Clinical Role and Susceptibility Testing for Newer Antimicrobial Agents

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Outline

- Background on antibiotic resistant bacteria
- Discussion of new antibiotics
  - General background, Clinical Utility, Susceptibility testing
    - β-lactam/β-lactamase inhibitor combinations
    - Cephalosporins
    - Fluoroquinolones
    - Tetracyclines
    - Glycopeptides
    - Oxazolidinones
- Conclusions

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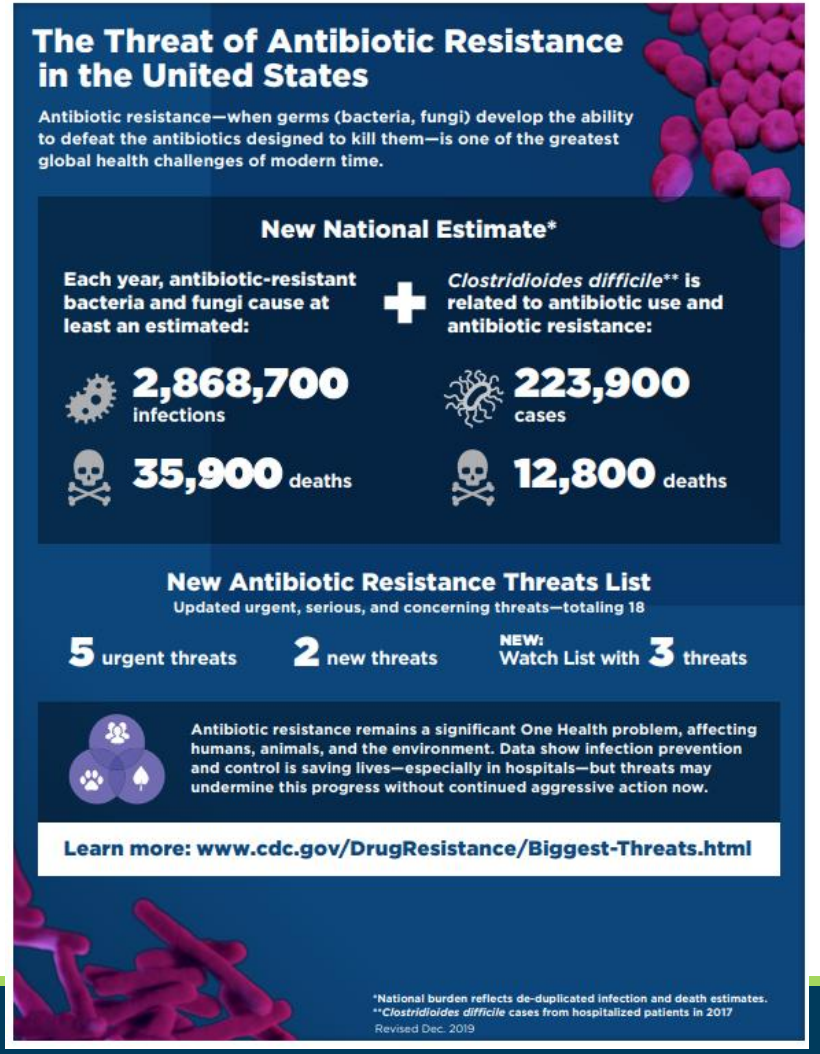
Multi-Drug Resistant Bacteria

- According to the CDC[1]:
  - >2.8 million infections annually
  - > 35,000 deaths
- Urgent threats include:
  - Carbapenem-resistant *Acinetobacter*
  - Carbapenem-resistant *Enterobacterales*
- Serious threats include:
  - ESBL-producing *Enterobacterales*
  - Vancomycin-resistant *Enterococcus* sp.
  - Methicillin-resistant *Staphylococcus aureus*



Multi-Drug Resistant Bacteria

- In 2016:
  - US Congress appropriated $160 million to CDC for AR
  - >330 innovative antibiotic resistance programs
  - > 30 countries involved

- On Sep 30, 2019 the US Federal Register was updated:
  - CMS is requiring all US hospitals to have active
    - Infection Control Programs
    - Antimicrobial Stewardship Programs
      - Must be implemented by March 30, 2020

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Multi-Drug Resistant Bacteria

- College of American Pathologists (CAP) indirectly working to control antibiotic resistance
- CAP has several requirements relating to antimicrobial stewardship programs (ASP)[2]
  - MIC.11380 Antimicrobial Susceptibility Test Interpretation Criteria
    - Requires ASP to review interpretive criteria annually
  - MIC.21943 Selection of Antimicrobial Agents to Report
    - Requires ASP to review which antibiotics are reported annually

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Beta-Lactam / Beta-Lactamase Inhibitor Combinations

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Traditional βL/βLi Combos

- Penicillin based β-lactam / β-lactamase inhibitor combinations[3]
  - Amoxicillin/Clavulonic Acid
  - Ampicillin/Sulbactam
  - Piperacillin/Tazobactam
- Penicillin class of antibiotics:
  - Bind to penicillin binding proteins
  - Inhibit final steps of cell wall synthesis
  - Bactericidal
- β-lactamase inhibitors:
  - Bind irreversibly to penicillinase enzymes
  - Limited antimicrobial activity

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Traditional βL/βLi Combos

- Active against many Gram + and Gram – organisms including:
  - Anaerobes
  - *Staphylococcus* sp.
  - *Streptococcus* sp.
  - *Enterococcus* sp.
  - Aerobic Gram – bacilli
- Notable difficulties with current options:
  - Resistance is now common, particularly in GNR

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Traditional βL/βLi Combos

- Resistance mechanisms to βL/βLi combos include:[4]
  - AmpC β-lactamases
    - Plasmid based (*E. coli, K. pneumoniae,* etc.)
    - Chromosomal (*Enterobacter cloacae*, etc.)
  - Carbapenemases including:
    - Serine carbapenemases:
      - *Klebsiella pneumoniae* carbapenemase (KPC)
    - Metallo β-lactamases
      - New Delhi metallo β-lactamase (NDM)
      - Verona Integron metallo β-lactamase (VIM)
      - Imipenemase (IMP)

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Cephalosporin/βLi Combos

- Cephalosporin based β-lactam / β-lactamase inhibitor combinations
  - Ceftazidime/Avibactam (AVYCAZ)
  - Ceftolozane/Tazobactam (ZERBAXA)
- Similar mechanism of activity as penicillin based βL/βLi combos
  - Bind to PBPs; inhibit cell wall synthesis
- Increased Gram - spectrum of activity
  - AmpC β-lactamases
  - Serine carbapenemases (KPC)
  - Oxacillinases

Ceftazidime/Avibactam

- Only available in IV formulation[3-5]
- Primary Indications include:
  - Complicated intra-abdominal infection
  - Complicated urinary tract infection
  - Hospital and ventilator acquired pneumonia
- Active against:
  - *Enterobacterales* expressing ESBLs, AmpC, KPC, OXA-48
  - Some carbapenem resistant *Pseudomonas aeruginosa*
- Inactive against
  - Metallo β-lactamases
  - *P. aeruginosa* w/ efflux pumps or porin mutations

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Ceftolozane/Tazobactam

- Only available in IV formulation[3,4,6]
- Primary Indications include:
  - Complicated intra-abdominal infection
  - Complicated urinary tract infection w/ pyelonephritis
  - Hospital and ventilator acquired pneumonia
- Active against:
  - *Enterobacterales* expressing ESBLs and AmpC
  - Carbapenem resistant *Pseudomonas aeruginosa*
    - Includes strains w/ efflux pumps and porin mutations
- Inactive against
  - Most carbapenemase producing *Enterobacterales*

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Carbapenem/βLi Combos

- Carbapenem based β-lactam / β-lactamase inhibitor combinations
  - Meropenem/Vaborbactam (VABOMERE)
  - Imipenem/Cilastatin/Relebactam (RECARBRIO)
- Similar mechanism of activity as penicillin based βL/βLi combos
  - Bind to PBPs; inhibit cell wall synthesis
- Increased Gram - spectrum of activity
  - AmpC β-lactamases
  - Serine carbapenemases (KPC)
  - Oxacillinases

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Meropenem/Vaborbactam

- Only available in IV formulation[3,4,7]
- Primary Indications include:
  - Complicated urinary tract infection
- Vaborbactam:
  - Primarily designed to bind to KPC carbapenemases
- Spectrum of activity nearly identical spectrum to meropenem
  - Restores meropenem activity in KPC producing bacteria
- Inactive against
  - Metallo β-lactamases
  - Oxacillinases
  - *P. aeruginosa* w/ efflux pumps or porin mutations

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Imipenem/Relebactam

- Only available in IV formulation[3,4,8]
- Primary Indications include:
  - Complicated urinary tract infection
  - Complicated intra-abdominal infections
  - Hospital and ventilator acquired pneumonia
- Similar spectrum of activity as imipenem
- Restores imipenem activity in:
  - KPC producing bacteria
  - Some imipenem resistant *P. aeruginosa* strains
- Inactive against
  - Metallo β-lactamases

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New βL/βLi Niche at AAH

- Ceftazidime/Avibactam
  - Utilized for KPC, OXA-48 expressing *Enterobacterales*
  - Occasional use in combination with Aztreonam for NDM
- Meropenem/Vaborbactam
  - Primarily used for ceftazidime/avibactam resistant KPC
- Ceftolozane/Tazobactam
  - Primarily utilized against carbapenem resistant *P. aeruginosa*
- Imipenem/Relebactam
  - Primarily used for ceftolozane/tazobactam resistant *P. aeruginosa*

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Susceptibility Testing of βL/βLi

- CLSI Breakpoints
  - *Enterobacterales* (Avycaz, Zerbaxa, Vabomere, Recarbrio)
  - *P. aeruginosa* (Avycaz, Zerbaxa, Recarbrio)
  - Viridans group *Streptococcus* sp. (Zerbaxa)
  - *H. influenzae* (Zerbaxa)
  - Anaerobes (Recarbrio)
- FDA Breakpoints
  - *B. fragilis* (Zerbaxa)
  - *A. baumannii* (Recarbrio)
  - *H. influenzae* (Recarbrio)

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Susceptibility Testing of βL/βLi

- Testing options include:
  - Disk Diffusion
  - MIC Strips (ETest and LioFilChem)
  - Sensititre (not Recarbrio)
  - AST Systems (Avycaz, Zerbaxa, Vabomere)

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Carbapenem/βLi Combos

Table 1. Activity of β-lactam Combination Agents Against Various Organism Groups and β-lactamases Commonly Produced by Gram-negative Organisms.

Agent	Spectrum of Activity								
	ESBL	Carbapenemase (β-lactamase) Class				*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Stenotrophomonas maltophilia*	*Burkholderia cepacia complex*
		A	B	C	D				
C/T	+	-	-	+	+*	+	+/-	+/-	+/-
CZA	+	+	-	+	+	+	-	-	ND
MEV	+	+	-	+	+*	-	-	-	ND
I/R	+	+	-	+	-	+/-	-	-	ND

C/T, ceftolozane-tazobactam; CZA, ceftazidime-avibactam; I/R, imipenem-relebactam; MEV, meropenem-vaborbactam

'+' drug is active; '-' drug is inactive; '+/-' drug may or may not have activity

ND, not determined. * May not have activity against some oxacillinases and carbapenemases of this class.

- CLSI AST NEWS UPDATE – SPRING 2018 EDITION

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Cephalosporins

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Traditional Cephalosporins

- Many different examples across four generations[3,4]
- Cephalosporin class of antibiotics:
  - Bind to penicillin binding proteins
  - Inhibit final steps of cell wall synthesis
  - Bactericidal
- Active against many Gram + and Gram – organisms including:
  - Anaerobes
  - *Staphylococcus* sp.
  - *Streptococcus* sp.
  - Aerobic Gram – negative bacilli

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Traditional Cephalosporins

- Notable difficulties with current options:
  - Resistance is now common, particularly in GNR
- Resistance mechanisms to βL/βLi combos include:
  - ESBLs (CTX-M, etc.)
  - AmpC β-lactamases
  - Carbapenemases including: KPC, NDM, VIM, IMP, OXA-48

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Cefiderocol

- Sold under the trade name FETROJA[3,4,9]
- Unique structure
  - Cephalosporin core
  - Iron binding side chains
- Depletes iron in environment leading to active cellular uptake
- Disrupts cell wall synthesis
- Unique structure limits ability to be hydrolyzed by β-lactamases
- Clinical indications include:
  - Complicated urinary tract infection

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Cefiderocol

- Active against:
  - ESBLs (CTX-M, etc.)
  - AmpC β-lactamases
  - Carbapenemases including: KPC, NDM, VIM, IMP, OXA-48
  - Carbapenem resistant *A. baumannii*
  - Carbapenem resistant *P. aeruginosa*
- No activity against Gram + bacteria
- No activity against anaerobic bacteria

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Cefiderocol AAH Niche

- Primarily utilized in MDR *P. aeruginosa* and *A. baumannii*
- Minimal use in *Enterobacterales*
- See resistance emerge during therapy w/ *A. baumannii*
- Primarily used as salvage therapy:
  - Very resistant Gram – infections
  - Studies indicate increased mortality over traditional therapeutic options

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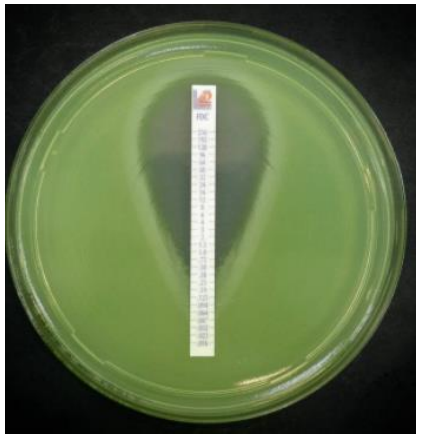
Cefiderocol Susceptibility Testing

- Disk Diffusion
  - FDA approved options
  - Uses standard Mueller Hinton Agar
- Broth Microdilution
  - Requires the use of iron-depleted CAMHB
  - Preparation instructions in CLSI M100
- MIC Test Strip (LioFilChem)
  - Available as research use only
  - Utilize standard Mueller Hinton Agar
- No automated AST options



Cefiderocol Susceptibility Testing

- FDA and CLSI clinical breakpoints differ
  - FDA breakpoints are more stringent

Organism	MIC Breakpoint (µg/mL)					
	CLSI Investigational Breakpoint			FDA Clinical Breakpoint		
	S	I	R	S	I	R
Enterobacterales	≤ 4	8	≥ 16	≤ 4	8	≥ 16
P. aeruginosa	≤ 4	8	≥ 16	≤ 1	2	≥ 4
Acinetobacter sp.	≤ 4	8	≥ 16	≤ 1	2	≥ 4
S. maltophilia	≤ 4	8	≥ 16			

Organism	Disk Diffusion Breakpoint (mm)					
	CLSI Investigational Breakpoint			FDA Clinical Breakpoint		
	S	I	R	S	I	R
Enterobacterales	≥ 16	12-15	≤ 11	≥ 16	9-15	≤ 8
P. aeruginosa	≥ 18	13-17	≤ 12	≥ 22	13-21	≤ 12
Acinetobacter sp.	≥ 15	11-14	≤ 10	≥ 19	12-18	≤ 11
S. maltophilia	≥ 17	13-16	≤ 12			

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Cefiderocol Susceptibility Testing – ACL Experience

- In First 9 Months of 2021 sent out the following isolates:
  - 10 *Enterobacterales* isolates
    - 6 KPC isolates = 100% susceptible
    - 3 NDM isolates = 66% susceptible
    - Overall 90% susceptible
- FDA and CLSI breakpoints are equivalent

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Cefiderocol Susceptibility Testing – ACL Experience

- In First 9 Months of 2021 sent out the following isolates:
  - 17 *A. baumannii* complex isolates
    - FDA Breakpoints = 47% susceptible
    - CLSI Breakpoints = 71% susceptible
- Reported results based on FDA breakpoints
- Resistant to most other options except amikacin and minocycline

Organisms	Isolates	CEFID
Acinetobacter baumannii complex	17	8 (17) 47

MIC Distribution

Organism: *Acinetobacter baumannii complex*
Antibiotic: CEFIDEROCOL

MIC	Count
0.5	2
1	6
2	3
4	1
8	1
16	2
>=64	2

Click cell for MIC Distribution report

Cefiderocol Susceptibility Testing – ACL Experience

- In First 9 Months of 2021 sent out the following isolates:
  - 22 *P. aeruginosa* isolates
    - FDA Breakpoints = 81% susceptible
    - CLSI Breakpoints = 95% susceptible
- Reported results based on FDA breakpoints

Organisms	Isolates	CEFID
Pseudomonas aeruginosa	22	18 (22) 81

MIC Distribution

Organism: *Pseudomonas aeruginosa*
Antibiotic: CEFIDEROCOL

MIC	Count
0.12	4
0.25	2
0.5	6
1	6
2	2
4	1
>=64	1

Click cell for MIC Distribution report

Fluoroquinolones

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Traditional Fluoroquinolones

- Traditional Fluoroquinolones[3,4]
  - Ciprofloxacin
  - Levofloxacin
  - Moxifloxacin
- Inhibit DNA gyrase and topoisomerase, disrupting DNA replication, bactericidal
- Available as IV, oral, or ophthalmic suspensions
- Active against many Gram + and Gram – organisms including:
  - *Staphylococcus* sp.
  - *Streptococcus* sp.
  - *Enterococcus* sp.
  - Aerobic Gram - bacilli

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Traditional Fluoroquinolones

- Resistance mechanisms include:
  - Mutations in FQ binding region of DNA gyrase and topoisomerase
  - Plasmid mediated resistance (blocks binding of antibiotic to target)
  - Upregulation of efflux pumps
- Notable difficulties with current options:
  - Limited activity against MRSA
  - Systemic fluroquinolones come with black box warning:
    - Significant risk of tendonitis/tendon rupture
    - Central nervous system issues

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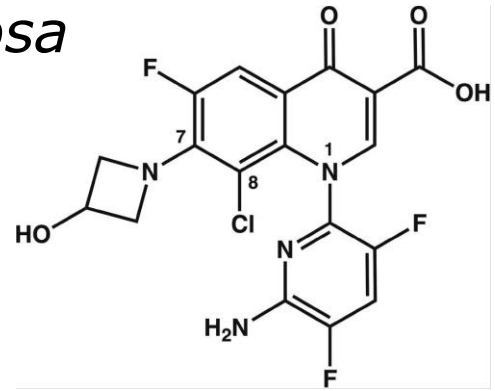
Delafloxacin

- Sold under trade name BAXDELA[3,4,10]
- Same mechanisms of action
- Similar spectrum of activity however:
  - Active against MRSA
  - Better anaerobic coverage than ciprofloxacin or levofloxacin
  - Better intracellular penetration
- Only antibiotic currently active against MRSA and *P. aeruginosa*
- Administered in either oral or IV formulation
- Excreted in stool and urine



Delafloxacin Cont'd

- Adverse reactions similar to other FQs
- Primary indications include:
  - Acute skin and soft tissue infection
- Off label indications include:[32]
  - Osteomyelitis
  - Prosthetic joint infection
  - Biofilm related infections
  - Oral option for some NTM infections

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Delafloxacin Cont'd

- There are no CLSI Breakpoints
- There are FDA disk diffusion and MIC breakpoints
- Susceptibility testing options include:
  - Disk diffusion
  - ETest
  - LioFilChem MIC Strip
  - Sensititre broth microdilution
  - Not available on automated systems
- AAH has not really found a niche for this antibiotic

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Tetracyclines and Glycylcyclines

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Traditional Tetracyclines

- Traditional tetracyclines include:[3,4]
  - Tetracycline
  - Doxycycline
  - Minocycline
  - Tigecycline (a glycylcycline)
- Bind 30S ribosomal subunit to block protein synthesis; bacteriostatic
- Available in oral or IV formulations (tigecycline IV only)
- Resistance mechanisms include:
  - Mutations in ribosomal binding site (ribosomal protection)
  - Upregulation of efflux pumps
  - Enzymatic inactivation

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Traditional Tetracyclines

- Active against many Gram + and Gram – organisms including:
  - *Staphylococcus* sp.
  - *Streptococcus* sp.
  - *Enterobacterales*
  - Aerobic Gram + bacilli
  - Many aerobic Gram – bacilli
- Inactive against:
  - Anaerobes often resistant
  - *Pseudomonas, Proteus* sp., *Providencia* sp., and *M. morganii* are intrinsically resistant

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Traditional Tetracyclines

- Currently utilized in:
  - Skin and soft tissue infection
  - Complicated intraabdominal infection
  - Urinary tract infection
  - Community acquired pneumonia
- Tissue penetration is excellent
- Contraindications include:
  - Increased mortality (tigecycline)
  - Yellowing teeth and inhibition of bone growth avoid use:
    - In utero
    - Children < 8

New Tetracyclines

- The newest generation of tetracyclines includes:[3,4]
  - Omadacycline (NUZYRA)
  - Eravacycline (XERAVA)
- Very similar characteristics as tigecycline including:
  - Derivative of minocycline (like tigecycline)
  - Binds to the 30S ribosomal subunit to block protein synthesis
  - Designed specifically to avoid traditional resistance mechanisms:
    - Ribosomal protection
    - Active efflux
  - Similar adverse effects observed

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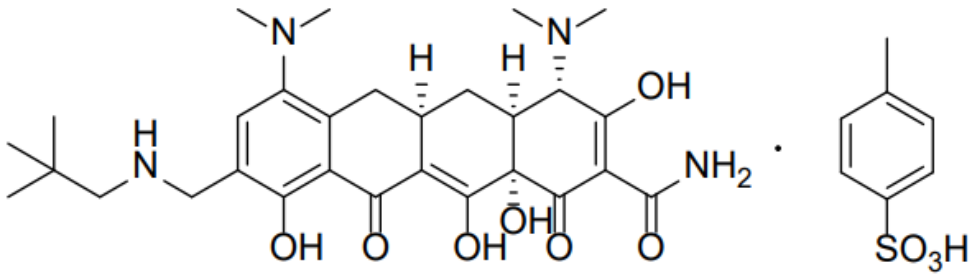
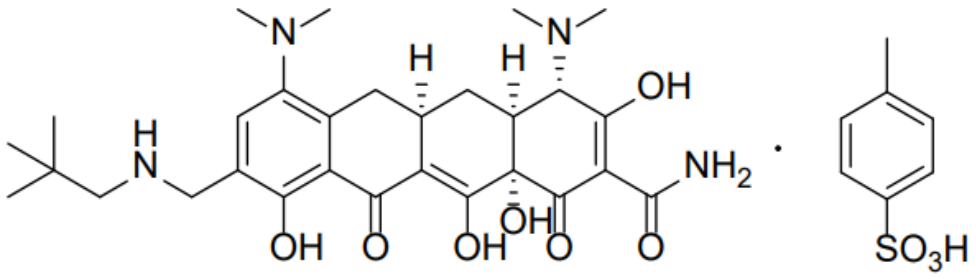
Omadacycline

- Sold under trade name NUZYRA[3-4,11-12,29]
- Primary indications
  - Community Acquired Pneumonia
  - Acute SSTI
- Oral and IV formulations
  - Requires loading dose then maintenance dose
- Incredibly expensive
  - Could exceed $5000 for treatment



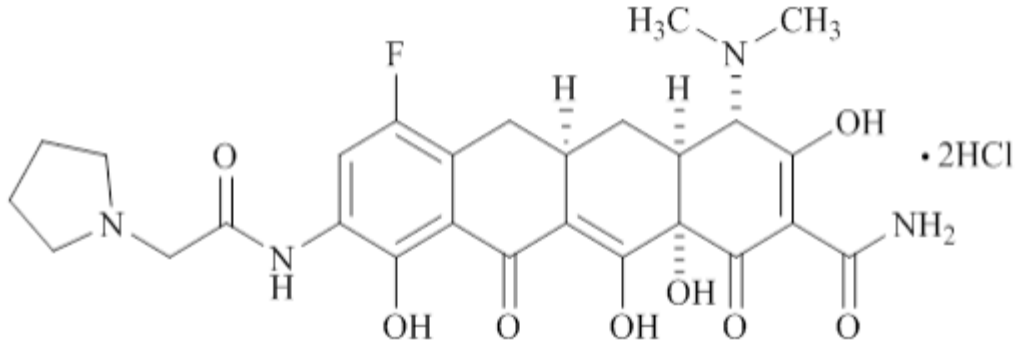
Omadacycline Cont'd

- Active against:
  - *S. aureus* (MRSA and MSSA)
  - *Enterococcus* sp. (including VRE)
  - Beta hemolytic *Streptococcus* sp.
  - Penicillin Resistant *S. pneumoniae*
  - ESBL producing *E. coli*
  - *Acinetobacter* sp.
  - *Stenotrophomonas maltophilia*



Eravacycline

- Sold under trade name XERAVA[3,4,13,30]
- At present only available in IV formulation
- Primary indications
  - Complicated intra-abdominal infection
  - Active against Gram + bacteria and Gram – bacteria
- Fewer GI symptoms than tigecycline



New Tetracycline Niche

- Rarely utilized for FDA approved indications:
  - SSTI and CAP (omadacycline)
  - Intra-abdominal infection (eravacycline)
- Eravacycline rarely utilized within AAH
- Omadacycline gets occasional use as oral step-down therapy for NTM infections

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Susceptibility Testing of New Tetracyclines

- Susceptibility testing is rarely warranted:
  - Activity against:
    - MRSA
    - CRE
    - CRAB[16]
  - Tigecycline susceptibility generally predicts susceptibility to:
    - Eravacycline[14]
    - Omadacycline[15]
  - No activity against:
    - *Pseudomonas aeruginosa, Morganella* sp., *Proteus* sp., and *Providencia* sp. are intrinsically resistant

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Susceptibility Testing of New Tetracyclines

- Omadacycline
  - No CLSI Breakpoints
  - FDA breakpoints, but depend on clinical presentation
  - MIC Test Strips available (LioFilChem)
  - Disk diffusion disks available
  - Not on automated AST systems

For Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae [a,†]	≤4	8	≥ 16	≥18	16-17	≤15
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 0.5	1.0	≥ 2.0	≥ 21	19-20	≤18
Staphylococcus lugdunensis	≤ 0.12	0.25	≥0.5	≥ 29	26-28	≤25
Enterococcus faecalis	≤ 0.25	0.5	≥ 1.0	≥18	16-17	≤15
Streptococcus anginosus group [b]	≤ 0.12	0.25	≥ 0.5	≥ 24	18-23	≤17
Streptococcus pyogenes	≤ 0.12	0.25	≥ 0.5	≥19	16-18	≤15

S = Susceptible; I = Intermediate; R = Resistant

[†] Omadacycline is not active *in vitro* against *Morganella* spp., *Proteus* spp., and *Providencia* spp.

[a] *Klebsiella pneumoniae* and *Enterobacter cloacae* only

[b] *Streptococcus anginosus* group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*

For Community Acquired Bacterial Pneumonia (CABP)

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae [a,†]	≤4	8	≥ 16	≥18	16-17	≤15
Staphylococcus aureus (methicillin- susceptible isolates only)	≤ 0.25	0.5	≥ 1.0	≥ 23	21-22	≤20
Haemophilus species [b]	≤2	4	≥ 8	≥ 20	17-19	≤16
Streptococcus pneumoniae	≤0.12	0.25	≥ 0.5	≥25	23-24	≤22

S = Susceptible; I = Intermediate; R = Resistant

[†] Omadacycline is not active *in vitro* against *Morganella* spp., *Proteus* spp., and *Providencia* spp.

[a] *Klebsiella pneumoniae* only

[b] *Haemophilus species includes H. influenzae and H. parainfluenzae*

Susceptibility Testing of New Tetracyclines

- Eravacycline
  - No CLSI Breakpoints
  - FDA breakpoints for:
    - *Enterobacterales*
    - Gram + Cocci
    - Anaerobes
  - MIC Test Strips available
  - Disk diffusion disks available
  - Not on automated AST systems

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae[a]	≤0.5	-	-	≥15	-	-
Staphylococcus aureus	≤0.06	-	-	-	-	-
Enterococcus faecalis and *Enterococcus faecium*	≤0.06	-	-	-	-	-
Streptococcus anginosus group[b]	≤0.06	-	-	-	-	-
Anaerobes[c]	≤0.5	-	-	-	-	-

S=Susceptible; I = Intermediate; R = Resistant
For disk diffusion, use paper disks impregnated with 20 mcg eravacycline

[a] Clinical efficacy was shown for *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia.*
[b] Clinical efficacy was shown for *S. anginosus, S. constellatus, S. intermedius.*
[c] Clinical efficacy was shown for *Clostridium perfringens, Parabacteroides distasonis, Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus.*

Glycopeptides and Lipoglycopeptides

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Traditional Glycopeptides

- Traditional Glycopeptides[3,4]
  - Vancomycin
  - Daptomycin
- Inhibit peptidoglycan cell wall synthesis
- Resistance mechanisms include:
  - Synthesis of abnormal peptidoglycan precursors, which decrease antibiotic binding capacity (VRE)
  - Increased production of peptidoglycan precursors, leading to thicker cell wall that traps antibiotics (VISA)

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Traditional Glycopeptides

- Active against most Gram + organisms including:
  - Anaerobes
  - *Staphylococcus* sp. (including MRSA)
  - *Enterococcus* sp.
  - Aerobic Gram + bacilli
- Notable difficulties with current options:
  - Vancomycin may require monitoring serum concentrations
  - Daptomycin is inactivated by alveolar surfactant

Lipoglycopeptides

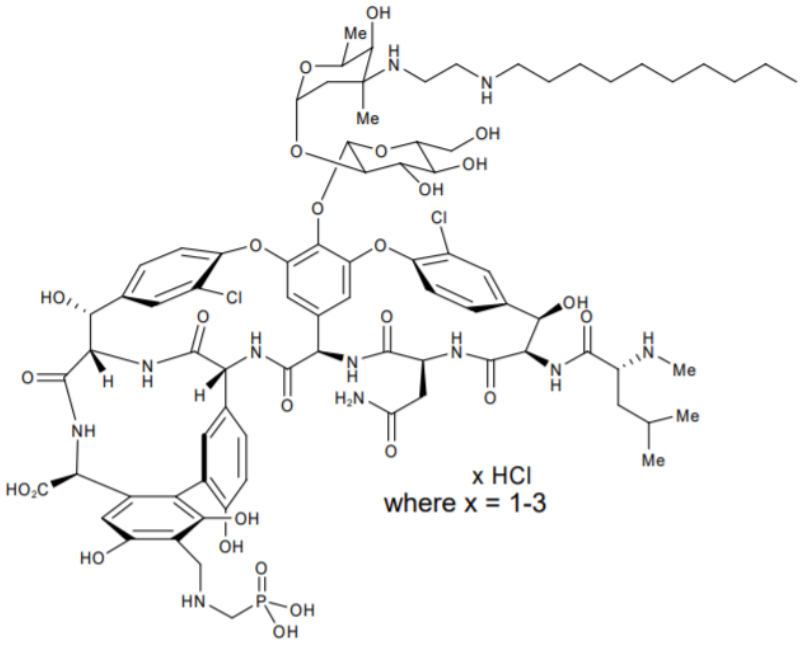
- Include:
  - Telavancin (VIBATIV)
  - Dalbavancin (DALVANCE)
  - Oritavancin (ORBACTIV and KIMYRSA)
- Dual mechanisms of action include:
  - Inhibit peptidoglycan cell wall synthesis
  - Depolarization of bacterial cell membrane
  - Maintain some activity against vancomycin resistant organisms
- Longer half-lives than glycopeptides (particularly true for dalbavancin and oritavancin)

Lipoglycopeptides Cont'd

- Primary Indications:
  - Complicated SSTI
    - *S. aureus* (MRSA and MSSA)
    - *Streptococcus* sp.
    - *Enterococcus* sp. (primarily vancomycin susceptible)
- Widely distributed throughout the body with good tissue penetration

Telavancin

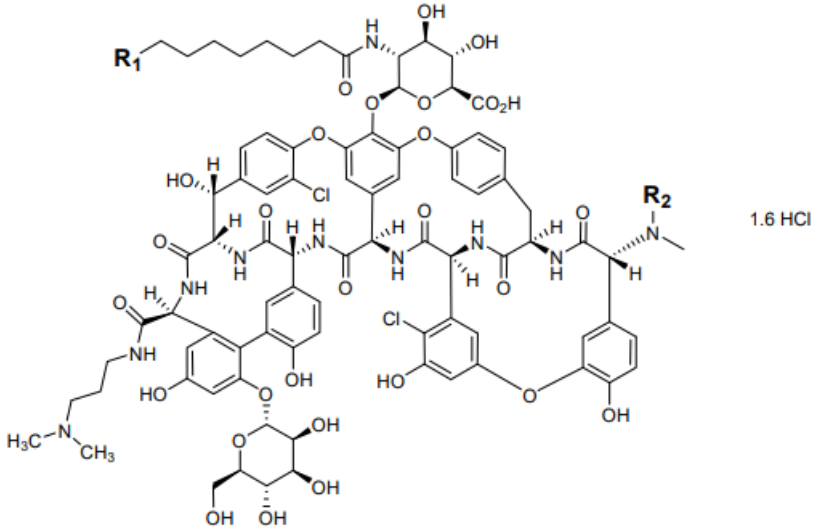
- Also indicated for HAP and VAP[3,4,17]
  - *S. aureus* (MSSA and MRSA)
  - Not affected by alveolar surfactants[27,28]
- Administered via IV, once daily
- Excreted in urine
- Contraindications
  - Fetal toxicity
  - Interferes with some coagulation tests
  - Interferes with some dipstick urine tests



Telavancin hydrochloride

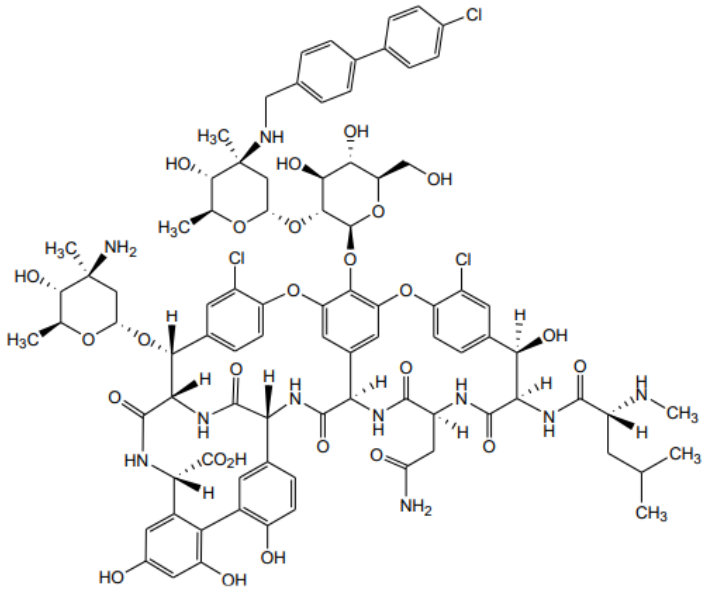
Dalbavancin

- Administered via IV[3,4,18]
  - Two infusions
  - 7 days apart
- Excreted in urine and stool
- Contraindications
  - May lead to elevated liver enzymes



Oritavancin

- Administered via IV[3,4,19,20]
  - One infusion due to long half life
- Excreted very slowly in urine and stool
- Contraindications
  - Interferes with some coagulation tests
  - Risk of bleeding with warfarin use
  - Increased risk for osteomyelitis over vancomycin



Lipoglycopeptides Niche

- Outpatient gram + SSTI
- Occasional use in IV drug users who can’t be discharged with a line
- Off label uses include:
  - Infectious endocarditis
  - Osteomyelitis
  - Weekly instead of daily dosing for long courses of therapy increases compliance
- These drugs are quite expensive

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Lipoglycopeptides Susceptibility Testing

- Susceptibility testing is rarely warranted:
  - Vancomycin susceptibility predicts susceptibility to:
    - Dalbavancin, oritavancin, telavancin[21-25]
    - *Staphylococcus* sp. (including MRSA)
    - *Streptococcus* sp.
    - *Enterococcus* sp.
  - Dalbavancin and telavancin:
    - only have activity against vanB strains of VRE[21,22,25,26]
    - Limited VISA/VRSA activity
  - Oritavancin:
    - VRE Strains are routinely inhibited by oritavancin [23,24,26]
    - Shows some activity against VISA/VRSA

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Lipoglycopeptides Susceptibility Testing

- There are CLSI breakpoints for:
  - *Staphylococcus* sp.
  - *Streptococcus* sp. (except *S. pneumoniae*)
  - *Enterococcus faecalis*
  - MIC breakpoints only
- Susceptibility testing options include:
  - ETest (telavancin)
  - LioFilChem MIC Strip (dalbavancin and telavancin)
  - Sensititre broth microdilution (all three)
  - Not available on automated systems

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Oxazolidinones

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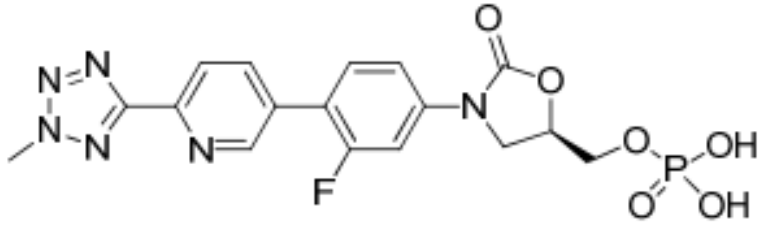
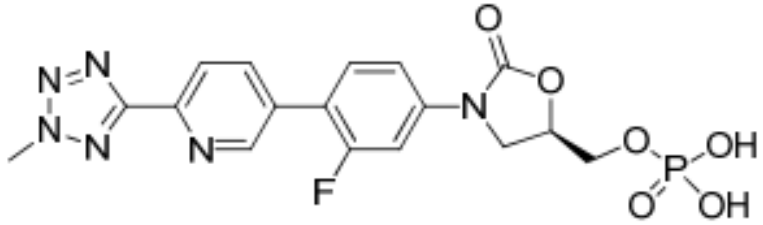
Tedizolid

- Sold under trade name SIVEXTRO[3,4,31]
- An oxazolidinone like linezolid
- Binds to 50S ribosomal subunit to inhibit protein synthesis, bacteriostatic
- Primary indications
  - Acute SSTI
    - *S. aureus* (MSSA and MRSA)
    - *Streptococcus* sp.
    - *Enterococcus faecalis* (including VRE)
    - *Enterococcus faecium* (including VRE)



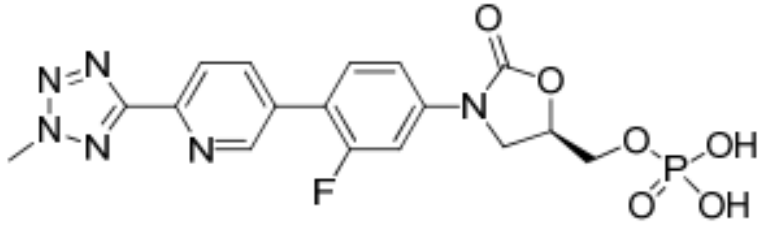
Tedizolid Cont’d

- Administered:
  - Once daily
  - Oral or IV formulations
- Does not get into CNS
- Contraindications
  - No significant contraindications
  - Less risk of serotonin syndrome than linezolid



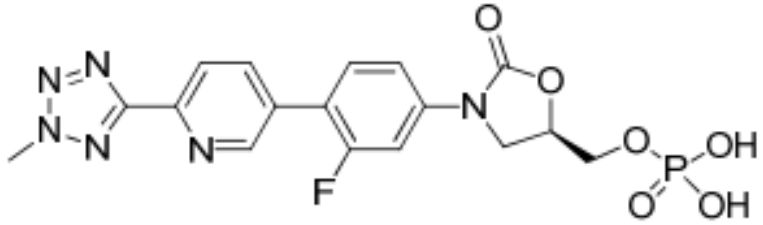
Tedizolid Susceptibility Testing

- There are CLSI Breakpoints for:
  - *Staphylococcus* sp.
  - *Streptococcus* sp. (except *S. pneumoniae*)
  - *Enterococcus faecalis*
- Susceptibility Testing
  - Linezolid susceptibility predicts tedizolid susceptibility[8]
  - *Staphylococcus* sp. (including MRSA)
  - *Streptococcus* sp.
  - *Enterococcus* sp.



Tedizolid Susceptibility Testing

- Susceptibility testing options:
  - Disk diffusion option (no Disk diffusion breakpoints)
  - MIC Strips available (LioFilChem)
  - Sensititre broth microdilution panels available
  - Not on any automated AST panels
- Within Advocate Aurora Health
  - Very rarely used



Conclusions

- The presence of antibiotic resistant bacteria represents a global threat
- There are some new antibiotics available to combat some of these resistant organisms
- Still working to define clinical niche for some
- Susceptibility testing not yet available on AST systems so labs must understand available testing options including:
  - If results can be predicted by another antibiotic
  - Whether appropriate test media is available
  - What interpretive criteria is available

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Questions ??

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