacterales, including KPCs but limited activity against MBL and OXA
- Indications: **cUTI**; AE: HA, phlebitis/infusion-site reactions, diarrhea.

cIAI = complicated intrabdominal infection

Newer Antibiotic Agents to Treat Gram-Negative Resistant Infections

Plazomicin (Zemdri®) – FDA approved 2018

- Aminoglycoside-inhibits bacterial protein synthesis and has dose-dependent bactericidal activity;
- Indication: **cUTI and pyelonephritis**; AE: nephrotoxicity and ototoxicity

Eravacycline (Xerava®) – FDA approved 2018

- Fluorocycline of the tetracycline class-inhibits bacterial protein synthesis;
- Indication: **cIAI** for 4 to 14 days; hypersensitivity reactions, permanent tooth discoloration, infusion site reactions, nausea, vomiting, diarrhea.

Cefiderocol (Fetroja®) – FDA approved 2019

- Novel catechol-substituted siderophore cephalosporin;
- Indication: **cUTI, HAP/VAP**;
- AE: diarrhea, infusion-site reactions, constipation, rash, candidiasis, cough, elevations in liver tests, HA, hypokalemia, nausea, hypomagnesemia, and atrial fibrillation.
- Has **FDA warning** for higher all-cause mortality versus other antibiotics in critically ill patients with multidrug-resistant gram-negative bacterial infections (mortatility rate of 34% in cefiderocol vs 18% in best-available therapy group).

cIAI = complicated intrabdominal infection

Newer Antibiotic Agents to Treat Gram-Negative Resistant Infections

Imipenem-Cilastatin/Relebactam (Recarbrio®) – FDA approved 2019

- Carbapenem with beta-lactamase inhibitor—activity against Enterobacterales (including ESBL and AmpC isolates) and *P. aeruginosa*
- Restores activity against *K. pneumoniae* isolates that harbor KPCs, but not active against *Acinetobacter* spp. or OXA-positive isolats.

Relebactam

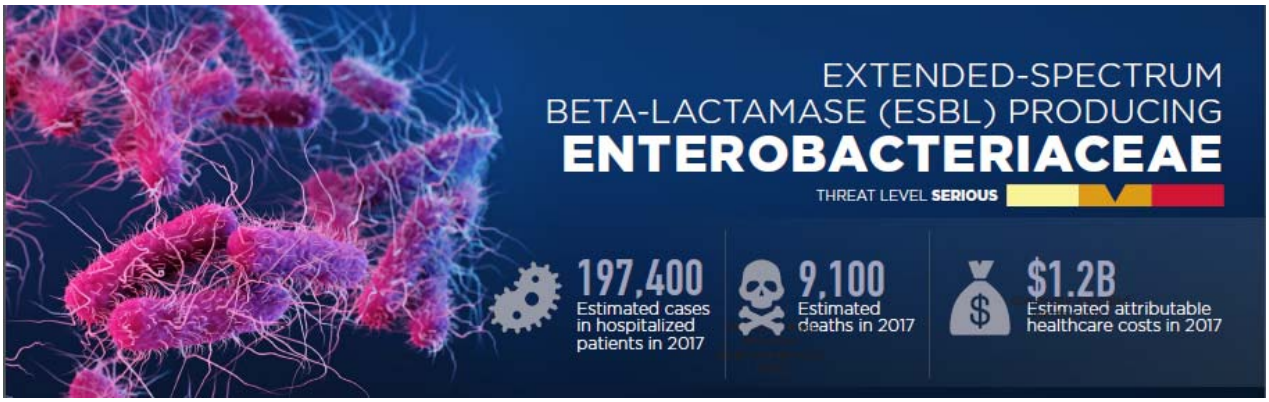
- Decreases the MIC values of imipenem in *P. aeruginosa* isolates fourfold.
- Indications: **cUTI, cIAI**; AE: nausea, diarrhea, elevated liver enzymes, increased eosinophils, rash.

cIAI = complicated intrabdominal infection

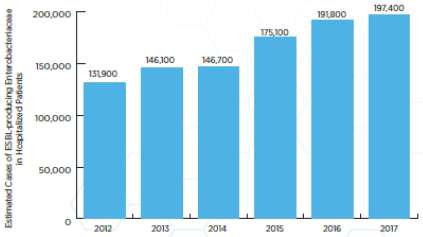
IDSA Updates to Gram-Negative Resistant Infections

- IDSA recently published 2 documents relating to gram-negative infections
  - IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram Negative Infections: Version 1.0 – Updated 3/5/2022
    - Focuses on Extended-Spectrum β-lactamase Producing Enterobacterales, Carbapenem-Resistant Enterobacterales and Pseudomonas aeruginosa with Difficult-to-Treat Resistance
    - IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0 (idsociety.org)
  - IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram Negative Infections: Version 2.0 –Updated 3/31/2022
    - Focuses on AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant Acinetobacter baumanni (CRAB) and Stenotrophomonas maltophilia infections
    - IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0 (idsociety.org)

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0 (idsociety.org)



CDC and partners are working to assess and address why cases of ESBL-producing Enterobacteriaceae have increased since 2012.



ESBL infections increased in the United States by 50% from 2012 to 2017

www.cdc.gov/DrugResistance/Biggest-Threats.html

ESBL-E

Taxonomy change in 2020

- Enterobacterales is the name of a new scientific order
- Enterobacteriaceae are now a family within the Enterobacterales order

ESBL-E

- Enzymes that inactivate most penicillins, cephalosporins and aztreonam but is generally susceptible to carbapenems
- Do not inactivate non-β-lactam agents (e.g., ciprofloxacin, TMS, AG)

Organisms carrying ESBL genes

- Are most prevalent in *E. coli, K. pneumonia, K. oxytoca* and *P. mirabilis* bacteria
- Can harbor additional genes or mutations that mediate resistance to a broad range of antibiotics

Any gram-negative organism has the potential to harbor ESBL genes

- CTX-M enzymes (CTX-M-15 in particular) are the most common ESBLs in the United States
- Non-susceptibility to ceftriaxone (MIC ≥ 2 mcg/mL) is often used as a proxy for ESBL production—this can be misleading if the organism is resistant due to other factors

TMS: trimethoprim-sulfamethoxazole, AG: Aminoglycosides)

When to Suspect that Infections due to GNB ESBL producers?

Endemic in your area

- Antibiogram

The patient has a history of MDR infections

- Or comes from an institution with high rates of MDR
- Or has been on broad-spectrum antibiotics

Regular phenotypic evaluation is suspicious

- In vitro resistance to penicillin, cefazolin, ceftriaxone, ceftazidime, aztreonam (not unique to ESBL)
- Partial susceptibility to BLI (TAZ/CLAV)

Molecular methods detect the resistance genes

- Example: Multiplex PCR of blood or sputum which may detect some but not all ESBL
  - Example: CTX-M

ESBL-E – Treatment Options: Uncomplicated Cystitis

Preferred Treatment Options	Alternative Treatment Options	Not Recommended
Nitrofurantoin	Amoxicillin-clavulanate (when susceptibilities are known)	Doxycycline
Trimethoprim-sulfamethoxazole	Single-dose aminoglycosides	
	Oral fosfomycin (*E. coli* only)	

ESBL-E – Treatment Options: Pyelonephritis and cUTI

Preferred Treatment Options	Alternative Treatment Options	Not Recommended
Ertapenem	Once-daily aminoglycosides	Piperacillin-tazobactam
Meropenem		Cefepime
Impenem-cilastatin		
Ciprofloxacin		
Levofloxacin		
Trimethoprim-sulfamethoxazole		

ESBL-E – Treatment Recommendations: Infections outside of urinary tract

Carbapenems are preferred

Piperacillin-tazabactam

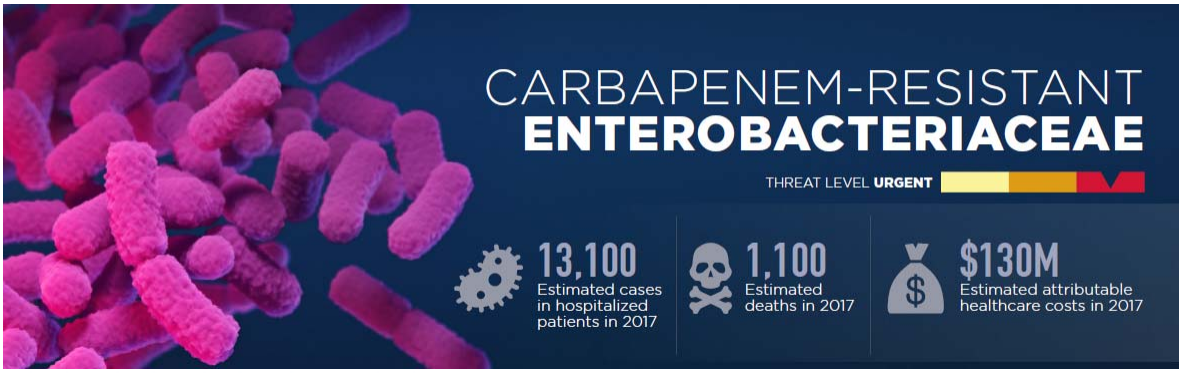
- Not recommended for invasive infections even if susceptibility is demonstrated
- Organisms may have increased expression of ESBL enzyme or presence of multiple β-lactamases during treatment
- MIC testing may be inaccurate when ESBL enzymes are present

Cefepime

- Not recommended for infections even if susceptibility is demonstrated

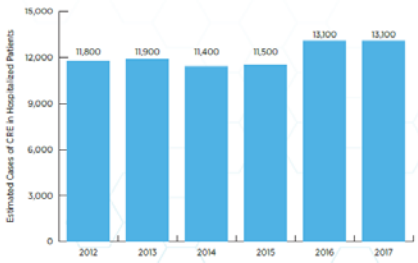
Cephamycins

- Cefoxitin and cefotetan are not recommended for treatment of ESBL-E infections (urinary or invasive infections)



CASES OVER TIME

Containment strategies have prevented further spread of some types of CRE in the United States, but continued action is needed.



www.cdc.gov/DrugResistance/Biggest-Threats.html

Carbapenem-Resistant Enterobacterales (CRE)

CRE are resistant to at least one carbapenem or producing a carbapenemase enzyme

- Bacteria that are intrinsically not susceptible to imipenem (*Proteus* spp., *Morganella* spp., *Providencia* spp.) require resistance to at least one other carbapenem to qualify as CRE

Divided into 2 groups

- Carbapenemase producing – account for ~30% of CRE in U.S. per the CDC
- Non-carbapenemase producing – a chromosomal mutation in a porin gene that limits the ability of carbapenems to get into the bacteria combined with acquisition or upregulation of a beta-lactamase
- **Knowing whether the CRE isolate is carbapenemase producing will guide treatment**

Common Carbapenemases

K. pneumonia carbapenemases (KPCs):

- Most common carbapenemases in U.S. and can be produced by any Enterobacterales

Oxacillinase (OXA-48)

New Delhi Metallo-β-lactamase (NDM)

Verona integron-encoded metallo-beta-lactamase (VIM)

Imipenem-hydrolyzing metallo-β-lactamases (IMPs)

CRE Treatment Recommendations

Infection Type	Preferred Treatment	Alternative Treatment
Uncomplicated Cystitis	Ciprofloxacin; Levofloxacin; TMP-SMX; nitrofurantoin; single-dose aminoglycoside	Fosfomycin (E. coli only) If preferred agents not active: Ceftazidime-avibactam; Meropenem-vaborbactam; Imipenem-cilastatin-relebactam; cefiderocol
Pyelonephritis and cUTI	Ciprofloxacin; Levofloxacin; TMP-SMX	Once-daily aminoglycosides (full treatment course) If preferred agents not active: Ceftazidime-avibactam; Meropenem-vaborbactam; Imipenem-cilastatin-relebactam; cefiderocol

CRE Treatment Recommendations:
Outside of the Urinary Tract Infections

Resistance Testing Results (See Legend Below)	CRE Activity	Preferred Treatment Options	Alternative Treatment Options
A	KPC, OXA-48	Ceftazidime-avibactam	Cefiderocol
A	KPC	Meropenem-vaborbactam Ceftazidime-avibactam Imipenem-cilastatin-relebactam	Cefiderocol
B		Extended-infusion meropenem	
C	KPC, OXA-48, NDM, VIM, IMP	Ceftazidime-avibactam + aztreonam (administered simultaneously) Cefiderocol	

Resistance Testing

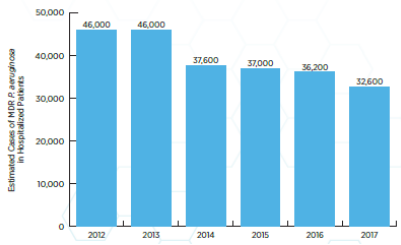
A – Resistant to ertapenem and meropenem and carbapenemase testing results are negative or not available

B – Resistant to ertapenem but susceptible to meropenem and carbepenemase testing results are negative or not available

C –Positive for carbapenemase-producing CRE

CASES OVER TIME

Continued infection control and appropriate antibiotic use are important to maintain decreases in MDR *P. aeruginosa* infections



www.cdc.gov/DrugResistance/Biggest-Threats.html

Pseudomonas aeruginosa with Difficult-to-Treat (DTR) Resistance

Multi-Drug Resistant (MDR) *P. aeruginosa* is defined as:

- *P. aeruginosa* not susceptible to at least one antibiotic in at least three antibiotic classes for which *P. aeruginosa* susceptibility is generally expected: penicillins, cephalosporins, FQ, AG and carbapenems

DTR is defined as:

- *P. aeruginosa* exhibiting non-susceptibility to all the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin

DTR is rarely caused by carbapenamase production

FQ: fluoroquinolones, AG: aminoglycosides

P. aeruginosa Treatment Recommendations

<u>MDR** resistant to carbapenems but sensitive to traditional β-lactams</u>**

- Administer traditional agent as high-dose extended infusion
- Novel β-lactam agents that test susceptible are alternative options for patients with moderate-severe disease or poor source control

<u>Preferred treatment of uncomplicated cystitis caused by **DTR- *P. aeruginosa*</u>**

- Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, cefiderocol, or a single-dose of an aminoglycoside

DTR P. aeruginosa Treatment Recommendations

Preferred treatment of cUTI and pyelonephritis

- Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol
- Once-daily aminoglycoside is an alternative option

Preferred treatment for infections outside of the urinary tract

- Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam, as monotherapy
- Cefiderocol is recommended as an alternative treatment option

Considerations of AmpC Beta Lactamases

All cephalosporins are destroyed except:

- Ceftolazone/Tazobactam
- Ceftazidime/Avibactam

Resistance is

- Constitutive (on a plasmid), easily detectable because it is present
  - E. Coli, Klebsiella
- Inducible (chromosomal), can be missed if not specifically looked for
  - **M**organella
  - **Y**ersinia
  - **S**erratia
  - **P**seudomona/Proteus/Providencia
  - **A**eromonas/Acinetobacter
  - **E**nterobacter

AmpC β-Lactamase-Producing Enterobacterales

Enterobacterales considered moderate to high risk for clinically significant AmpC production due to an inducible ampCgene

- *Enterobacter cloacae*
- *Klebsiella aerogenes* (formerly Enterobacter aerogenes)
- *Citrobacter freundii*

Resistance due to *ampC* induction

- Can be observed after even a few doses of ceftriaxone or ceftazidime exposure

Except when treating uncomplicated cystitis

- Avoid treatment with ceftriaxone or ceftazidime even if isolates test susceptible

Emergence of resistance after exposure to agent like ceftriaxone is ~ 8% - 40%

AmpC β-Lactamase-Producing Enterobacterales

Piperacillin/tazobactam

- Has the potential to be hydrolyzed by AmpC production and is not recommended for serious infections

Cefepime

- Is suggested for treatment when the MIC ≤ 2 mcg/mL

Carbapenem

- Is recommended when cefepime MIC is ≥4 mcg/mL, if susceptible—as ESBL co-production may be present

Newer β-lactam and β-lactam-β-lactamase inhibitor combinations

- Should be reserved when carbapenem resistance is present

AmpC β-Lactamase-Producing Enterobacterales

FQ, AG, TMP-SMX, tetracycline, and other non-beta-lactam antibiotics

- Do not induce *ampC* and are also not substrates for AmpC hydrolysis

TMP-SMX and FQ

- Can be considered for invasive infections according to source of infection, clinical status and if susceptible

Nitrofurantoin, TMP-SMX or a single-dose of an aminoglycoside

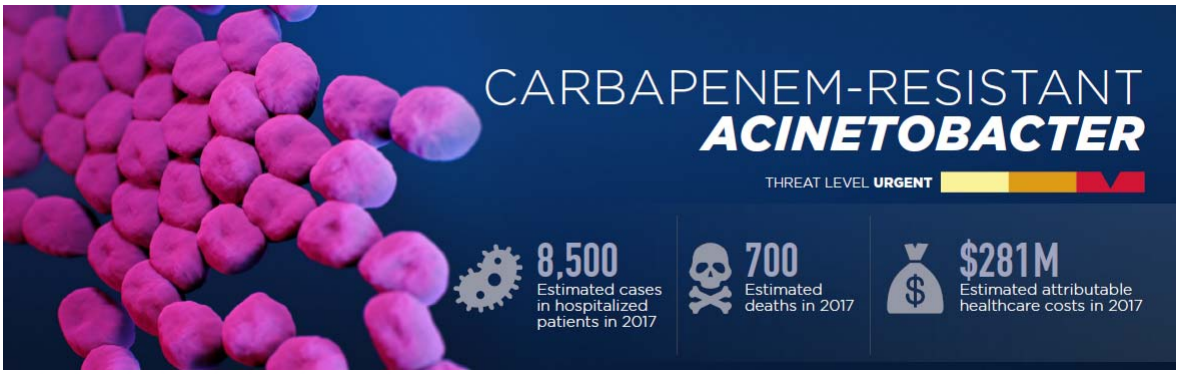
- Can be considered for uncomplicated cystitis

FQ: fluoroquinolones, AG: aminoglycosides, TMP-SMX: Trimethoprim-Sulfamethoxazole

Treatment Options for Gram Negative Bacilli ESBL and AmpC producers

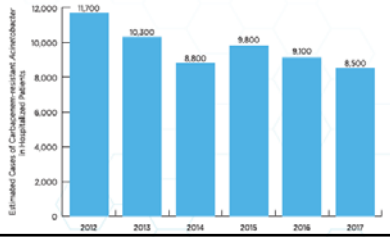
Antimicrobial	ESBL Producers	AmpC
Cefepime	If MIC is low	If MIC is low
Ceftolazone/Tazobactam	Yes	Yes
Ceftazidime/Avibactam	Yes	Yes
Cefiderocol	Yes	Yes
Carbapenems	Yes	Yes

Curr Opin Infect Dis: 2020;33:78



CASES OVER TIME

Continued infection control and appropriate antibiotic use are important to maintain decreases in carbapenem-resistant *Acinetobacter* infections.



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PERCENT OF GERMS THAT TESTED NON-SUSCEPTIBLE (NOT SENSITIVE) TO OTHER TYPES OF ANTIBIOTICS

Select Antibiotics	2013	2014	2015	2016	2017
Any fluoroquinolone	98%	93%	97%	92%	89%
Any extended-spectrum β-lactam	80%	75%	81%	79%	75%
Ampicillin/sulbactam	62%	62%	59%	64%	61%
Trimethoprim/ sulfamethoxazole	84%	74%	81%	77%	66%

Germs refer to isolates (pure samples of germs) from eight of CDC's Emerging Infections Program sites. See Technical Appendix for antibiotic susceptibilities details.

General Aproach to Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) Infections

A single (susceptible) active agent can be used for mild infections

- High-dose ampicillin-sulbactam is preferred (sulbactam is active component)
- Alternate options include minocycline, high-dose tigecycline, polymixin B (colistin for cystitis) or Cefiderocol

Combination therapy with at least 2 agents is suggested for moderate to severe infections

- High-dose ampicillin-sulbactam as a component of therapy even if not susceptible as it can saturate altered PBP targets
- Tetracycline derivatives (minocycline), tigecycline, polymixin B (colistin for urinary infections), extended-infusion meropenem or cefiderocol
- The combination of a polymyxin and meropenem, without a third agent, is not suggested

Stenotrophomonas maltophilia: General Approach to Treatment

Mild infections

- Preferred: TMP-SMX (most preferred) or minocycline monotherapy
- Alternative: tigecycline, levofloxacin or cefiderocol monotherapy

Moderate-Severe infections

- Preferred: Combination therapy with TMP-SMX and minocycline
- Alternative: TMP-SMX monotherapy and if there is a delay in clinical improvement then add one of the following: minocycline (preferred), tigecycline, levofloxacin or cefiderocol
- Last line: combination of ceftazidime-avibactam and aztreonam when intolerance or inactivity of other agents are anticipated

Summary

1. Use novel antibacterial agents wisely
2. Sensitivity results will guide therapy
3. Refer to the IDSA guidelines when you encounter MDR-DTR gram negative organisms

References

- CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.
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