Turning the Tide on Serious Gram-negative Infections in Hospitals

Proceedings from a live webinar originally presented:

November 13, 2019
12:00 p.m. - 1:00 p.m. ET

Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education

- ACPE #: 0204-000-19-423-H01-P
- 1.0 hr, knowledge-based

Faculty

Sara Revolinski, Pharm.D., BCPS
Director of Experiential Education and Assistant Professor
Medical College of Wisconsin School of Pharmacy
Pharmacist Specialist, Infectious Diseases
Froedtert Hospital
Milwaukee, Wisconsin

Included in handout

www.ashpadvantage.com/gramnegative

Provided by ASHP
Supported by an educational grant from Merck

Part One

Turning the Tide on Serious Gram-negative Infections in Hospitals

Sara Revolinski, Pharm.D., BCPS
Director of Experiential Education and Assistant Professor
Medical College of Wisconsin School of Pharmacy
Pharmacist Specialist, Infectious Diseases
Froedtert Hospital
Milwaukee, Wisconsin

Provided by ASHP
Supported by an educational grant from Merck

Disclosures

In accordance with ACCME and ACPE Standards for Commercial Support, ASHP policy requires that all faculty, planners, reviewers, staff, and others in a position to control the content of this presentation disclose their financial relationships. In this activity, only the individual below has disclosed a relevant financial relationship. No other persons associated with this presentation have disclosed any relevant financial relationships.

- Scott T. Micek, Pharm.D., BCPS, FCCP
  - Paratek Pharmaceuticals: advisory board (has divested himself of this relationship)

Learning Objectives

At the conclusion of this knowledge-based activity, participants should be able to

- Describe the epidemiology and mechanisms of drug resistance among Gram-negative bacterial infections
- Compare and contrast antibiotic options for treating serious Gram-negative infections
- Identify strategies to ensure safety and effectiveness of antibiotics when treating Gram-negative infections

Impact of Gram-negative Infections

- Gram-negative resistance continues to increase
  - Partially due to antibiotic use
- Morbidity and mortality due to Gram-negative infections continue to increase
- Treatment is challenging
  - Few antibiotics available to treat
  - Multiple resistance mechanisms present in one organism
  - Resistance develops rapidly

Eichenberger EM et al. *Antibiotics (Basel).* 2019; 8(2). pii: E37. doi:10.3390/antibiotics8020037.

Resistant Gram-negative Organisms

- Extended-spectrum beta-lactamase (ESBL) – producing Enterobacteriaceae
- AmpC beta-lactamase-producing Enterobacteriaceae
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*

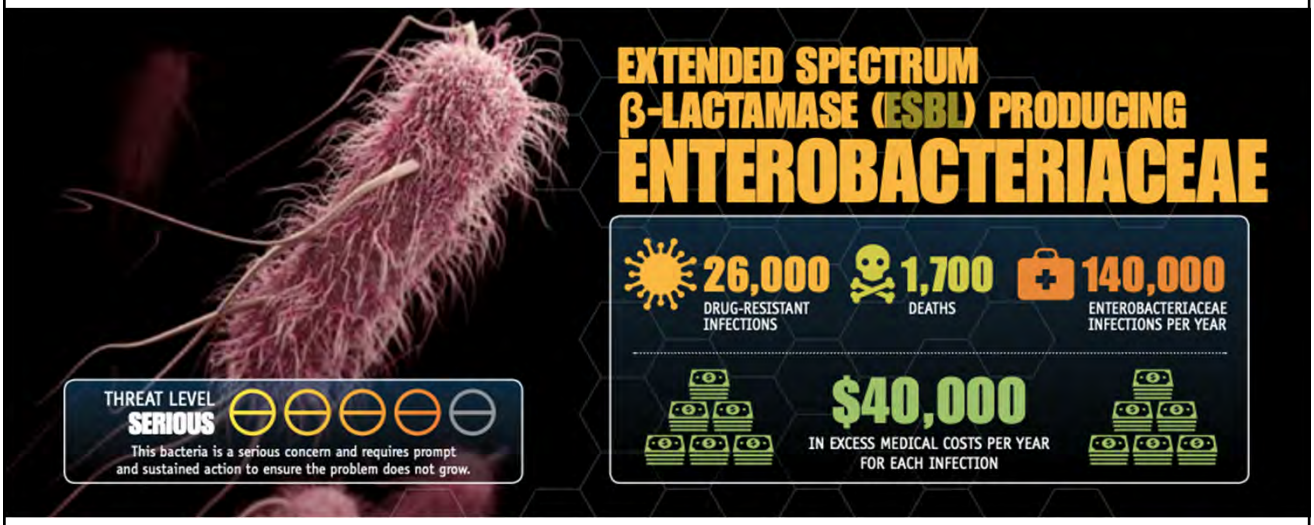
Multiple other mechanisms – not covered today

Kaye KS et al. *Pharmacotherapy*. 2015; 35:949-62.
Rodriguez-Bano J. *Clin Microbiol Rev*. 2018;31:1-41.

Impact of Gram-negative Resistance in the U.S.

Resistant Organism	Infections per Year	Deaths per Year	
ESBL-producing Enterobacteriaceae	26,000	1,700	SERIOUS
AmpC-producing Enterobacteriaceae	Not Reported	Not Reported	
CRE	9,000	600	URGENT
MDR *P. aeruginosa*	6,700	440	SERIOUS
MDR *Acinetobacter* spp.	7,300	500	

CDC. https://www.cdc.gov/drugresistance/biggest-threats.html#cre (accessed 2019 Oct 31).



Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats report. https://www.cdc.gov/drugresistance/biggest-threats.html#cre (accessed 2019 Oct 31).

ESBL Epidemiology

- ESBLs and AmpCs are the enzymes mainly responsible for resistance to 3rd-generation cephalosporins
- Historically nosocomial but community prevalence is increasing (urinary tract infections)
- Plasmid-mediated (easy to transmit)
  - Other resistance genes are commonly harbored

Meini S et al. *Infection.* 2019; 47:363-75.
Rodriguez-Bano J et al. *Expert Rev Anti Infect Ther*. 2008; 6:671-83.

Extended-Spectrum Beta-Lactamases (ESBLs)

- Hydrolyze beta-lactam antibiotics
  - 1st-3rd generation cephalosporins (**EX**cluding cephamycins)
  - 4th generation cephalosporins - variable
  - Penicillins
  - Aztreonam
- May be inhibited by beta-lactamase inhibitors

Nathisuwan S et al. *Pharmacotherapy*. 2001; 21:920-8.
Paterson DL. *Am J Med*. 2006; 119(6 suppl 1):S20-8.

ESBL Detection

Disk Diffusion

- Plate ceftazidime and cefotaxime alone AND with clavulanate
- ESBL producers show ≥ 5-mm increase in diameter WITH clavulanate

Broth Microdilution

- Microdilutions for ceftazidime and cefotaxime alone AND with clavulanate
- ESBL producers show ≥ 3-fold dilution decrease in MIC WITH clavulanate

CLSI M100-ED29: http://em100.edaptivedocs.net/GetDoc.aspx?doc=CLSI%20M100%20ED29:2019&scope=user (accessed 2019 Oct 31).

ESBL Detection

- Polymerase chain reaction (PCR) tests to detect genetic material encoding ESBL production
- Automated testing systems may screen for ESBLs
- If detected (not routinely feasible at all labs), susceptibility reports should be adjusted to reflect resistance to
  - Penicillins
  - 1st-3rd generation cephalosporins
  - Aztreonam

Kazemian H et al. *Med Princ Pract*. 2019 Apr 16. doi:10.1159/000500311 [Epub ahead of print].

Susceptibility Reports: ESBL-Producers

Antibiotic	MIC (mcg/mL)	Interpretation
ampicillin	64	resistant
ampicillin/sulbactam	32/16	resistant
cefazolin	16	resistant
cefepime	64	resistant
cefoxitin	1	susceptible
ceftriaxone	8	resistant
ciprofloxacin	0.5	susceptible
gentamicin	2	susceptible
meropenem	0.25	susceptible
piperacillin/tazobactam	128	resistant

Johns Hopkins ABX guide. https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/All_Topics/A.

Treatment

- Treatment of choice(?): carbapenems
  - Consider extended infusion dosing over intermittent infusion
- Potential options
  - Ceftazidime/avibactam
  - Ceftolozane/tazobactam
  - Polymyxins
  - Tigecycline

Falagas ME et al. *J Hosp Infect*. 2009; 73:345-54.

	Ceftazidime/avibactam	Ceftolozane/tazobactam
Spectrum of Activity	- Effective against ESBLs, *P. aeruginosa*, AmpCs, and *K. pneumoniae* carbapenemases (KPCs) - Unreliable activity against *Acinetobacter* spp. - Use in combination with metronidazole if Gram-negative anaerobe concern	- Variably effective against ESBLs - Effective against *P. aeruginosa* - Unreliable activity against *Acinetobacter* spp. and AmpCs - No activity against carbapenemases - Use in combination with metronidazole if Gram-negative anaerobe concern
Dosing	Normal dose: 2.5 g IV every 8 hr (each dose over 2 hr) Adjust in renal impairment	Normal dose (administer over 1 hr): - cIAI/cUTI: 1.5 g IV every 8 hr - HAP/VAP: 3 g IV every 8 hr Adjust in renal impairment

cIAI = complicated intraabdominal infection; cUTI = complicated urinary tract infection; HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia

Kaye KS et al. *Pharmacotherapy*. 2015; 35:949-62.
Van Duin D et al. *Clin Infect Dis*. 2016; 63:234-41.

Polymyxins

Spectrum of Activity	- Enterobacteriaceae and non-fermenting Gram-negative bacilli including multidrug resistant strains (ESBL, AmpC, CRE) - Not effective against *Proteus* spp. or *Providencia* spp.
Dosing	Polymyxin B - 2-2.5 mg/kg IV load then 1.25-1.5 mg/kg IV every 12 hr (actual body weight) Colistin - 300 mg IV of colistin base activity (CBA) load, then 150-180 mg IV CBA twice daily - Adjust for patients with renal impairment
Adverse Effects	- Nephrotoxicity (may be more likely with colistin than polymyxin B) - Neurotoxicity
Key Points	- Select polymyxin B over colistin for severe infections - Select colistin over polymyxin B for urinary tract infection (UTI) - Consider using as part of combination therapy in severe infections

Rodriguez-Bano J et al. *Expert Rev Anti Infect Ther*. 2008; 6:671-83.
Tsuji BT et al. *Pharmacotherapy.* 2019; 39:10-39.

Tigecycline

Spectrum of Activity	- Effective against ESBLs, *Acinetobacter* spp., AmpCs, CRE - Not effective against *P. aeruginosa*, *Proteus* spp., or *Providencia* spp.
Dosing	- 100 mg IV x1 then 50 mg IV twice daily - Consider 200 mg IV x1 then 100 mg IV twice daily for MDR infections
Adverse Effects	- Nausea/vomiting - Hematologic - Hepatotoxicity/pancreatitis
Key Points	- Avoid in UTI and bloodstream infections due to low concentrations - Increased mortality with use? - Consider using as part of combination therapy in severe infections

Gong J. *Medicine (Baltimore)*. 2019; 98:e17091. doi:10.1097/MD.0000000000017091.
Rodriguez-Bano J et al. *Expert Rev Anti Infect Ther*. 2008; 6:671-83.

Treatment: Clinical Controversies

- Cephamycins
  - Not well studied in clinical settings
  - Not effective if other mechanisms of resistance are also present
  - Resistance may develop while on therapy
- Aminoglycosides
  - Often ineffective due to resistance
  - Potential option as part of empiric combination therapy
- Fluoroquinolones
  - Use only if susceptibility reports prove susceptibility

Falagas ME et al. *J Hosp Infect*. 2009; 73:345-54.
Rodriguez-Bano J et al. *Expert Rev Anti Infect Ther*. 2008; 6:671-83.

Treatment: Do NOT Use

- Cephalosporins (excluding cephamycins, ceftazidime/avibactam, and ceftolozane/tazobactam)
  - Avoid use of 1st-3rd generation
  - Cefepime may be considered with MIC ≤ 2 mcg/mL if high doses are used (2 g IV every 8 hr in normal renal function)
- Piperacillin/tazobactam
  - Treatment failures have been reported
  - Higher mortality compared with meropenem in Gram-negative infections resistant to 3rd generation cephalosporins

Falagas ME et al. *J Hosp Infect*. 2009; 73:345-54.
Harris PNA et al. *JAMA*. 2018; 320:984-94.
Rodriguez-Bano J et al. *Expert Rev Anti Infect Ther*. 2008; 6:671-83.
Van Duin D et al. *Clin Infect Dis*. 2016; 63:234-41.

Risk Factors for ESBLs

- Antibiotic use
  - Cephalosporins
  - Fluoroquinolones
- Invasive lines, catheters, and procedures
- Prolonged duration of hospital stay
- Comorbid conditions: diabetes, malignancy
- Advanced age and female sex in community-acquired UTIs

Rodriguez-Bano J et al. *Expert Rev Anti Infect Ther*. 2008; 6:671-83.

ESBL Clinical Pearls

- Carbapenems are drugs of choice
  - Use extended infusion over intermittent infusions if able
- May consider carbapenem-sparing therapy
  - May be expensive
- Avoid polymyxin or tigecycline monotherapy for severe infections
- Optimize dosing in severe infections

Antimicrobial Stewardship Considerations

- Use of carbapenems increases the incidence of CRE
- Potential methods to mitigate spread of CRE
  - Carbapenem-sparing antibiotic regimens
  - Targeting empiric therapy to patients with risk factors in high prevalence settings
- Ensure effective therapy
  - Combination therapy
  - Appropriate dosing

Rodriguez-Bano J et al. *Expert Rev Anti Infect Ther*. 2008; 6:671-83.

AmpC Beta-Lactamases

- Typically occur in Enterobacteriaceae and some non-fermenting Gram-negative bacilli
- Chromosomally- or plasmid-mediated
- Hydrolyze beta-lactam antibiotics
  - 1st-3rd generation cephalosporins (**IN**cluding cephamycins)
  - Penicillins

Meini S et al. *Infection.* 2019; 47:363-75.
Nathisuwan S et al. *Pharmacotherapy*. 2001; 21:920-8.
Paterson DL. *Am J Med*. 2006; 119(6 suppl 1):S20-8.

AmpC Beta-Lactamases

- NOT (typically) inhibited by common beta-lactamase inhibitors (sulbactam, tazobactam, clavulanate)
  - *Morganella morganii* is inhibited by tazobactam
- Inhibited by avibactam and vaborbactam

Meini S et al. *Infection.* 2019; 47:363-75.
Nathisuwan S et al. *Pharmacotherapy*. 2001; 21:920-8.
Paterson DL. *Am J Med*. 2006; 119(6 suppl 1):S20-8.

Chromosomal AmpC

- Chromosomal gene in ESCPM organisms
  - E: *Enterobacter* spp. and *Klebsiella (Enterobacter) aerogenes*
  - S: *Serratia marcescens*
  - C: *Citrobacter freundii*
  - P: *Providencia stuartii*
  - M: *Morganella morganii*
- Expression can be constitutive or inducible

Meini S et al. *Infection.* 2019; 47:363-75.

Chromosomal AmpC Induction by Antibiotics

Strong Inducer Hydrolyzed by AmpC	Strong Inducer Not hydrolyzed by AmpC	Weak Inducer Hydrolyzed by AmpC
Aminopenicillins	Carbapenems	Ureidopenicillins (piperacillin)
1st generation Cephalosporins		3rd generation Cephalosporins
Cephamycins		Aztreonam
Clavulanate (does not inhibit AmpC)	POTENTIAL TREATMENT OPTION	IT'S COMPLICATED
DO NOT USE		

Meini S et al. *Infection.* 2019; 47:363-75.

Weak Inducers, Hydrolyzed by AmpC

- Most bacterial populations have mutants that constitutively produce AmpC at low levels → derepressed mutants
- Weak inducer antibiotics select for derepressed mutants
- Initially these antibiotics may appear susceptible per microbiology report, but then develop resistance after therapy
- AVOID use of these antibiotics in suspected AmpC infections

Meini S et al. *Infection.* 2019; 47:363-75.

Plasmid-Mediated AmpC

- Predominantly constitutively expressed
- Found most commonly in Enterobacteriaceae
  - *Escherichi coli*
  - *Klebsiella* spp.
  - *Proteus mirabilis*

Meini S et al. *Infection.* 2019; 47:363-75.

AmpC Detection

- Clinical and Laboratory Standards Institute (CLSI) has no recommendations for identification in clinical practice
- Generally not done in clinical practice
- Reviewing susceptibility reports can assist

Tamma PD et al. *Clin Infect Dis*. 2019; 69:1446-55.

AmpC Detection - Methods

- Use cloxacillin or boronic acid in combination with a cephamycin
  - Cloxacillin and boronic acid may inhibit AmpC
  - Reduction in MIC with addition of cloxacillin or boronic acid may signify AmpC
- Rapid diagnostics
  - PCR to detect genetic material encoding AmpC
  - Matrix-assisted laser desorption/ionization – time of flight (MALDI TOF)

Kazemian H et al. *Med Princ Pract*. 2019 Apr 16. doi:10.1159/000500311 [Epub ahead of print].
Li C et al. *J Hosp Infect*. 2018; 99:200-7.

Susceptibility Reports

Chromosomal AmpC

- May appear susceptible to 3rd generation cephalosporins in absence of induction by antibiotics
- Resistance develops upon exposure to antibiotic inducers

Plasmid-Mediated AmpC

- Susceptibility reports show resistance to 3rd generation cephalosporins

Tamma PD et al. *Clin Infect Dis*. 2019; 69:1446-55.

Susceptibility Reports: *Enterobacter* spp.

Antibiotic	MIC (mcg/mL)	Interpretation
ampicillin	16	resistant
ampicillin/sulbactam	32/16	resistant
cefazolin	≥ 64	resistant
cefepime	2	susceptible
cefoxitin	64	resistant
ceftriaxone	0.5	susceptible
ciprofloxacin	0.5	susceptible
gentamicin	4	susceptible
meropenem	0.5	susceptible
piperacillin/tazobactam	16/4	susceptible

Johns Hopkins ABX guide. https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/All_Topics/A.

Susceptibility Reports: *E. coli*

Antibiotic	MIC (mcg/mL)	Interpretation
ampicillin	16	resistant
ampicillin/sulbactam	32/16	resistant
cefazolin	≥ 64	resistant
cefepime	2	susceptible
cefoxitin	128	resistant
ceftriaxone	8	resistant
ciprofloxacin	0.5	susceptible
gentamicin	4	susceptible
meropenem	0.5	susceptible
piperacillin/tazobactam	128	resistant

Johns Hopkins ABX guide. https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/All_Topics/A.

Treatment

Severe Infections

- Carbapenems
- Ceftazidime/avibactam
- Meropenem/ vaborbactam

Mild-to-Moderate Infections or Step-Down Therapy

- Cefepime
- Fluoroquinolones
- Sulfonamides
- Nitrofurantoin (UTI)

Meini S et al. *Infection.* 2019; 47:363-75.
Tamma PD et al. *Clin Infect Dis*. 2019; 69:1446-55.

Meropenem/vaborbactam

- Spectrum of activity (expanded from meropenem)
  - ESBLs
  - AmpCs
  - KPCs
- Dose: 4 g IV every 8 hr (administered as extended infusion, over 3 hr)
  - Adjust in renal impairment

Wright H. *Clin Microbiol Infect*. 2017; 23:704-12.

Treatment: Clinical Controversies

- Cefepime
  - Optimize dose (2 g IV every 8 hr)
  - Consider use if MIC ≤ 2 mcg/mL
  - Risk of failure if concomitant ESBL
  - May be best for non-severe infections
- Piperacillin/tazobactam: conflicting data

Meini S et al. *Infection.* 2019; 47:363-75.
Tamma PD et al. *Clin Infect Dis*. 2019; 69:1446-55.

Treatment: Do NOT Use

- Do not use even if susceptibility report demonstrates susceptibility
  - 1st-3rd generation cephalosporins
  - Aminopenicillins
  - Ureidopenicillins
  - Ceftolozane/tazobactam
- Inducible resistance could result in initial treatment response, then subsequent failure

Meini S et al. *Infection.* 2019; 47:363-75.
Tamma PD et al. *Clin Infect Dis*. 2019; 69:1446-55.

Risk Factors for AmpC-Producing Organisms

- Similar to ESBLs
- Antibiotic use
  - 3rd generation cephalosporins
- High severity of infection
- Comorbid conditions: malignancy, immunosuppression

Tsui K et al. *J Microbiol Immunol Infect*. 2012; 45:193-9.
Zerr DM et al. *Antimicrob Agents Chemother*. 2016; 60:4237-43.

AmpC Clinical Pearls

- Microbiology lab unlikely to provide testing to definitively identify AmpC-producing organisms
- Identify organisms that constitutively produce AmpC and adjust therapy accordingly
- Optimal treatment
  - Severe infections: carbapenems, ceftazidime/avibactam
  - Moderate infections: cefepime, non-beta-lactam antibiotics

Tamma PD et al. *Clin Infect Dis*. 2019; 69:1446-55.

Antimicrobial Stewardship Considerations

- Increased use of carbapenems has driven emergence and spread of carbapenem-resistant Enterobacteriaceae
- Possible methods to stem resistance
  - Use carbapenem-sparing regimens
  - Target empiric therapy for AmpC-producing organisms to patients with risk factors in high-prevalence settings

Rodriguez-Bano J et al. *Expert Rev Anti Infect Ther*. 2008; 6:671-83.

Which antibiotic should never be used to treat AmpC (even if susceptibility reports state it is susceptible)?

a. Cefepime
b. Ceftazidime/avibactam
c. Ceftriaxone
d. Meropenem

CDC. Antibiotic resistance threats report. https://www.cdc.gov/drugresistance/biggest-threats.html#cre (accessed 2019 Oct 31).

Carbapenem-Resistant Enterobacteriaceae (CRE) Epidemiology

- Carbapenem resistance can be conferred by carbapenemases and non-enzymatic methods
- Carbapenemases are carried on plasmids and are easily transmissible
- 7% of hospital-acquired Gram-negative infections in the U.S. from 2010-2014 were attributed to CRE-producing organisms
  - *Klebsiella pneumoniae* carbapenemases (KPCs) are the most common carbapenemase in the U.S.

Cui X et al. *Front Microbiol*. 2019; 10:1823. doi:10.3389/fmicb.2019.01823.
Weiner LM et al. *Infect Control Hosp Epidemiol.* 2016; 37:1288-301.

	KPCs	Metallo-beta-lactamases (MBLs) (NDM, VIM, IMP)	OXAs
Hydrolyzed BLs	All	All except aztreonam	Penicillins Carbapenems
Inhibited by traditional BLIs	Minimally (not clinically relevant)	No	No
Inhibited by avibactam	Yes	No	Yes
Inhibited by vaborbactam or relebactam	Yes	No	No
Common organisms	*K. pneumoniae* *E. coli* *Enterobacter* spp.	*K. pneumoniae* *E. coli*	*K. pneumoniae*

BL = beta-lactam
BLI = beta-lactamase inhibitor

Sheu CC et al. *Front Microbiol*. 2019; 10:80. doi:10.3389/fmicb.2019.00080.

CRE Detection

- Traditional susceptibility tests typically demonstrate carbapenem resistance based on breakpoints
  - Do not differentiate between carbapenemase production and other mechanisms of resistance
  - May not detect inefficient carbapenemases
- Carbapenemases can be rapidly spread, therefore important to identify

Cui X et al. *Front Microbiol*. 2019; 10:1823. doi:10.3389/fmicb.2019.01823.
Kazemian H et al. *Med Princ Pract*. 2019 Apr 16. doi:10.1159/000500311 [Epub ahead of print].

Carbapenemase Detection - Methods

- Modified Hodge Test
- Calorimetric tests (e.g., Carba-NP)
  - Color changes with hydrolysis of beta-lactam antibiotic
- Modified carbapenem inactivation method
- Rapid diagnostic tests
  - PCR to detect genetic material encoding CRE (KCP, NDM, VIM, IMP, OXA)
  - MALDI-TOF

Cui X et al. *Front Microbiol*. 2019; 10:1823. doi:10.3389/fmicb.2019.01823.
Kazemian H et al. *Med Princ Pract*. 2019 Apr 16. doi:10.1159/000500311 [Epub ahead of print].

Susceptibility Reports: CRE

Antibiotic	MIC (mcg/mL)	Interpretation
ampicillin	32	resistant
ampicillin/sulbactam	32/16	resistant
cefazolin	≥ 64	resistant
cefepime	32	resistant
cefoxitin	128	resistant
ceftriaxone	8	resistant
ciprofloxacin	8	resistant
gentamicin	16	resistant
meropenem	8	resistant
piperacillin/tazobactam	128	resistant

Johns Hopkins ABX guide. https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/All_Topics/A.

Treatment of CRE

- No definitive treatment of choice
- Antibiotic therapy depends on multiple factors
  - Type of carbapenemase
  - Site of infection
  - Severity of infection
  - Patient characteristics and comorbidities
  - Susceptibility profile

Sheu CC et al. *Front Microbiol*. 2019; 10:80. doi:10.3389/fmicb.2019.00080.

Antibiotic Treatment Options

KPC	MBLs (NDM, VIM, IMP)	OXA
Dual regimen with a carbapenem plus: - A polymyxin - Tigecycline - An aminoglycoside - A second carbapenem	Dual or triple regimen with a carbapenem plus: - A polymyxin - Tigecycline - An aminoglycoside - Aztreonam (if no other resistance mechanisms)	Ceftazidime/avibactam
Ceftazidime/avibactam	Ceftazidime/avibactam + ertapenem?	Ceftazidime (if no other resistance mechanisms)
Meropenem/vaborbactam	Ceftazidime/avibactam + aztreonam?	

Kaye KS et al. *Pharmacotherapy*. 2015; 35:949-62.
Sheu CC et al. *Front Microbiol*. 2019; 10:80. doi:10.3389/fmicb.2019.00080.

Antibiotic Considerations

Meropenem

- Best backbone for combination therapy
- High-dose, extended infusion (2 g IV every 8 hr or 1 g IV every 4 hr)
- Most effective if MIC ≤ 8 mcg/mL

Ertapenem

- May be used as the second carbapenem in dual carbapenem therapy for KPCs
- Dose at 2 g IV every 24 hr

Cui X et al. *Front Microbiol*. 2019; 10:1823. doi:10.3389/fmicb.2019.01823.
Sheu CC et al. *Front Microbiol*. 2019; 10:80. doi:10.3389/fmicb.2019.00080.

Antibiotic Considerations

Tigecycline

- Consider for IAI or pneumonia
- Consider high dose for severe infections (200 mg load, then 100 mg IV twice daily)
- Part of combination therapy for CRE

Amino-glycosides

- Gentamicin/tobramycin – consider up to 15 mg/kg/day if severe
- Amikacin – consider up to 30 mg/kg/day if severe
- Plazomicin – may use for UTI, minimal data

Cui X et al. *Front Microbiol*. 2019; 10:1823. doi:10.3389/fmicb.2019.01823.
Karaiskos I et al. *Front Public Health*. 2019; 7:151. doi:10.3389/fpubh.2019.00151.
Sheu CC et al. *Front Microbiol*. 2019; 10:80. doi:10.3389/fmicb.2019.00080.

Antibiotic Considerations

Ceftazidime/ avibactam	• Consider use as part of combination therapy to minimize emergence of resistance • Decreased efficacy in renal impairment?
Meropenem/ vaborbactam	• Improved outcomes compared with "best available therapy" • Administered as extended infusion

Cui X et al. *Front Microbiol*. 2019; 10:1823. doi:10.3389/fmicb.2019.01823.
Sheu CC et al. *Front Microbiol*. 2019; 10:80. doi:10.3389/fmicb.2019.00080.
Wunderink RG et al. *Infect Dis Ther*. 2018; 7:439-55.

New Treatment Options

- Newly approved antibiotics with minimal clinical data
  - Eravacycline
  - Plazomicin
  - Imipenem/cilastatin/relebactam

Eravacycline

Spectrum of Activity	- Effective against ESBLs, *Acinetobacter* spp., AmpCs, KPCs, NDMs, and OXAs (more potent than tigecycline) - Not effective against *P. aeruginosa*
Dosing	- 1 mg/kg IV every 12 hr
Adverse Effects	- Nausea/vomiting - Hepatotoxicity/pancreatitis
Key Points	- FDA approved for intraabdominal infection (IAI) only

Eravacycline. In: Lexidrugs. Lexicomp (accessed 2019 Oct 31).
Wright H. *Clin Microbiol Infect*. 2017; 23:704-12.

Plazomicin

Spectrum of Activity	- Effective against ESBLs and KPCs - Effective against aminoglycoside-modifying enzyme-producing organisms (may use if organism is resistant to other aminoglycosides) - Effective against OXA-producing *A. baumannii* - Not active against NDMs - No benefit over other aminoglycosides against *P. aeruginosa*
Dosing	- 15 mg/kg IV every 24 hr - Adjust dose in renal impairment - Use therapeutic drug monitoring
Key Points	- FDA-approved for UTI only - Some data for use in bloodstream infections and pneumonia (off-label)

Plazomicin. In: Lexidrugs. Lexicomp (accessed 2019 Oct 31).
Shaeer KM. *Pharmacotherapy*. 2019;39:77-93.
Wright H et al. *Clin Microbiol Infect*. 2017; 23:704-12.

Copyright © 2019 American Society of Health-System Pharmacists, Inc. All rights reserved.

28

Imipenem/cilastatin/relebactam

Spectrum of Activity	- Similar to ceftazidime/avibactam - Effective against ESBLs, AmpCs, KPCs - Not effective against NDMs and OXAs - Improved activity against *P. aeruginosa* compared with imipenem/cilastatin - No additional activity against *Acinetobacte*r spp. compared with imipenem/cilastatin
Dosing	- 1.25 g IV every 6 hr (infuse over 30 min) - Adjust in renal impairment
Key Points	- FDA approved for IAI and UTI

Imipenem, cilastatin, relebactam. In: Lexidrugs. Lexicomp (accessed 2019 Oct 31).
Wright H. *Clin Microbiol Infect*. 2017; 23:704-12.
Zhanel GG. *Drugs.* 2018;78:65-98.

Combination Therapy

- Increased risk of mortality with monotherapy compared with combination therapy
  - Studies did not include novel beta-lactamase inhibitors, such as avibactam, vaborbactam, and relebactam
- Consider avoiding the use of ceftazidime/avibactam and meropenem/vaborbactam as monotherapy to minimize emergence of resistance

Martin A et al. *Open Forum Infect Dis*. 2018; 5:ofy150. doi:10.1093/ofid/ofy150.
Sheu CC et al. *Front Microbiol*. 2019; 10:80. doi:10.3389/fmicb.2019.00080.
Wunderink RG et al. *Infect Dis Ther*. 2018; 7:439-55.

Risk Factors for CRE

- Previous antibiotic use
  - Carbapenems
  - Polymyxins
- ICU admission
- Prolonged duration of hospital stay
- High severity of infection
- Immunosuppression
- Multiple comorbidities

Karaiskos I et al. *Front Public Health*. 2019; 7:151. doi:10.3389/fpubh.2019.00151.

CRE Clinical Pearls

- High risk of morbidity and mortality
- No gold standard antibiotic therapy
  - Site of infection
  - Severity of infection
  - Resistance pattern and type of carbapenemase
- Consider combination therapy
- Use aggressive dosing in severe infection

Antimicrobial Stewardship Considerations

- Consider use of combination therapy to decrease emergence of resistance
- Consider empiric coverage for CRE if
  - Patient has history of CRE
  - Patient has had significant exposure to carbapenems
- Optimize dose
- Employ rapid diagnostic technology if feasible

Which resistance mechanism is represented by the culture results below?

a. AmpC
b. ESBL
c. KPC
d. NDM
e. OXA

Antibiotic	MIC (mcg/mL)	Interpretation
ampicillin	64	resistant
ampicillin/sulbactam	32/16	resistant
cefazolin	16	resistant
cefepime	64	resistant
cefoxitin	1	susceptible
ceftriaxone	8	resistant
meropenem	0.25	susceptible
piperacillin/ tazobactam	128	resistant

Multidrug-Resistant *Acinetobacter baumannii and Pseudomonas aeruginosa*

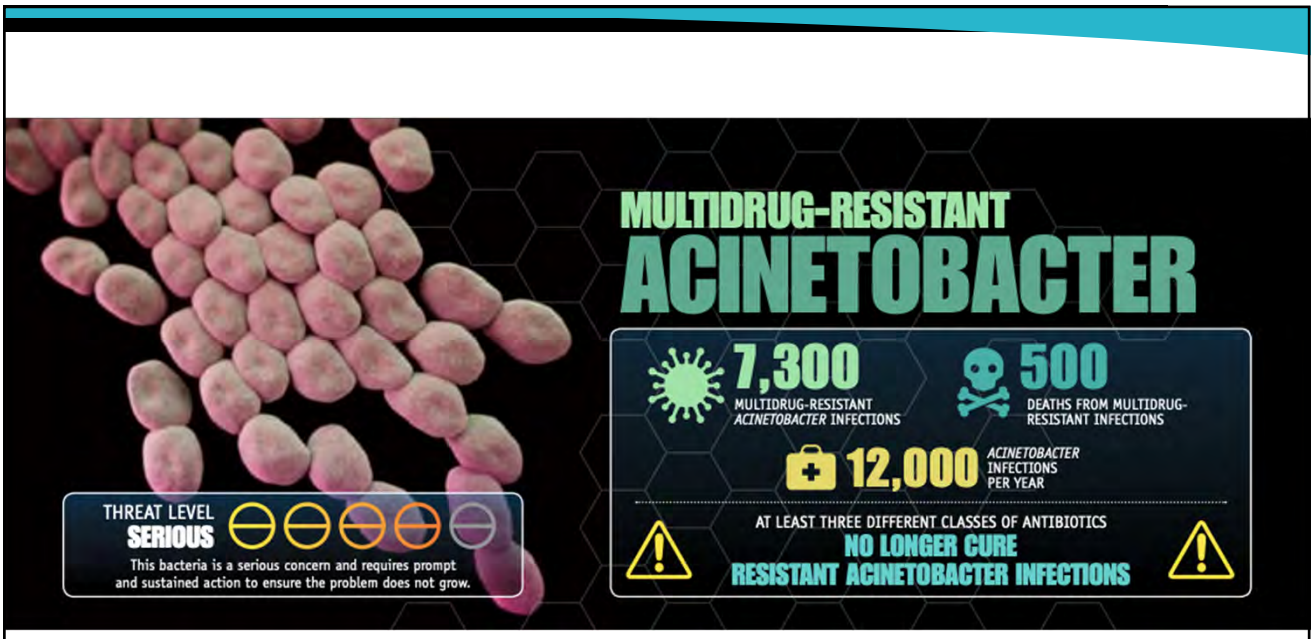
- Nonfermenting Gram-negative bacilli
- Multidrug and extensive drug resistant organisms (XDR) are increasing in prevalence
  - Due to multiple mechanisms (enzymatic inactivation, efflux pumps, porin loss, and alteration in target sites)

McGowan JE Jr. *Am J Med*. 2006; 119(6 suppl 1):S29-36.
Nasr P. *J Hosp Infect*. 2019 Oct 4. pii: S0195-6701(19)30409-8. [Epub ahead of print]

Epidemiology

- *Acinetobacter* spp.
  - Increasing rates of carbapenem resistance (2010-2014)
    - 47% in central line-associated infections
    - 64% in catheter-associated UTIs (CAUTIs)
  - 69% of isolates in CAUTI were classified as MDR (2014)
- *Pseudomonas aeruginosa*
  - 9% of isolates in U.S. are XDR (2010-2014)

Eichenberger EM et al. *Antibiotics (Basel).* 2019; 8(2). pii: E37. doi:10.3390/antibiotics8020037.
Weiner LM et al. *Infect Control Hosp Epidemiol.* 2016; 37:1288-301.



CDC. Antibiotic resistance threats report. https://www.cdc.gov/drugresistance/biggest-threats.html#cre (accessed 2019 Oct 31).

CDC. Antibiotic resistance threats report. https://www.cdc.gov/drugresistance/biggest-threats.html#cre (accessed 2019 Oct 31).

Susceptibility Reports: *P. aeruginosa* or *A. baumannii*

Antibiotic	MIC (mcg/mL)	Interpretation
amikacin	8	sensitive
aztreonam	16	resistant
cefepime	64	resistant
ceftazidime	64	resistant
ciprofloxacin	4	resistant
gentamicin	4	sensitive
meropenem	8	resistant
piperacillin/tazobactam	≥ 128	resistant

Johns Hopkins ABX guide. https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/All_Topics/A.

Treatment

Acinetobacter spp.

- Carbapenems
- Ampicillin/sulbactam
- Polymyxins
- Tigecycline
- Minocycline
- Eravacycline
- Amikacin

Pseudomonas aeruginosa

- If susceptible: cefepime, piperacillin/tazobactam, ceftazidime, levofloxacin, ciprofloxacin
- Carbapenems
- Ceftolozane/tazobactam
- Ceftazidime/avibactam
- Polymyxins
- Aminoglycosides

Tsuji BT et al. *Pharmacotherapy.* 2019; 39:10-39.

Combination Therapy – MDR *Acinetobacter* spp.

- Recommended for carbapenem-resistant strains
- Use 2 agents to which organism is susceptible
  - If susceptible only to polymyxins, consider combination therapy with a polymyxin and 1-2 other agents to which organism is not susceptible (a carbapenem should be one of those agents)

Tsuji BT et al. *Pharmacotherapy.* 2019; 39:10-39.

Combination Therapy – MDR *P. aeruginosa*

- May not be necessary if susceptible to ceftolozane/tazobactam or ceftazidime/avibactam
- Consider combination therapy in severe infections/septic shock
  - Try to use 2 agents to which organism is susceptible, if possible
  - If susceptible only to polymyxins, consider combination therapy with a polymyxin and another agent to which the organism is not susceptible

Karaiskos I et al. *Front Public Health*. 2019; 7:151. doi:10.3389/fpubh.2019.00151.
Tsuji BT et al. *Pharmacotherapy.* 2019; 39:10-39.

Risk Factors for Drug Resistance

Acinetobacter spp.

- Antibiotic use
  - Carbapenems
  - 3rd generation cephalosporins
  - Fluoroquinolones
- Intensive care unit stay
- Invasive procedures

Pseudomonas aeruginosa

- Antibiotic use
  - Carbapenems
  - Fluoroquinolones
  - Antipseudomonal beta-lactams
- Malignancy/neutropenia
- Parenteral nutrition
- Mechanical ventilation
- Critical illness

Eichenberger EM et al. *Antibiotics (Basel).* 2019; 8(2). pii: E37. doi:10.3390/antibiotics8020037.
Karaiskos I et al. *Front Public Health*. 2019; 7:151. doi:10.3389/fpubh.2019.00151.

Clinical Pearls

- MDR *Acinetobacter* spp. often require combination therapy
- MDR *P. aeruginosa* may be treated with monotherapy if low minimum inhibitory concentrations

Antimicrobial Stewardship

- Goals related to antibiotic use
  - Optimize efficacy
  - Minimize toxicity and collateral damage

Barlam TF et al. *Clin Infect Dis*. 2016; 62(10):e51-e77.

Antimicrobial Stewardship Strategies

- Know your local prevalence and antibiogram
- Develop institutional treatment guidelines
- Optimize dosing
- Employ combination therapy if warranted
- Employ rapid diagnostic technology, if feasible
- Educate prescribers, pharmacists, and healthcare practitioners
- Partner with infection prevention and control staff

Barlam TF et al. *Clin Infect Dis*. 2016; 62(10):e51-e77.

Key Takeaways

- Educate pharmacists and other healthcare providers about Gram-negative resistance
- Educate pharmacists and other healthcare providers about antibiotic therapy options and dosing strategies for resistant Gram-negative infections
- Employ 1 additional antimicrobial stewardship technique for optimizing the management of Gram-negative infections

Abbreviations Used in Presentation

AmpC	Ambler class C
BL	beta-lactam
BLI	beta-lactamase inhibitor
CAUTI	catheter-associated urinary tract infection
CBA	colistin base activity
CDC	Centers for Disease Control and Prevention
cIAI	complicated intraabdominal infection
CLSI	Clinical and Laboratory Standards Institute
CRE	carbapenem-resistant Enterobacteriaceae
cUTI	complicated urinary tract infection
ESBL	extended-spectrum beta-lactamase
ESCPM	E: *Enterobacter* spp. and *Klebsiella (Enterobacter) aerogenes;* S: *Serratia marcescens;* C: *Citrobacter freundii;* P: *Providencia stuartii;* M: *Morganella morganii*
FDA	Food and Drug Administration
HAP	hospital-acquired pneumonia
IAI	intraabdominal infection
ICU	intensive care unit
IMP	imipenemase
IV	intravenous
KPC	*Klebsiella pneumoniae* carbapenemase
MALDI TOF	matrix-assisted laser desorption/ionization–time of flight
MDR	multidrug resistant
MIC	minimum inhibitory concentration
NDM	New Delhi metallo-beta-lactamase
OXA	oxacillinase
PCR	polymerase chain reaction
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
VIM	Verona integron-encoded metallo-beta-lactamase
XDR	extensive drug resistant

Gram-Negative Resistance

	ESBL-Producing Organisms	AmpC-Producing Organisms	CRE	MDR *Pseudomonas aeruginosa* or *Acinetobacter baumannii*
Mechanism of Antibiotic Resistance	Enzymatic inactivation (beta-lactamase) *May harbor more than 1 type of resistance	Enzymatic inactivation (cephalosporinase) *May harbor more than 1 type of resistance	Enzymatic inactivation (carbapenemase) Efflux pumps Porin loss *May harbor more than 1 type of resistance	Often multifactorial, including: Enzymatic inactivation Efflux pumps Porin loss Alteration in target site
Class of Beta-Lactamase	Class A Serine Beta-lactamase	Class C Serine Beta-lactamase	KPCs: Class A, Serine Beta-lactamase OXAs: Class D, Serine Beta-lactamase NDMs: Class B, Metallo Beta-lactamase	
Which Beta-Lactamase Inhibitors are Effective? (for enzyme-producing strains only)	Avibactam Relebactam Vaborbactam Tazobactam (variable) Clavulanic acid and sulbactam (variable, not clinically relevant)	Avibactam Relebactam Vaborbactam Tazobactam (*Morganella morganii* only)	KPCs: Avibactam Relebactam Vaborbactam OXAs: Avibactam	*Acinetobacter* spp.: Sulbactam *Pseudomonas* spp.: Tazobactam Avibactam Relebactam
Antibiotic Treatment of Choice	Carbapenems: Use extended infusion Other antibiotic options may be considered	Carbapenems Other antibiotic options may be considered	Depends on clinical scenario	*Acinetobacter* spp.: Carbapenems If carbapenem resistant – combination therapy *Pseudomonas* spp.: Depends on susceptibility

References
Falagas ME et al. *J Hosp Infect*. 2009;73:345-54.; Karaiskos I et al. *Front Public Health*. 2019;7:151. doi:10.3389/fpubh.2019.00151.; Kaye KS et al. *Pharmacotherapy*; 2015;35:949-62.; McGowan JE Jr. *Am J Med*. 2006;119(6 suppl 1):S29-36.; Meini S et al. *Infection.* 2019;47:363-75.; Nasr P. *J Hosp Infect*. 2019 Oct 4. pii:S0195-6701(19)30409-8. [Epub ahead of print].; Nathisuwan S et al. *Pharmacotherapy.* 2001;21:920-8.; Paterson DL. *Am J Med*. 2006;119(6 suppl 1):S20-8.; Sheu CC et al. *Front Microbiol*. 2019;10:80.; Tamma PD et al. *Clin Infect Dis*. 2019;69:1446-55.; Tsuji BT et al. *Pharmacotherapy*. 2019;39:10-39.; Van Duin D et al. *Clin Infect Dis*. 2016;63:234-41.; Wright H. *Clin Microbiol Infect*. 2017;23:704-12.

List of Antibacterial Classes*

Aminoglycosides
- Amikacin
- Gentamicin
- Neomycin
- Plazomicin
- Streptomycin
- Tobramycin

Cephalosporins
- First generation
  - Cefadroxil
  - Cefazolin
  - Cephalexin
- Second generation
  - Cefaclor
  - Cefprozil
  - Cefuroxime
- Third generation
  - Cefdinir
  - Cefditoren
  - Cefixime
  - Cefotaxime
  - Cefpodoxime
  - Ceftazidime
  - Ceftazidime and avibactam
  - Ceftibuten
  - Ceftolozane and tazobactam
  - Ceftriaxone
- Fourth generation
  - Cefepime
- Fifth generation
  - Ceftaroline

Miscellaneous β-lactams
- Carbapenems
  - Doripenem
  - Ertapenem
  - Imipenem and cilastatin sodium
  - Meropenem
  - Meropenem and vaborbactam
- Cephamycins
  - Cefotetan
  - Cefoxitin
- Monobactams
  - Aztreonam

Chloramphenicol
- Chloramphenicol

Macrolides
- Erythromycins
  - Erythromycin (various)
- Other macrolides
  - Azithromycin
  - Clarithromycin
  - Fidaxomicin

Penicillins
- Natural penicillins
  - Penicillin G (various)
  - Penicillin V
- Aminopenicillins
  - Amoxicillin
  - Amoxicillin and clavulanate
  - Ampicillin
  - Ampicillin and sulbactam
- Penicillinase-resistant penicillins
  - Dicloxacilin
  - Nafcillin
  - Oxacillin
- Extended-spectrum penicillins
  - Piperacillin and tazobactam

Quinolones
- Ciprofloxacin
- Delafloxacin
- Gemifloxacin
- Levofloxacin
- Moxifloxacin
- Ofloxacin

Sulfonamides
- Co-trimoxazole
- Sulfadiazine
- Sulfasalazine

Tetracyclines
- Tetracyclines
  - Demeclocycline
  - Doxycycline
  - Minocycline
  - Tetracycline
- Aminomethylcyclines
  - Omadacycline
  - Sarecycline
- Fluorocyclines
  - Eravacycline
- Glycylcyclines
  - Tigecycline

Miscellaneous antibacterials
- Bacitracins
  - Bacitracin
- Cyclic lipopeptides
  - Daptomycin
- Glycopeptides
  - Dalbavancin
  - Oritavancin
  - Telavancin
  - Vancomycin
- Lincomycins
  - Clindamycin
  - Lincomycin
- Oxazolidinones
  - Linezolid
  - Tedizolid
- Pleuromutilins
  - Lefamulin
- Polymyxins
  - Colistimethate/colistin
  - Polymyxin B
- Rafamycins
  - Rifamycin
  - Rifaximin
- Streptogramins
  - Quinupristin and dalfopristin

* Source: *AHFS Drug Information 2019*. Bethesda, MD: American Society of Health-System Pharmacists; 2019.