RWJBarnabas HEALTH

ANTIBACTERIAL TREATMENT FOR MULTI-DRUG RESISTANT GRAM-NEGATIVE INFECTIONS

A presentation for HealthTrust Members
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Speaker & Preceptor Disclosure

- The presenter and her preceptor have no financial relationships with any commercial interests pertinent to this presentation.

- This program may contain the mention of drugs, brands or suppliers presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular drug, brand or supplier.

Pharmacist & Nurse Learning Objectives

- Recognize general spectrums of activity for antibacterial agents used to treat multi-drug resistant (MDR) gram negative infections
- Assess appropriateness of antibacterial doses based on indication, weight, and/or recommended adjustments
- Identify pertinent monitoring parameters and characteristic side effects of antibacterial therapy

Technician Learning Objectives

- Recall brand and generic names of newer novel broad-spectrum antibiotics
- Differentiate various available dosage formulations for discussed antibacterial agents
- Recognize common antibiotic agents used in the treatment of MDR gram-negative infections

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BACKGROUND

Antimicrobial-Resistant Infections

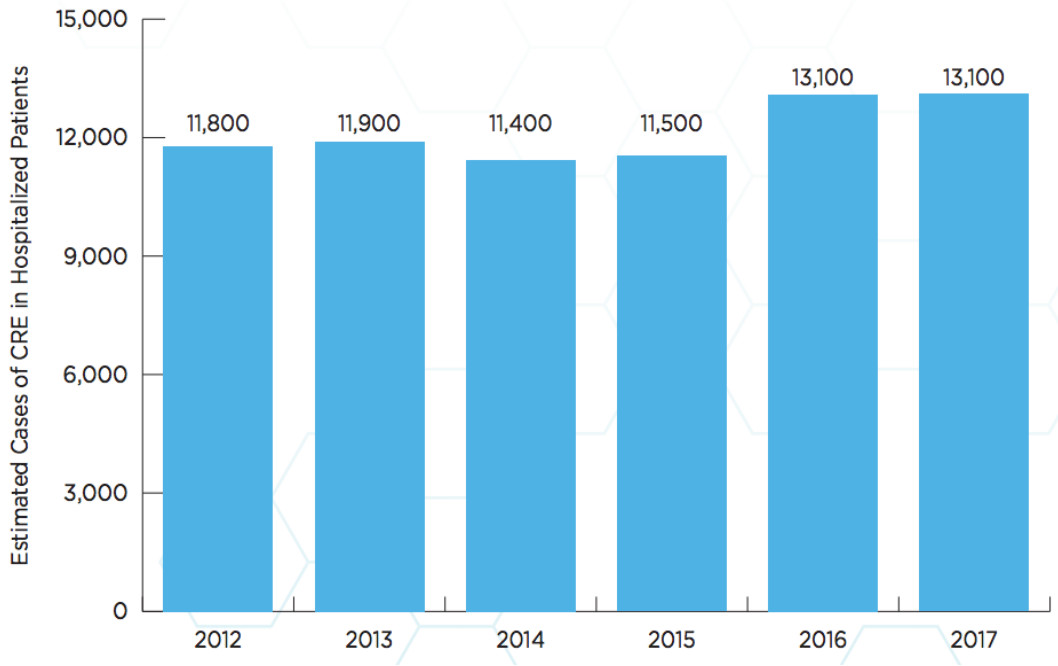
- Cause over 2.8 million infections each year in United States
  - Results in about 35,000 deaths each year
- Associated with substantial cost
  - Approximately $20 billion in excess spending each year
- Widespread, international issue
  - United States: plasmid-mediated *K. pneumoniae* carbapenemase (KPC)
  - India: plasmid-mediated bla_{NDM-1} gene resistance to carbapenems
  - China: plasmid-mediated *mcr-1* gene in *E. coli* resulting in colistin resistance

Sources: Marston HD, et al. *JAMA*. 2016;316(11):1193.

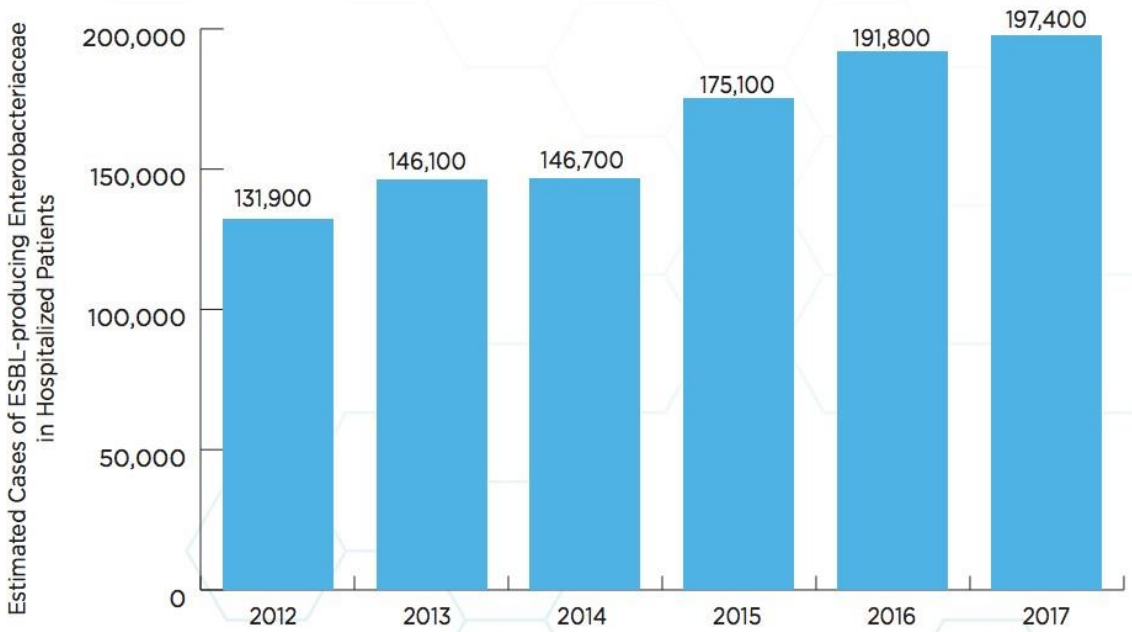
CDC [Internet]. 2019. [cited 2020 Jan 19]. Available at: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Growing Resistance

Carbapenem-Resistant Enterobacteriaceae (CRE) Cases Over Time



Extended Spectrum Beta-Lactamase (ESBL)-Producing Enterobacteriaceae Cases Over Time



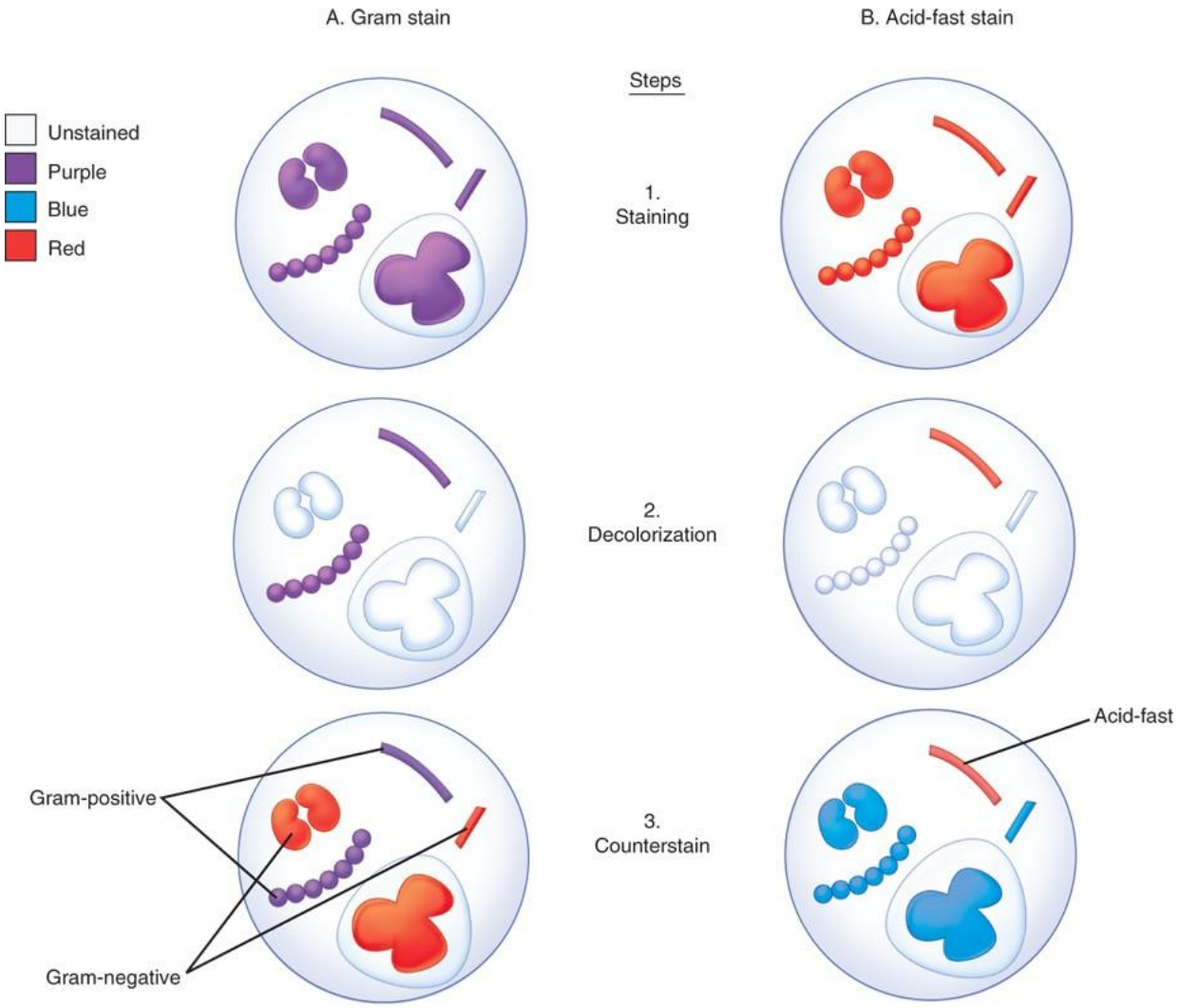
Source: CDC [Internet]. 2019. [cited 2020 Jan 19]. Available at: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Gram-Negative Infections

- Particularly efficient at acquiring resistance mechanisms
- Predominant type of infection in United States intensive care units
  - Approximately 70%
- Common infections:
  - Pneumonia
  - Bloodstream
  - Urinary tract

Source: Peleg AY, et al. *NEJM*. 2010;362(19):1804-13.

Gram Staining Procedure

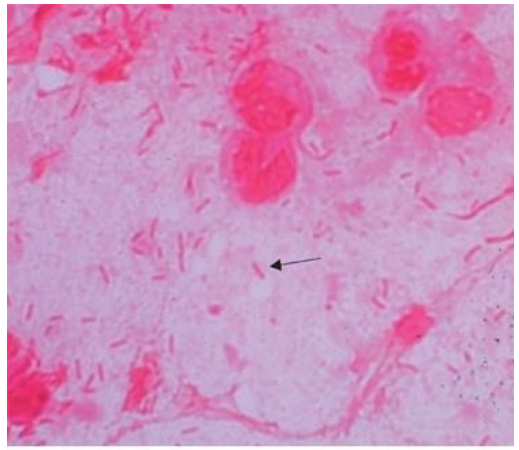


Source: Kenneth J. Ryan:
Sherris Medical Microbiology, Seventh Edition

Gram-Negative Bacteria

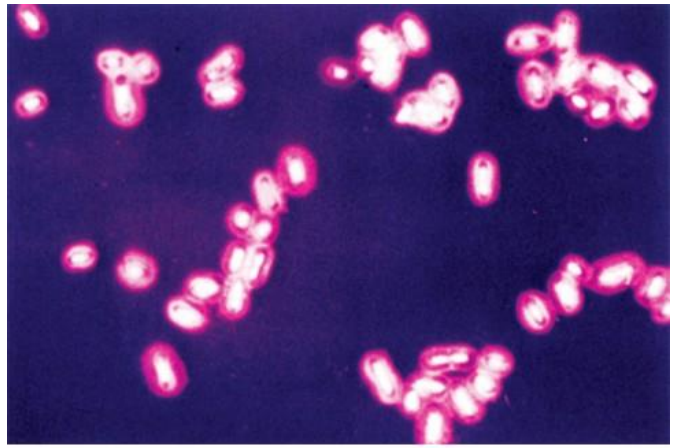
- *Acinetobacter spp.*
- *Enterobacter*
- *Escherichia coli*
- *Klebsiella*
- *Proteus*
- *Pseudomonas aeruginosa*
- *Salmonella*
- *Serratia*

Escherichia coli



Source: Kenneth J. Ryan:
Sherris Medical Microbiology, Seventh Edition

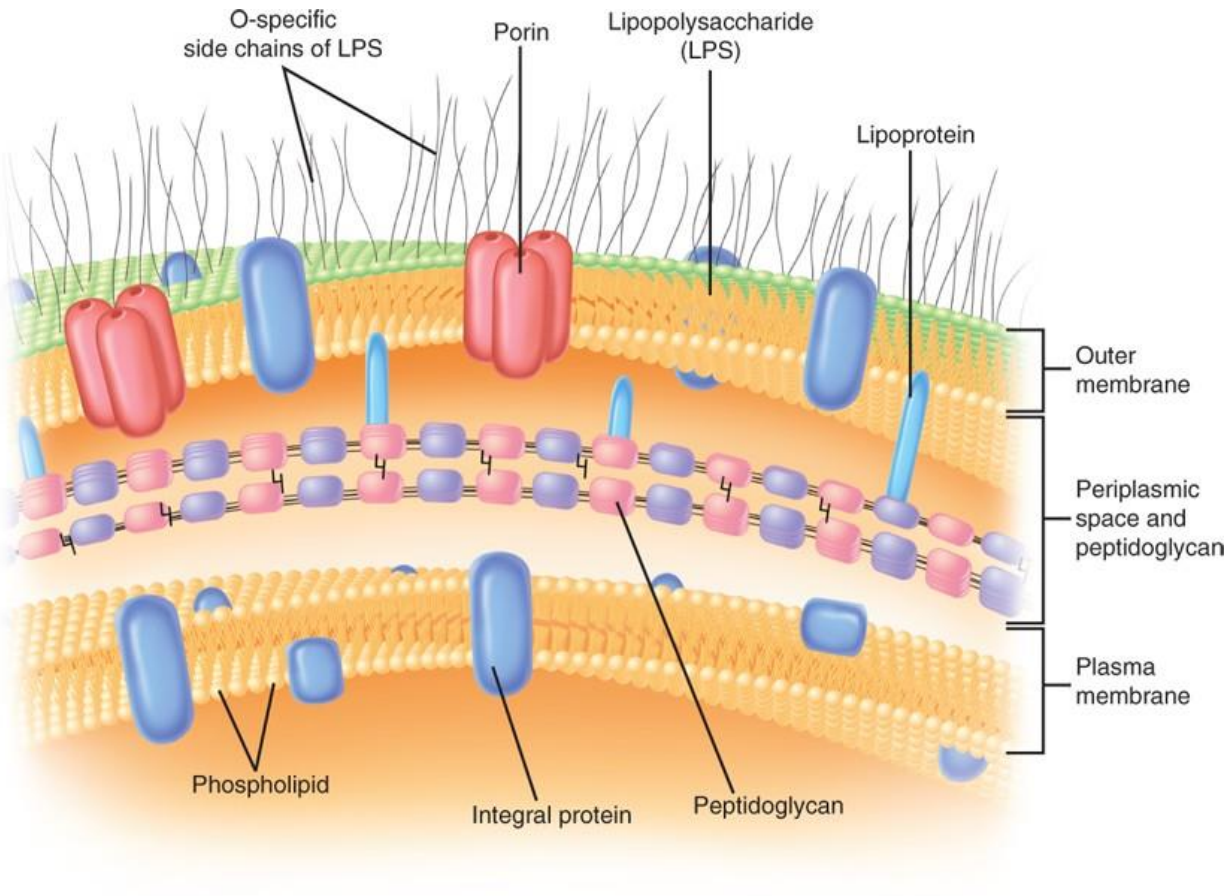
Klebsiella pneumoniae



Source: Kenneth J. Ryan:
Sherris Medical Microbiology, Seventh Edition

Gram-Negative Bacteria

- Cell envelope is a major target of antibiotic activity and consists of:
  - Cell membrane
  - Peptidoglycan-containing cell wall
  - Outer membrane of lipopolysaccharide

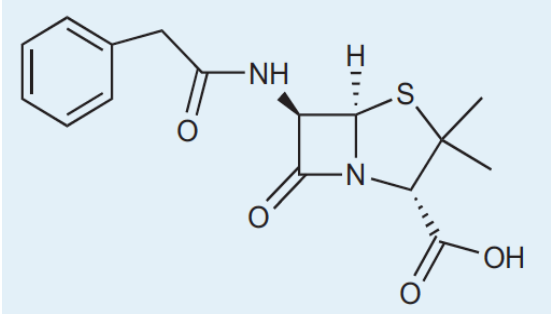


Source: Kenneth J. Ryan:
Sherris Medical Microbiology, Seventh Edition

Source: Guitor AK, et al. *Chest*. 2018;154(5):1202-12

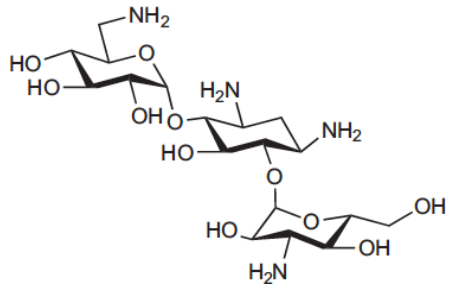
Antibacterials

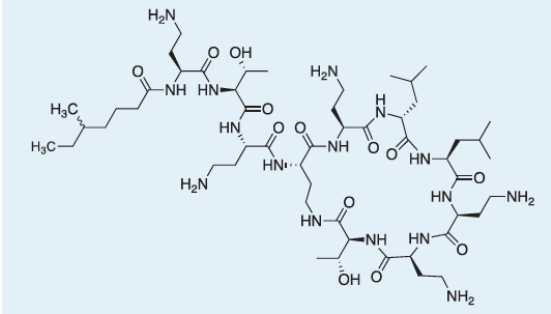
- Antibiotic agents that overcome bacteria by targeting essential cellular processes:
  - Protein synthesis
  - DNA replication
  - RNA production
  - Cell envelope synthesis



Beta-lactams
(e.g., penicillin G)

Aminoglycosides
(e.g., gentamicin)





Lipopeptides
(e.g., colistin)

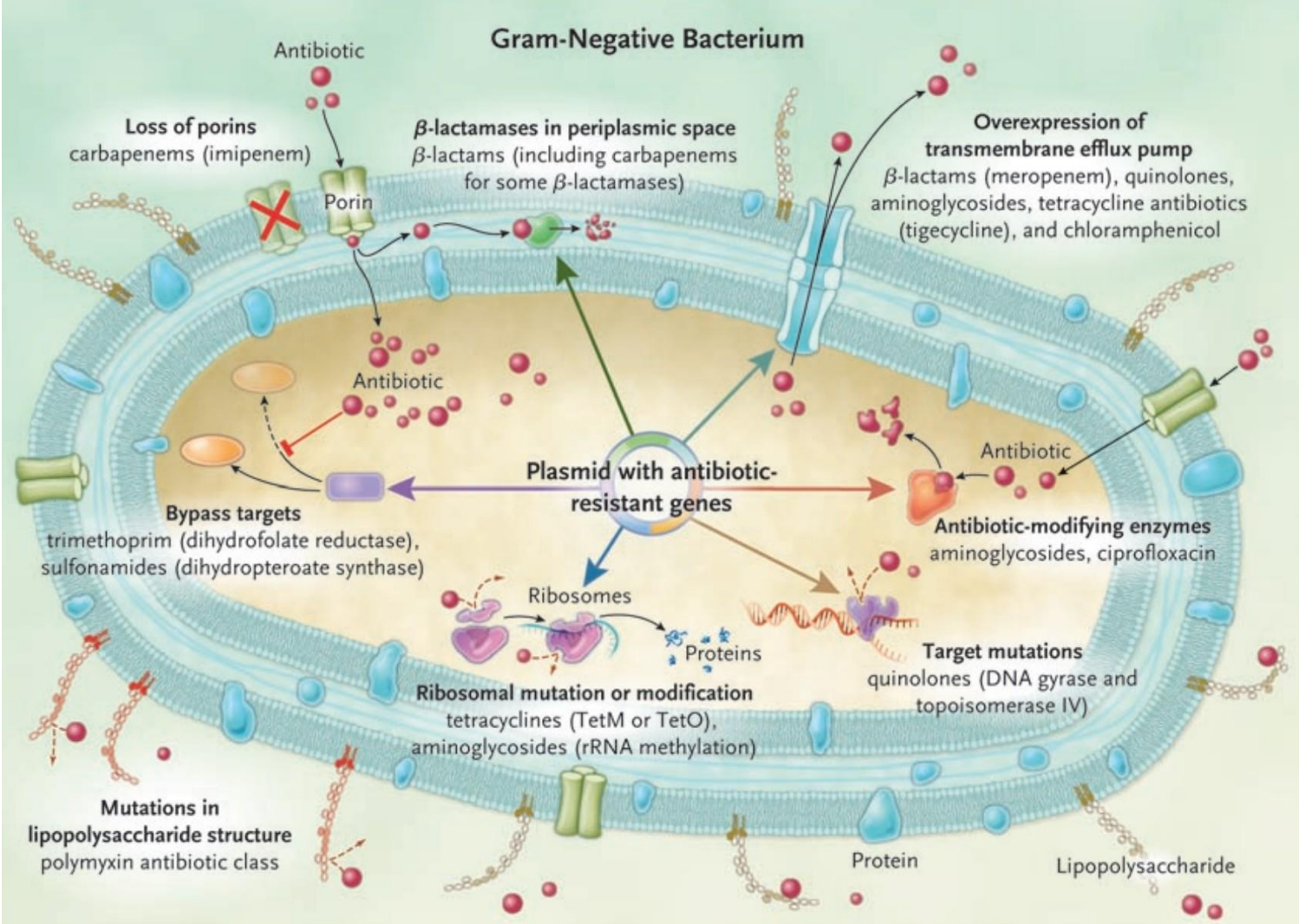
Source: Guitor AK, et al. *Chest*. 2018;154(5):1202-12

Bacterial Cell Resistance Mechanisms

- Changes to outer membrane
  - Modification or reduced porin expression
  - Overexpression of active efflux pumps
- Inactivation of antibiotic within cell
  - Plasmid- or chromosomally-encoded enzymes
  - Beta-lactamases within periplasmic space
- Target site modification

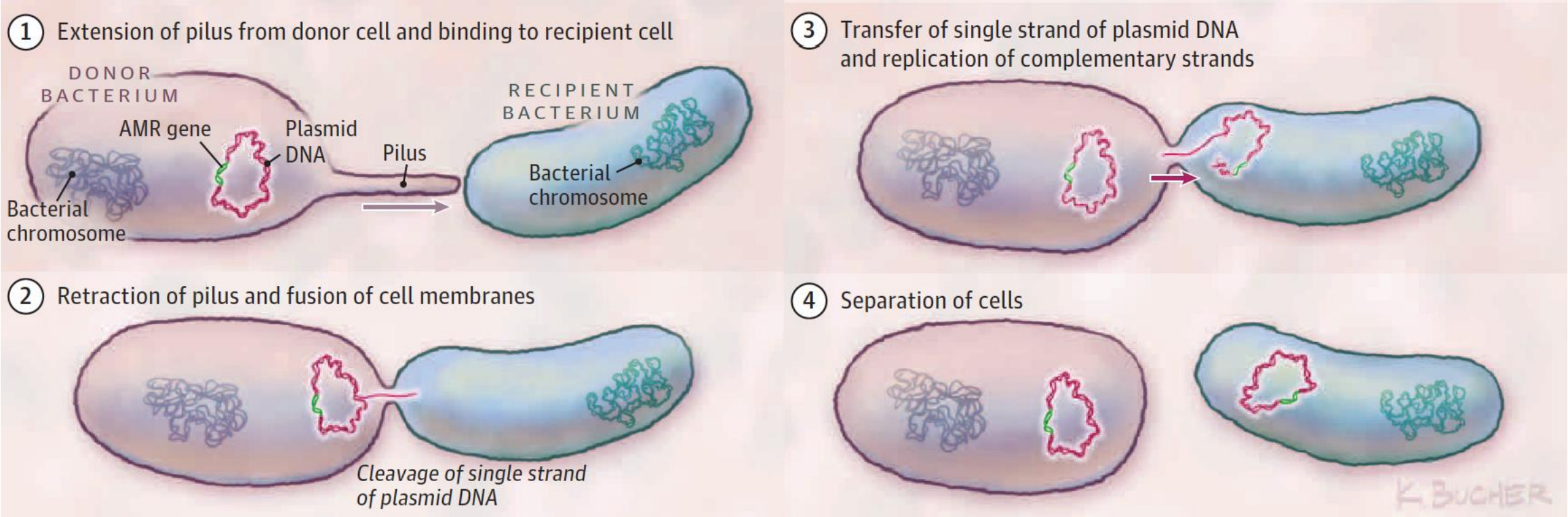
Sources: Guitor AK, et al. *Chest*. 2018;154(5):1202-12. Drawz SM, et al. *Clin Microbiol Rev*. 2010 Jan;23(1):160-201. Lambert PA. Adv Drug Deliv Rev. 2005;57(10):1471-85.

Bacterial Cell Resistance Mechanisms



Source: Peleg AY, et al. *NEJM*. 2010;362(19):1804-13.

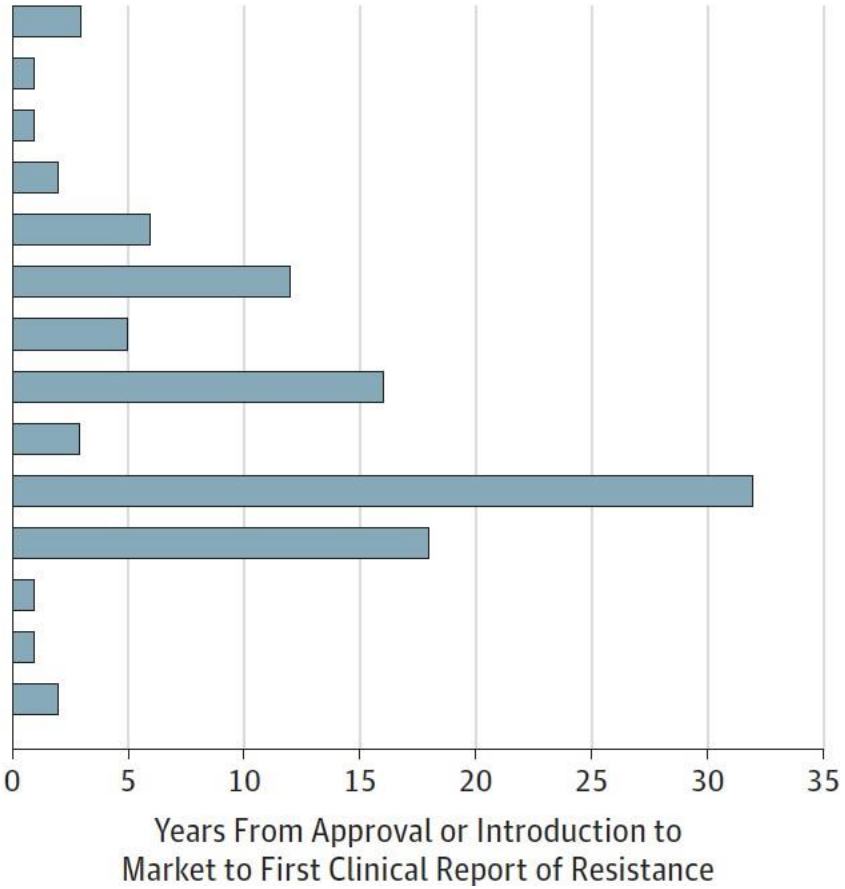
Plasmid Transmission



Source: Marston HD, et al. *JAMA*. 2016;316(11):1193.

Resistance Development

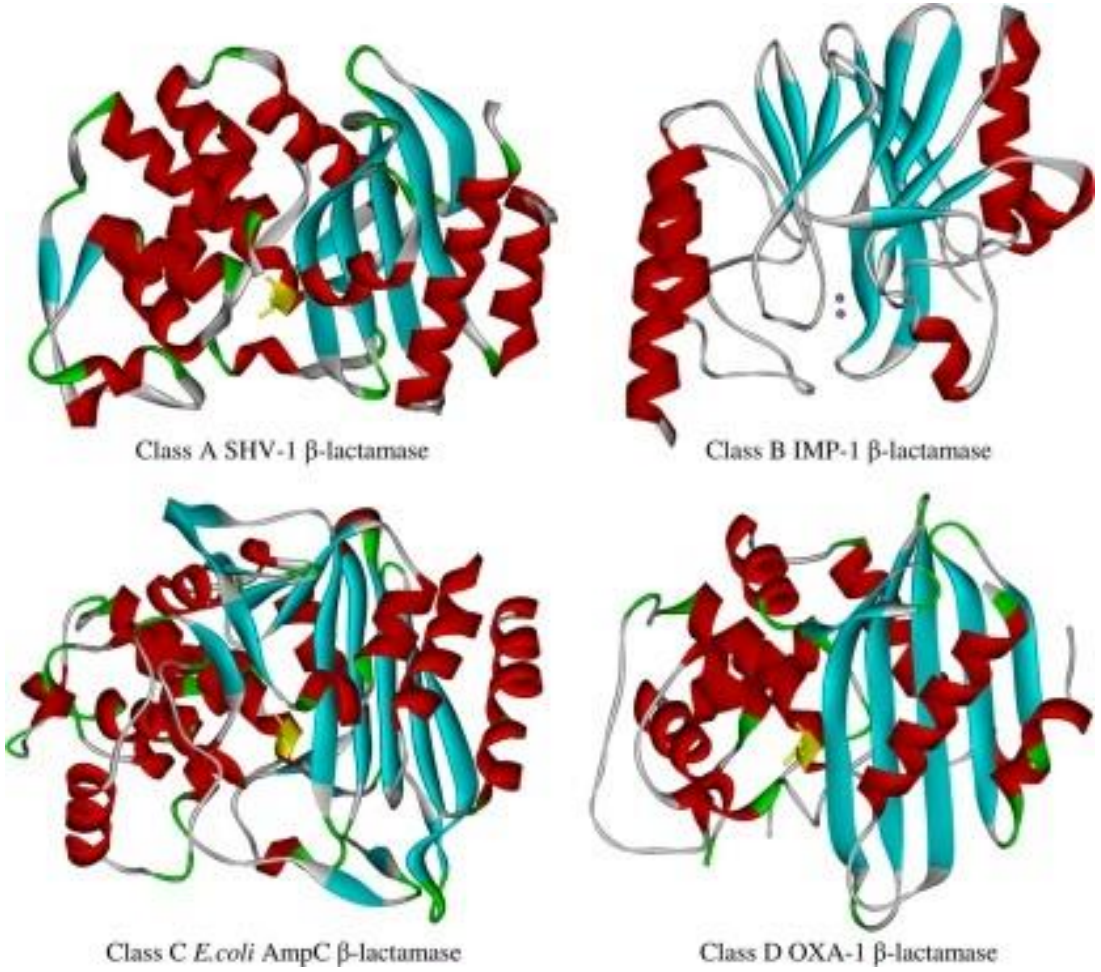
Class	Antibiotic	Year of Approval or Introduction to Market
β-Lactams	Penicillin	1942
	Methicillin	1960
	Cephalothin	1964
	Amoxicillin-clavulanic acid	1984
Carbapenems	Imipenem-cilastatin	1985
Amphenicols	Chloramphenicol	1950
Tetracyclines	Tetracycline	1953
Aminoglycosides	Streptomycin	1946
Macrolides	Erythromycin	1952
Glycopeptides	Vancomycin	1958
Quinolones	Nalidixic acid	1964
Streptogramins	Quinupristin-dalfopristin	1999
Oxazolidinones	Linezolid	2000
Lipopeptides	Daptomycin	2003



Source: Marston HD, et al. *JAMA*. 2016;316(11):1193.

Beta-Lactamases

- Beta-lactamases
  - Enzymes that break down beta-lactam antibiotics
  - Mechanism of resistance
  - Many types
- Beta-lactamase inhibitors
  - Clavulanate
  - Sulbactam
  - Tazobactam
  - Avibactam
  - Vaborbactam
  - Relebactam



Source: Drawz SM, et al. *Clin Microbiol Rev*. 2010 Jan;23(1):160-201.

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EXTENDED-SPECTRUM BETA-LACTAMASES

Extended-Spectrum Beta-Lactamases (ESBLs)

- First reported case in 1983
  - Bacteria capable of hydrolyzing 3rd generation cephalosporins
- Pathogens may include many Enterobacteriaceae:
  - *Klebsiella* species
  - *E. coli*
- At-risk populations:
  - Those exposed to healthcare settings
  - Healthy individuals with no exposure to healthcare settings
  - International travelers

Sources: Centers for Disease Control and Prevention. https://www.cdc.gov. Accessed October 12, 2019. Arnold RS, *South Med J*. 2011 Jan;104(1):40-5.

Extended-Spectrum Beta-Lactamases (ESBLs)

- Resistance to most beta-lactams, including:
  - Penicillins
  - Cephalosporins
    - Typically through 3rd generation
    - Cefepime may have variable activity
  - Monobactams
- Carbapenems retain spectrum of activity
  - Resistance quickly developing
  - Drug class of choice due to *in vivo* activity

Sources: Centers for Disease Control and Prevention. https://www.cdc.gov. Accessed October 12, 2019. Drawz SM, et al. *Clin Microbiol Rev*. 2010 Jan;23(1):160-201.

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CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE*

Carbapenem-Resistant *Enterobacteriaceae* (CRE)

- First isolate in United States reported in 2001
- Broadly-resistant gram-negative bacteria
  - Carbapenems do not retain activity
- At-risk populations:
  - Patients in healthcare settings (nursing homes, hospitals, etc.)
  - Use of ventilators, urinary catheters, or intravenous catheters
  - Long-term antibiotic therapy
- Concerning mortality rates
  - May cause death in up to 50% of patients

Sources" Paterson DL, et al. *Clin Microbiol Rev*. 2005 Oct;18(4):657-86. Centers for Disease Control and Prevention. https://www.cdc.gov. Accessed October 12, 2019.

Carbapenemases

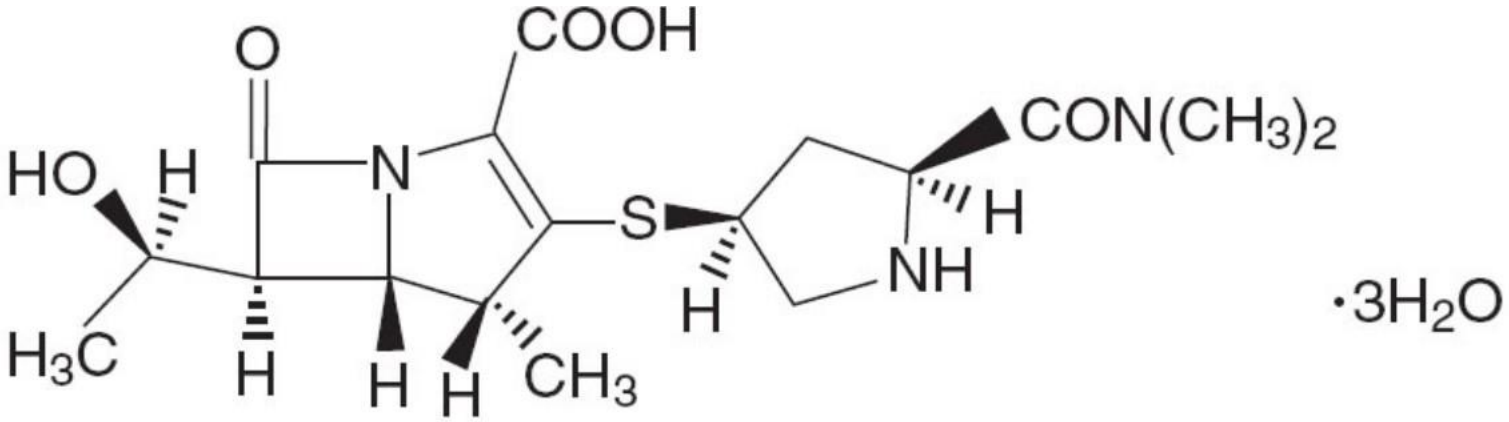
- Broadest beta-lactam resistance mechanism
- *Klebsiella pneumoniae* carbapenemase (KPC)
  - Most common type of carbapenemase in the United States
  - Transmitted via plasmids to other bacteria
- Metallo-beta lactamases
  - Resistance in all beta-lactams except monobactams
  - More common outside of United States
- OXA-type carbapenemases
  - Resistant to clavulanate, sulbactam, and tazobactam

Sources: Drawz SM: , et al. *Clin Microbiol Rev*. 2010 Jan;23(1):160-201. Centers for Disease Control and Prevention. https://www.cdc.gov. Accessed October 12, 2019.

TREATMENT OPTIONS

Carbapenems

- Mechanism: inhibition of bacterial cell wall synthesis
- Agents:
  - Doripenem
  - Ertapenem
  - Imipenem-cilastatin
  - Meropenem



- Spectrum of activity:
  - Broad-gram negative spectrum including ESBLs
  - Ertapenem has no activity on *P. aeruginosa* and *Acinetobacter*

Sources: Doribax ® (doripenem) [package insert]. Raritan, NJ: Ortho-McNeil; 2009. Merrem® IV (meropenem for injection)[package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016. Primaxin ® (imipenem-cilastatin) [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2016. Invanz ® (ertapenem for injection) [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2012.

Carbapenems

- Warnings
  - Hypersensitivity reactions
  - Lowered seizure threshold
  - Decreased valproic acid levels
    - Exception: doripenem
  - Thrombocytopenia in renal dysfunction
  - *C. difficile* infection
- Dose adjustments:
  - Renal

SBMC Formulary Options: Carbapenems
meropenem
ertapenem

SBMC Restrictions: Carbapenems
• Must be order by an infectious disease physician
• Only one dose will be dispensed for orders unapproved by infectious disease providers

Sources: Doribax ® (doripenem) [package insert]. Raritan, NJ: Ortho-McNeil; 2009. Merrem® IV (meropenem for injection)[package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2016. Primaxin ® (imipenem-cilastatin) [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2016. Invanz ® (ertapenem for injection) [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2012.

Carbapenems

- Double carbapenem coverage
  - Synergistic salvage therapy with unknown mechanism
  - Use of two different carbapenems
- *In vitro* data studied enzymes:
  - KPC, VIM, NDM, and OXA
- *In vivo* data studied enzymes:
  - KPC only
- Often used to avoid more toxic polymyxins
  - Consider option in patients who are not critically ill

Source: White BP, et al. *Infect Dis*. 2019;51(3):161-7.

White, et al.

Study	Size	Carbapenem #1	Carbapenem #2	Clinical Cure	30-day mortality	60-day mortality	Notes
Cprek, Gallagher (2016) [35]	*n* = 18 (7 BSI)	Meropenem 2 g Q8H or Doripenem 500 mg Q8H	Ertapenem 1 g Q24H	3/7 (42.8%)	1/7 (14%)	–	100% of patients were admitted to the ICU
Oliva, et. al (2016) [27]	*n* = 15 (5 BSI)	Meropenem 2 g Q8H[A]	Ertapenem 1 g Q24H		–	1/15 (6.7%)	
Souli, et al. (2017) [37]	*n* = 27 (13 BSI)	Meropenem 2 g Q8H[A]	Ertapenem 1 g Q24H	10/13 (76.9%)	3/13 (23%)	–	
Oliva, et al. (2017) [28]	*n* = 32	Meropenem 2 g Q8H[A]	Ertapenem 1 g Q24H	24/32 (75%)	–	6/32 (18.7%)	Double carbapenem therapy (*n* = 18) versus double carbapenem therapy + colistin (*n* = 14) was tested in this study.
Venugopalan, et al. (2017) [36]	*n* = 36 (18 = double carbapenem therapy)	Doripenem 2 g Q8H[B]	Ertapenem 1 g Q24H	13/18 (72%)	5/16 (31.2%)	–	6 patients treated as primary therapy, 12 patients were treated as salvage therapy
De Pascale, et al. (2017) [16]	*n* = 144 (83 BSI)	Meropenem 2 g Q8H[A]	Ertapenem 2 g/day; Q12/24H	50/84 (60.2%)	34/84 (40.4%)	–	Study showed association between double carbapenem use and increased survival; majority of the patients had septic shock.

A= 3-hour extended infusion

B= 4-hour extended infusion

Source: White BP, et al. *Infect Dis.* 2019;51(3):161-7.

Aminoglycosides

- Mechanism: binds to bacterial ribosome and inhibits protein synthesis
- Indications: serious infections caused by susceptible pathogens
  - Part of combination therapy in treatment of bacterial sepsis, meningitis, respiratory tract, gastrointestinal tract, skin, bone, and soft tissue;
  - Urinary tract infections may allow for solo therapy
- Gram-negative spectrum of activity:
  - *Citrobacter, Enterobacter, E. coli, Klebsiella, Proteus, Serratia, P. aeruginosa*
- Agents:
  - Gentamicin
  - Amikacin
  - Tobramycin
  - Plazomicin

Sources: Gentamicin [package insert]. Lake Zurich, IL: Fresnius Kabi USA, LLC.; 2013. Tobramycin [package insert]. New York, NY: Pfizer Inc.; 2011. Amikacin sulfate [package insert]. Schaumburg, IL: Sagent Pharmaceuticals, Inc.; 2018. Zemdri [plazomicin) [package insert]. South San Francisco, PA: Achaogen, Inc.; 2018.

Aminoglycosides

- Warnings:
  - Ototoxicity, nephrotoxicity, neuromuscular blockade
  - Fetal harm
  - Potential anaphylaxis due to sodium metabisulfite hypersensitivity
- Dosing: **use ideal (IBW) or adjusted body weight (ABW)**
  - Adjusted body weight when total body weight (TBW) ≥130% ideal body weight
  - Traditional versus extended interval dosing
- Monitoring:
  - Peak and trough levels

SBMC Formulary Options: Aminoglycosides
amikacin
gentamicin
tobramycin

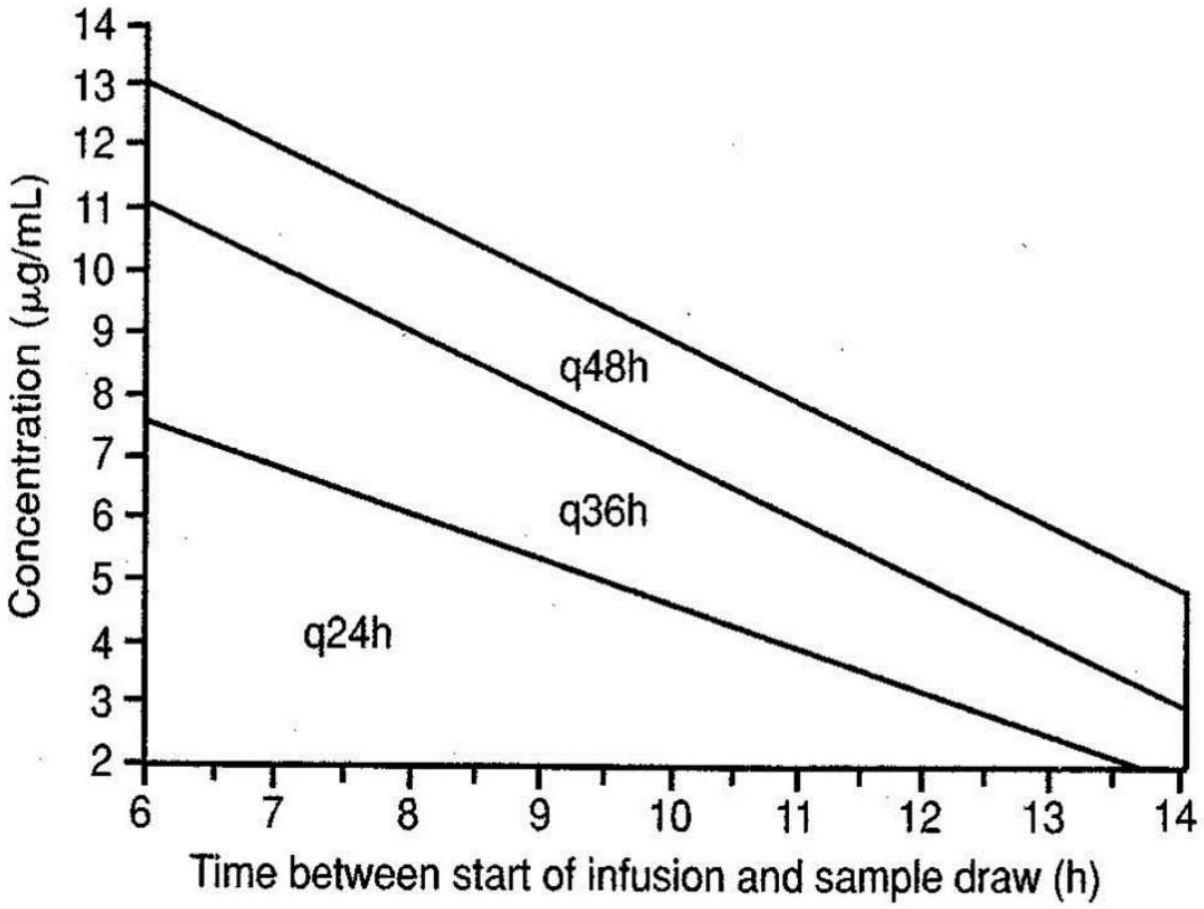
$$ABW = IBW + 0.4(TBW - IBW)$$

Sources: Gentamicin [package insert]. Lake Zurich, IL: Fresnius Kabi USA, LLC.; 2013. Tobramycin [package insert]. New York, NY: Pfizer Inc.; 2011. Amikacin sulfate [package insert]. Schaumburg, IL: Sagent Pharmaceuticals, Inc.; 2018. Zemdri [plazomicin) [package insert]. South San Francisco, PA: Achaogen, Inc.; 2018

Aminoglycosides: Extended Interval Dosing

Drug	Dose (mg/kg/dose)
gentamicin	5 - 7
tobramycin	5 - 7
amikacin	20

CrCl (mL/min)	Interval (hours)
60	every 24
40 - 59	every 36
20 - 39	every 48



Sources: Nicolau DP, et al. *Ther Drug Monit*. 1996;18(3):263. Bailey TC, et al. *Clin Infect Dis*. 1997;24(5):786-795.

Aminoglycosides: Conventional Dosing

Drug	Loading Dose (mg/kg)	Maintenance Dose (mg/kg/dose)	Goal Peak* (mcg/mL)	Goal Trough (mcg/mL)
gentamicin	2	1.5 - 2	6 – 10	<1
tobramycin	2	1.5 - 2	6 - 10	<1
amikacin	7.5	5 – 7.5	20 - 30	<4

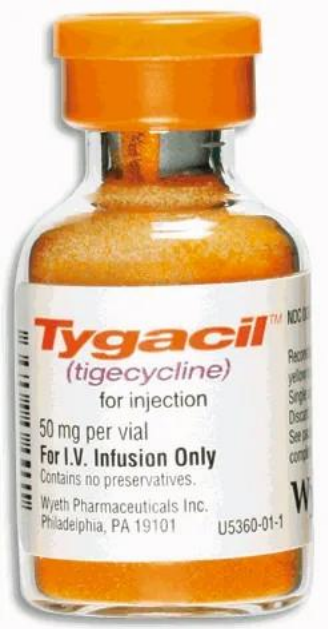
*Peaks are indication-specific; used in conventional dosing only

GFR (mL/min/1.73 m^2)	>50	10 - 50	<10
Interval (hours)	8	12 - 48	48 - 72

Source: Aronoff GR, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed, Philadelphia, PA: American College of Physicians, 2007.

Tigecycline

- Mechanism: inhibits bacterial protein translation in 30S ribosomal subunit
- Gram-Negative spectrum of activity (clinical infections)
  - *Citrobacter, Enterobacter cloacae, E. coli,* beta-lactamase negative *Haemophilus influenzae, K. pneumoniae, Legionella*
  - **No action against** *Proteus* strains, *Providencia*, or *P. aeruginosa*
- Indications
  - Complicated skin and skin structure infections
  - Complicated intra-abdominal infections
  - Community-acquired bacterial pneumonia
- Dose: 100 mg initial intravenous dose, then 50 mg every 12 hours
  - Administered over 30 to 60 minutes
  - No dose adjustment in renal impairment



Source: Tygacil® (tigecycline) [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2010.

Tigecycline

- Warnings
  - Increased all-cause mortality versus comparison in Phase 3 and 4 clinical trials
  - Lower cure rates and higher mortality in ventilator-associated pneumonia
  - Hepatic dysfunction, liver failure, and fatal pancreatitis
- Common side effects
  - Nausea, vomiting, diarrhea, abdominal pain
- Significant drug interactions
  - Increased INR with warfarin use
- Storage and preparation
  - Reconstituted solution color should be yellow to orange; discard if green or black
  - May be stored at room temperature for maximum of 24 hours after reconstitution

SBMC Restrictions: Tigecycline
• Must be order by an infectious disease physician
• Only one dose will be dispensed for orders unapproved by infectious disease providers

source: Tygacil® (tigecycline) [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2010.

Polymyxins: Colistimethate

- Mechanism: bacterial membrane penetration and disruption
- Indication: treatment or prevention of susceptible bacterial infections ONLY
- Gram-negative spectrum of activity:
  - *Enterobacter aerogenes, E. coli, K. pneumoniae, P. aeruginosa*
  - **Not indicated** for *Neisseria* or *Proteus*
- Dose: loading + maintenance
  - Maintenance doses based on renal function
  - Weight-based dosing no longer recommended
  - Colistimethate sodium = 150 mg colistin base
- Available for inhalation as off-label route of administration

SBMC Restrictions: Colistimethate
• Must be order by an infectious disease physician
• Only one dose will be dispensed for orders unapproved by infectious disease providers

Source: Coly-Mycin® M (colistimethate for injection) [package insert]. Bristol, TN: Monarch Pharmaceuticals, Inc.; 2006.

Tsuji BT, et al. *Pharmacotherapy*. 2019;39(1):10-39.

Polymyxins: Polymyxin B

- Mechanism: increase permeability of bacterial cell membrane causing death
- Indication: serious susceptible infections when other agents contraindicated
- Gram-negative spectrum of activity: all **except** *Proteus*
  - *P. aeruginosa* infections of meninges, urinary tract, and bloodstream
- Dose: loading + maintenance
  - 2 – 2.5 mg/kg load followed by 1.25 – 1.5 mg/kg every 12 hours (total body weight)
  - New guidelines recommend against renal dose adjustments
    - Potential for underdosing in adjustment for renal function
  - 1 mg polymyxin B base = 10,000 units polymyxin B
- Intramuscular, intrathecal, and ophthalmic routes available

Sources: Polymyxin B [package insert]. Bedford, OH: Ben Venue Laboratories, Inc., Inc.; 2011. Tsuji BT, et al. Pharmacotherapy. 2019;39(1):10-39.

Polymyxins

- Warnings:
  - Neurotoxicity
  - Nephrotoxicity
  - Respiratory paralysis from neuromuscular blockade
    - Use extreme caution with concurrent administration of neuromuscular-blocking agents
  - *Clostridiodes difficile* infection
- Side effects
  - Gastrointestinal upset, nephrotoxicity, parasthesias, respiratory distress, fever

Source: Polymyxin B [package insert]. Bedford, OH: Ben Venue Laboratories, Inc., Inc.; 2011. Coly-Mycin® M (colistimethate for injection) [package insert]. Bristol, TN: Monarch Pharmaceuticals, Inc.; 2006.

Combination Therapy for CRE

- Combination therapy used to reduce mortality
  - Especially in regimens including carbapenems

Tumbarello et al. 2012	
Population	Multicenter retrospective cohort study at three Italian teaching hospitals of bloodstream infections caused by KPC-producing *K. pneumoniae* (n= 125)
Intervention	Combination therapy vs. monotherapy (tigecycline, colistin, or gentamicin)
Endpoints	Death within 30 days of first positive blood culture
Statistics	Significantly less mortality in combination therapy group with tigecycline, colistin, and meropenem Odds ratio 0.11(95% CI, 0.02 – 0.69; p= 0.01)

Source: Tumbarello M, et al. *Clin Infect Dis*. 2012;55(7):943-50.

Beta-Lactam-Beta-Lactamase Inhibitors (BLBLIs)

Brand Name	Generic Name	Approval
Zerbaxa®	ceftolozane-tazobactam	December 2014
Avycaz®	ceftazidime-avibactam	February 2015
Vabomere™	meropenem-vaborbactam	August 2017
Recarbrio™	imipenem-cilastatin-relebactam	July 2019

Source: U.S. Food and Drug Administration. https://www.fda.gov. Accessed October 12, 2019.

Novel Cephalosporin BLBLI Spectrum of Activity

- Ceftolozane-tazobactam
  - Broad gram-negative coverage (including *P. aeruginosa*)
  - Covers most ESBL-producing Enterobacteriaceae
  - Different doses depending on indication
- Ceftazidime-avibactam
  - Broad gram-negative coverage (including *P. aeruginosa*)
  - Covers most Enterobacteriaceae
    - ESBL
    - CRE: some OXA-type and KPC but no metallo-beta-lactamases
  - No *Acinetobacter* coverage

SBMC Formulary Options: BLBLIs
ceftolozane/tazobactam
ceftazidime/avibactam

SBMC Restrictions: BLBLIs
• Must be order by an infectious disease physician
• Only one dose will be dispensed for orders unapproved by infectious disease providers

Source: U.S. Food and Drug Administration. https://www.fda.gov. Accessed October 12, 2019.

Novel Carbapenem BLBLI Spectrum of Activity

- Meropenem-vaborbactam
  - Broad gram-negative coverage
    - Lower minimum inhibitory concentration than meropenem alone
  - Covers most KPC CRE
    - No metallo-beta-lactamase or OXA-type coverage
  - No enhanced clinical activity for either *P. aeruginosa* or *Acinetobacter*
- Imipenem-cilastatin-relebactam
  - Broad gram-negative coverage
    - Lower minimum inhibitory concentration than imipenem alone
  - Covers most KPC CRE
    - No metallo-beta-lactamase or OXA-type coverage
  - No enhanced clinical activity for either *Stenotrophomonas* or *Acinetobacter*

Source: U.S. Food and Drug Administration. https://www.fda.gov. Accessed October 12, 2019.

Novel Carbapenem BLBLIs

- **Use is only for multi-drug resistant infections**
  - See resistance patterns
- FDA-approved indications:
  - Complicated urinary tract infections
  - Complicated intra-abdominal infections with metronidazole
    - Exception: meropenem-vaborbactam
  - Hospital- and ventilator- acquired pneumonia
    - Ceftazidime-avibactam only

Avycaz®
ceftazidime and avibactam
for injection (2.5 g)

ZERBAXA.
ceftolozane and tazobactam
for injection (1.5 g)

Sources: Avycaz® [ceftazidime-avibactam) [package insert]. Madison, NJ: Alelrgan, Inc.; 2019. Zerbaxa® (ceftolozane-tazobactam) [package insert]. Lexington, MAL Cubist Pharmaceuticals U.S.; 2014. Vabomere™ [meropenem-vaborbactam) [package insert]. Parsippany, NJ: The Medicines Company; 2017. Recarbrio™[imipenem-cilastatin-relebactam) [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2019.

Choice for CRE Treatment

- BLBLIs are preferred over other agents when susceptibility is present
  - May also be used in combination with other agents

CRACKLE Study, 2018	
Population	Multicenter prospective observational study of patients with carbapenem resistant *Enterobacteriaceae* infection (n= 137)
Intervention	Ceftazidime-avibactam versus colistin initiation in CRE treatment
Endpoints	All-cause hospital mortality 30 days after treatment initiation
Statistics	Significant difference favoring initial treatment with ceftazidime-avibactam (difference, 23%; 95% bootstrap confidence interval, 9 – 35%; p= 0.001)

Source: van Duin D, et al., *Clin Infect Dis*. 2018. Jan 6;66(2):163-171.

Choice for CRE Treatment

TANGO II Trial, 2018	
Population	Phase 3, multinational, open-label, randomized control trial study of patients with carbapenem resistant *Enterobacteriaceae* infection (n= 47) - Bacteremia, hospital-acquired/ventilator-associated pneumonia, complicated intra-abdominal, complicated urinary tract, or acute pyelonephritis infection
Intervention	Meropenem-vaborbactam versus best available treatment - Mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or ceftazidime-avibactam alone
Endpoints	Clinical cure (primary)
Statistics	Clinical cure: 21/32 versus 5/15 (95% CI, 3.3% to 61.3%; p= 0.03) at end of treatment 19/32 versus 4/15 (95% CI, 3.3% to 61.3%; p= 0.02) at test of cure

Source: Wunderink RG, et al. *Infect Dis Ther*. 2018 Dec;7(4):439-455.

Novel Carbapenem BLBLIs

- Warnings
  - Hypersensitivity reactions
  - Decreased seizure threshold
  - *C. difficile* infection
  - Decreased serum valproic acid levels
    - Meropenem-vaborbactam and imipenem-cilastatin-relebactam
- Renal dose adjustments required

NEW
VABOMERE™
meropenem and vaborbactam for injection (4 g)

RECARBRIO™
(imipenem, cilastatin, and relebactam) for injection 1.25 g

Avycaz® (ceftazidime-avibactam) [package insert]. Madison, NJ: Alelrgan, Inc.; 2019. Zerbaxa® (ceftolozane-tazobactam) [package insert]. Lexington, MAL Cubist Pharmaceuticals U.S.; 2014. VabomereTM (meropenem-vaborbactam) [package insert]. Parsippany, NJ: The Medicines Company; 2017. RecarbrioTM (imipenem-cilastatin-relebactam) [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2019.

Novel Tetracycline Derivative: Eravacycline

- Approval: 2018
- FDA Indication: complicated intraabdominal infections
  - 1 mg/kg every 12 hours
- Dose adjustments
  - Concomitant use of a strong CYP3A4 inducer
  - Severe hepatic impairment

XERAVA™
(eravacycline) for injection

Source: Xerava™ (eravacycline) [package insert]. Watertown, MA: Tetraphase Pharmaceuticals, Inc.; 2019.

Eravacycline: Spectrum

- Spectrum both *in vitro* and clinically:
  - Gram-positive and anaerobic activity present
  - Gram-negative activity:
    - *Acinetobacter* (in vitro)
    - *Citrobacter freundii*
    - *Enterobacter cloacae*
    - *Escherichia coli*
    - *Klebsiella oxytoca*
    - *Klebsiella pneumoniae*

Source: Xerava™ (eravacycline) [package insert]. Watertown, MA: Tetraphase Pharmaceuticals, Inc.; 2019.

Eravacycline: Warnings

- Antianabolic effects
- *C. difficile* superinfection
- Hypersensitivity
- Hepatotoxicity
- Pancreatitis
- Photosensitivity
- Pseudotumor Cerebri

*Caution use in children under eight years of age due to permanent tooth discoloration, enamel hypoplasia, or reversible inhibition of bone growth

Source: Xerava™ (eravacycline) [package insert]. Watertown, MA: Tetraphase Pharmaceuticals, Inc.; 2019.

Novel Cephalosporin: Cefiderocol

- Approval: November 14, 2019
- FDA Indication: complicated UTI (including pyelonephritis)
  - For those with limited or no other treatment options
  - 2 grams intravenously every 8 hours
- Warning: increased all-cause mortality in carbapenem-resistant gram-negative infections
- Dose adjustments
  - CrCl ≥ 120 mL/min
  - CrCl< 60 mL/min

Source: Fetroja® [cefiderocol) [package insert]. Florham Park, NJ: Shionogi Inc.; 2019.

Novel Cephalosporin: Cefiderocol

- Novel mechanism
  - Able to enter bacteria via siderophore transport system by binding iron
- Spectrum
  - No relevant gram-positive or anaerobic coverage
  - Demonstrated *in vitro* activity against:
    - *S. maltophilia*
    - *Enterobacteriaceae*
      - Includes some isolates with ESBLs or carbapenemases
    - *P. aeruginosa* and *A. baumannii*
      - Includes some isolates resistant to amikacin, ciprofloxacin, and meropenem

Source: Fetroja® [cefiderocol) [package insert]. Florham Park, NJ: Shionogi Inc.; 2019.

SUMMARY OF OPTIONS

Summary

MDR *Pseudomonas*
Aminoglycosides (usually in combination with β-lactam): • Amikacin • Gentamicin • Plazomicin • Tobramycin
Carbapenems (usually combination therapy): • Doripenem • Imipenem-cilastatin • Meropenem
Beta-lactam-beta-lactamase inhibitors • Ceftolozane-avibactam • Ceftazidime-avibactam • Imipenem-cilastatin-relebactam*
Polymyxins (usually combination therapy): • Polymyxin B • Colistimethate
Cefiderocol

Acinetobacter
Carbapenems: • Doripenem • Imipenem-cilastatin • Meropenem
Aminoglycosides (usually combined with another agent): • Amikacin • Gentamicin • Plazomicin • Tobramycin
Polymyxins: • Polymyxin B • Colistimethate
Tigecycline
Eravacycline
Cefiderocol

Summary, *continued*

ESBL
Carbapenems: • **Doripenem** • **Ertapenem** • **Imipenem-cilastatin** • **Meropenem**
Aminoglycosides (usually in combination therapy) • Amikacin • Gentamicin • Plazomicin • Tobramycin
Beta-lactam-beta-lactamase inhibitors • Ceftolozane-avibactam • Ceftazidime-avibactam
Tigecycline
Eravacycline
Cefiderocol

Carbapenem Resistant *Enterobacteriaceae*
Beta-lactam-beta-lactamase inhibitors • **Ceftazidime-avibactam (KPC, OXA)** • **Meropenem-vaborbactam (KPC)** • **Imipenem-cilastatin-Relebactam (KPC)**
Aminoglycosides (usually in combination therapy) • Amikacin • Gentamicin • Plazomicin • Tobramycin
Polymyxins (usually in combination therapy) • Polymyxin B • Colistimethate
Tigecycline (usually in combination therapy)
Dual carbapenem therapy
Eravacycline
Cefiderocol

BOLD= agents of choice

Remaining Questions

- What is the best agent for resistant organisms?
  - *Acinetobacter*
  - *Pseudomonas*
  - *Stenotrophomonas*
- What is the role of newer agents?
  - Cefiderocol
  - Plazomicin
  - Combination therapy

RESOURCES

Infectious Diseases Society of America

- Community of 12,000 specialist infectious disease professionals
- Clinical practice guidelines
  - https://www.idsociety.org/practice-guideline/practice-guidelines/#/name_na_str/ASC/0/+/
- Journals
  - *Clinical Infectious Diseases*
  - *Journal of Infectious Diseases*
  - *Open Forum Infectious Diseases*
- Publications
  - *IDSA News*
  - *Science Speaks*

IDSA
Infectious Diseases Society of America

Hospital Antibiogram

- Provides the most specific information for the institution's patient population
  - Localized susceptibilities

Except for Isolate Total all numbers represent the % of isolates sensitive to an antibiotic	Isolate Total	Ampicillin	Ampicillin/Sulbactam	Amikacin ***	Aztreonam	Cefazolin	Ceftazidime *	Ceftriaxone	Cefepime	Ceftazidime/Avibactam ***	Ceftolozane/Tazobactam	Ertapenem	Gentamicin	Levofloxacin	Meropenem *	Minocycline ***	Nitrofurantoin	Piperacillin/Tazobactam	Tigecycline *	Trimethoprim/Sulfamethoxazole	Tobramycin	%ESBL-R	%CRE
Acinetobacter baumann/calcoaceticus/lw	82	0%	42%	93% (27/29)	0%	0%	26%	5%	17%				32%	26%	32%	7%(2/27)	0%	26%	37%	32%	42%		
Burkholderia cepacia	5				0%	0%	80%	0%					20%	40%	100%			0%	40%	80%	20%		
Citrobacter freundii	36				81%	0%	78%	78%	100%			100%	100%	92%	100%		97%	83%	97%	86%	97%		
Citrobacter koseri/diver/amalon	47				98%	98%	100%	95%	100%			100%	98%	98%	100%		76%	95%	100%	98%	98%		
Enterobacter aerogenes	76				93%	0%	91%	89%	100%			97%	100%	100%	99%		8%	86%	96%	99%	100%		
Enterobacter cloacae Complex	176				83%	0%	83%	80%	96%	100%(6/6)		95%	98%	98%	99%		29%	84%	94%	89%	95%		
Escherichia coli	1828	44%	52%	81%(9/11)	91%	84%	93%	87%	97%	67%(4/6)		100%	88%	71%	100%		94%	95%	100%	68%	87%		
Escherichia coli ESBL	209	0%	25%		30%	0%	47%	1%	73%			100%	72%	8%	100%		89%	85%	100%	29%	50%	11%	
Escherichia coli Not ESBL	1620	50%	55%		99%	94%	99%	98%	100%			100%	90%	79%	100%		95%	96%	100%	73%	91%		
Klebsiella oxytoca	74	0%	57%		96%	76%	99%	96%	100%			100%	100%	100%	100%		84%	93%	95%	99%	100%		
Klebsiella pneumoniae	608	0%	71%	67%(4/6)	87%	85%	89%	87%	96%	100%(4/4)		96%	93%	93%	98%		27%	88%	94%	82%	89%		4%
Klebsiella pneumoniae ESBL	63	0%	0%		5%	0%	21%	2%	74%			89%	49%	58%	100%		4%	56%	96%	18%	26%	10%	
Klebsiella pneumoniae Not ESBL	545	0%	79%		97%	95%	97%	97%	98%			97%	98%	97%	97%		30%	91%	94%	89%	96%		
Morganella morganii	64	0%	4%		96%	0%	93%	91%	98%			100%	96%	82%	100%		0%	96%	0%	84%	98%		
Proteus mirabilis	354	73%	80%		97%	86%	98%	89%	96%			100%	88%	68%	100%		0%	99%	0%	77%	93%		
Providencia stuartii /rettgeri	22	11%	23%		100%	0%	100%	92%	100%			100%	0%	8%	100%		0%	100%	0%	62%	0%		
Pseudomonas aeruginosa	438	0%	1%	69%(22/32)		0%	90%	0%	90%	33/34 97%	71%(24/34)		91%	77%	92%		0%	94%	0%	0%	97%		
Salmonella spp	17	70%	80%		100%	0%	90%	90%	100%			100%	0%	100%	100%		60%	100%	100%	100%	0%		
Seratia marcescens	83				100%	0%	98%	98%	100%			100%	100%	94%	100%		0%		95%	100%	93%		
Stenotrophomonas maltophilia	32													72%		91% (10/11)				66%			

KNOWLEDGE CHECK

Knowledge Check 1: Technicians

Which of the following is the generic medication name for Avycaz®?

A. Ceftolozane-tazobactam
B. Ampicillin-sulbactam
C. Meropenem-vaborbactam
D. Ceftazidime-avibactam
E. Imipenem-cilastatin-relebactam

Response 1: Technicians

Which of the following is the generic medication name for Avycaz®?

A. Ceftolozane-tazobactam
B. Ampicillin-sulbactam
C. Meropenem-vaborbactam
D. **Ceftazidime-avibactam**
E. Imipenem-cilastatin-relebactam

Knowledge Check 2: Technicians

Which of the following antibiotics would likely be utilized for a multi-drug resistant gram-negative bacterial infection?

A. Cefazolin
B. Meropenem-vaborbactam
C. Ampicillin-sulbactam
D. Metronidazole

Response 2: Technicians

Which of the following antibiotics would likely be utilized for a multi-drug resistant gram-negative bacterial infection?

A. Cefazolin
B. **Meropenem-vaborbactam**
C. Ampicillin-sulbactam
D. Metronidazole

Knowledge Check 3: Technicians

Which of the following antibiotics can be used as an inhalation solution for the treatment of respiratory MDR GNB infections?

A. Colistimethate sodium
B. Piperacillin-tazobactam
C. Meropenem-vaborbactam
D. Amoxicillin

Response 3: Technicians

Which of the following antibiotics can be used as an inhalation solution for the treatment of respiratory MDR GNB infections?

A. **Colistimethate sodium**
B. Piperacillin-tazobactam
C. Meropenem-vaborbactam
D. Amoxicillin

Knowledge Check 1: Pharmacists & Nurses

A patient's positive *K. pneumoniae* urine culture comes back with the following sensitivities listed below. Which of the following antibiotics may the pathogen possibly be susceptible to?

A. Levofloxacin
B. Ceftriaxone
C. Meropenem
D. Ceftazidime-avibactam
E. Piperacillin-tazobactam

Antibiotic	Sensitivity
Levofloxacin	R
Piperacillin-tazobactam	R
Cefepime	R
Meropenem	I
Imipenem	R
ESBL	+

Response 1: Pharmacists & Nurses

A patient's positive *K. pneumoniae* urine culture comes back with the following sensitivities listed below. Which of the following antibiotics may the pathogen possibly be susceptible to?

A. Levofloxacin
B. Ceftriaxone
C. Meropenem
D. **Ceftazidime-avibactam**
E. Piperacillin-tazobactam

Antibiotic	Sensitivity
Levofloxacin	R
Piperacillin-tazobactam	R
Cefepime	R
Meropenem	I
Imipenem	R
ESBL	+

Knowledge Check 2: Pharmacists & Nurses

When administering prolonged gentamicin therapy, which of the following is NOT an important monitoring parameter?

A. Gentamicin peak levels
B. Gentamicin trough levels
C. Vision tests compared to baseline measurement
D. Hearing compared to baseline measurement
E. Serum creatinine

Response 2: Pharmacists & Nurses

When administering prolonged gentamicin therapy, which of the following is NOT an important monitoring parameter?

A. Gentamicin peak levels

B. Gentamicin trough levels

C. Vision tests compared to baseline measurement

D. Hearing compared to baseline measurement

E. Serum creatinine

Knowledge Check 3: Pharmacists & Nurses

Patient AC has been receiving 50 mg of intravenous tigecycline every 12 hours. Since yesterday, AC's creatinine clearance decreased from 70 mL/min to 20 mL/min. Should this dose be adjusted?

A. Yes

B. No

Response 3: Pharmacists & Nurses

Patient AC has been receiving 50 mg of intravenous tigecycline every 12 hours. Since yesterday, AC's creatinine clearance decreased from 70 mL/min to 20 mL/min. Should this dose be adjusted?

A. Yes

B. No

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CONCLUSION

Conclusion

- MDR infections are associated with considerable mortality and cost
- Gram-negative bacteria may acquire antibiotic resistance through various mechanisms
- Recently-approved novel agents provide additional options for MDR treatment with the potential for less toxicity
- Resistance development continues to drive the need for new antibiotics

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Thank You!!

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