Resilience vs. Resistance:
Winning the Battle Against Vancomycin-Resistant Infections

Domenic M. Biello Jr. and Jenny Zhao
PGY-1 Pharmacy Residents
UConn Health John Dempsey Hospital

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Pharmacist Objectives

01 Explain the common mechanisms of bacterial resistance and their impact on antibiotic efficacy

02 Recognize the importance of early and effective management of resistant bacterial infections

03 Identify first- and second-line treatment options for vancomycin-resistant Enterococcus (VRE)

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Pharmacy Technician Objectives

01 Identify strategies to prevent dispensing errors when handling antibiotics and increase awareness of high-risk medications

02 Describe proper storage, reconstitution, and other considerations for antibiotics used for resistant infections

03 Recognize common dosing of antibiotics used for resistant bacterial infections

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Disclosures

Dr. Zhao has no actual or potential conflict of interest associated with this presentation.

Dr. Biello Jr. has no actual or potential conflict of interest associated with this presentation.

Dr. Kuszewski has no actual or potential conflict of interest associated with this presentation.

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Background

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Background

- Enterococci are gram-positive cocci, facultative anaerobes that present in pairs and chains
- Most commonly lives in the gastrointestinal (GI) tract
- *Enterococcus faecalis* is the most common cause of *Enterococcal* infections
  - Susceptible to beta-lactams and aminoglycosides
  - *Enterococcus faecium* tends to be highly resistant to the same antibiotics

Levitus M, Perera TB. Nih.gov. https://www.ncbi.nlm.nih.gov/books/NBK513233/; CDC. https://www.cdc.gov/antimicrobial-resistance/media/pdfs/vre-508.pdf

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Disease History

VRE = Vancomycin Resistant Enterococci

- Enterococci classified as enteric gram-positive cocci and later included in the *Streptococcus* genus
- Enterococci recognized as common cause of hospital-acquired infections (1970s)
- Enterococci removed from the genus *Streptococcus* (1980s)
- Isolates of VRE demonstrated in Europe (1980s)
- Developed in the US, likely due to increased vancomycin use
- Multiple epidemics plaquing hospitals (1990s to 2000s)
- Second overall healthcare-associated infection (2011 to 2014)
- Future directions

Miller WR, et al. *Infect Dis Clin North Am.* 2020;34(4):751-771.

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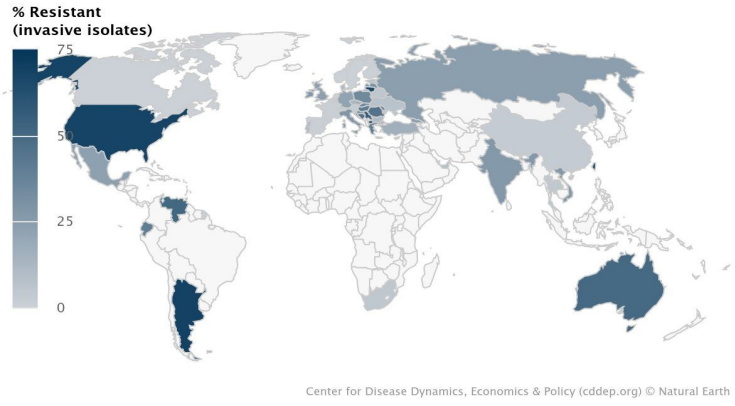
Disease Prevalence and Resistance Patterns

Resistance of *Enterococcus faecium* to Vancomycin



https://resistancemap.onehealthtrust.org/AntibioticResistance.php

- *Enterococcus faecium* is listed on the WHO as a high priority pathogen
- *Enterococcus faecalis* is the more common enterococcal infection
- Most cephalosporins, as monotherapy have no activity
- Increasing reports of acquired resistance to daptomycin and linezolid

CDC. https://www.cdc.gov/vre/about/index.html; Gorrie C, et al. *Microb Genom.* 2019;5(7):e000283.

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$500+ million

CDC excess annual healthcare cost (2017)

54,500

Estimated cases in hospitalized patients (2017)

30%

Estimated vancomycin resistant enterococcal infections (2017)

5,400

CDC estimated annual deaths (2017)

CDC. https://www.cdc.gov/vre/about/index.html

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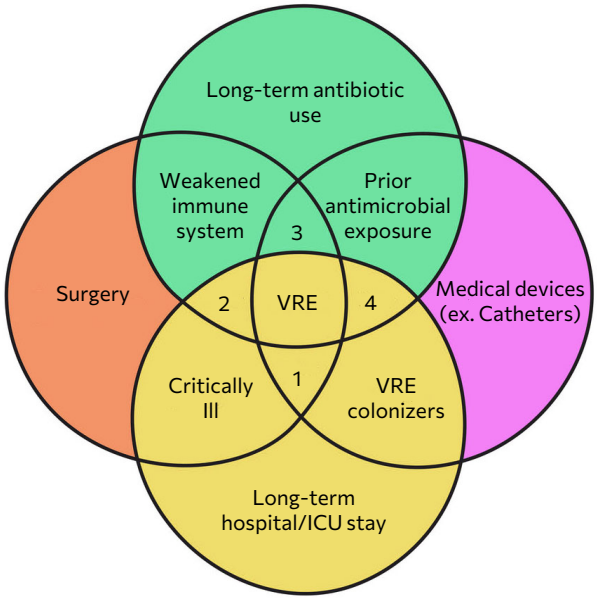
Who is at risk?

1. Long term care facility (LTCF)
2. Transplant
3. Hematological malignancies
4. Poor healthcare prevention strategies/skills



CDC. https://www.cdc.gov/vre/about/index.html; Joshi S, et al. *Infect Dis Clin North Am.* 2021;35(4):953-968.

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Various VRE Resistance Mechanisms

Peptidoglycan Cell Wall Change

D-Ala-D-Ala terminus is changed to:

D-Ala-D-Lac
- Van A, B, D, M

D-Ala-D-Ser
- Van C, E, G, L, N

Transmissible / Inducible

Horizontal gene transfer

Main transmissible determinants:
- cfr
- optraA
- PoxtA

VanB may express vanB gene cluster leading to vanB operon activation

Efflux Pumps / Target Protection

Drug efflux pumps
- Typically carried on plasmids tet(k) and tet(L)

Target protection at the ribosome
- Mediated by genes such as Tn916 [tet(M), tet(O), tet(S)]

Faron ML, et al. *J Clin Microbiol.* 2016;54(10):2436-2447.; Miller WR, et al. *Infect Dis Clin North Am.* 2020;34(4):751-771.

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Prevention Strategies

1. *In vitro* susceptibility testing
2. Hand hygiene
3. Chlorhexidine bathing
4. Environmental cleaning
5. Antimicrobial stewardship
6. Active surveillance
7. Colonization and decolonization

Joshi S, et al. *Infect Dis Clin North Am.* 2021;35(4):953-968.; https://www.med.unc.edu/casp/wp-content/uploads/sites/563/2019/06/UNC-VRE-Guideline.pdf

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Question 1

How do Enterococci develop resistance to vancomycin?

A. The terminus of the peptidoglycan cell wall changes

B. Production of enzymes inactivate vancomycin

C. Decreased outer membrane permeability

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Question 2

What prevention strategy involves early and effective therapy intervention?

A. Chlorhexidine bathing

B. Hand Hygiene

C. Antimicrobial Stewardship

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Treatment

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General Treatment Recommendations

Enterococcus species cultured

Urinary Tract Infection (UTI)	Bacteremia	Infective Endocarditis (IE)	Intraabdominal Infection (IAI)
1st line: monotherapy with high dose ampicillin **Alternative**: nitrofurantoin or fosfomycin	**1st line**: monotherapy ampicillin ± gentamycin for synergy **Alternative**: ampicillin + ceftriaxone	**1st line**: linezolid **Alternative**: high dose daptomycin ± ampicillin or ceftaroline	**1st line**: tigecycline Avoid tigecycline for vancomycin-resistant *Enterococcus* bacteremia

If significant resistance to other antimicrobial therapies, the two preferred treatments are linezolid and daptomycin.

Levitus M, Perera TB. Nih.gov. https://www.ncbi.nlm.nih.gov/books/NBK513233/; Eichel VM, et al. / *Hosp Infect.* 2023;141:119-128.

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Oxazolidinones

	Linezolid (Zyvox)	Tedizolid (Sivextro)
Mechanism of Action (MOA)	Inhibits bacterial protein synthesis	Inhibits bacterial protein synthesis
Dosing / Adjustments	600mg IV or PO every 12 hours Hemodialysis (HD): Dose post HD	200mg IV or PO every 24 hours No renal or hepatic adjustments
Adverse Drug Events (ADEs) / Comments	Serotonin syndrome, lactic acidosis, optic neuritis, myelosuppression	Thrombocytopenia, neutropenia
Storage	Store at 25°C (77°F) Excursions: 15-30°C (59-86°F) Reconstituted: room temperature for up to 21 days	Store at 20-25°C (68-77°F) Excursions: 15-30°C (59-86°F) Reconstituted: room temperature for up to 24 hours

Zyvox (linezolid) [package insert]; Sivextro (tedizolid phosphate) [package insert]

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Streptogramin, Glycylcyline

	Quinupristin/Dalfopristin (Synercid)	Tigecycline (Tygacil)
MOA	Inhibit protein synthesis	Inhibits protein translation
Dosing / Adjustments	7.5 mg/kg IV every 8 to 12 hours No renal or hepatic adjustments	100mg IV loading dose followed by 50mg IV every 12 hours Hepatic adjustments required
ADEs / Comments	Injection site reactions, asymptomatic hyperbilirubinemia, arthralgia/myalgia	Acute pancreatitis Avoid in pregnancy and pediatrics
Storage	Store at 2-8°C (36-46°F) Reconstituted: room temperature for up to 5 hours	Store at 20-25°C (68-77°F) Excursions: 15-30°C (59-86°F) Reconstituted: room temperature for up to 24 hours

Synercid (quinupristin and dalfopristin) [package insert]; Cubicin (daptomycin) [package insert]; Tigecycline [package insert]

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Cyclic Lipopeptide

	Daptomycin (Cubicin)
MOA	Inhibits protein, DNA, and RNA synthesis
Dosing / Adjustments	SSTI: 4 mg/kg IV every 24 hours Bacteremia, IE: 6 mg/kg every 24 hours Severe: 8 to 12 mg/kg IV every 24 hours Renal adjustments required, dose post HD
ADEs / Comments	Myopathy, neuropathy, acute eosinophilic PNA Inactivated by pulmonary surfactant
Storage	Store at 2-8°C (36-46°F) Reconstituted: room temperature for up to 12 hours

Synercid (quinupristin and dalfopristin) [package insert]; Cubicin (daptomycin) [package insert]; Tigecycline [package insert]

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Lipoglycoprotein

	Telavancin (Vibativ)	Dalbavancin (Dalvance)	Oritavancin (Orbactiv)
MOA	Disrupts cell wall synthesis and membrane integrity	Disrupts cell wall synthesis	Inhibits cell wall transglycosylation and transpeptidation; disrupts membrane integrity
Dosing / Adjustments	10 mg/kg IV every 24 hours Renal adjustments required	1000 mg IV day 1; 500 mg IV day 8 Renal adjustments required	1200 mg IV once No renal or hepatic adjustments
ADEs / Comments	BBW: increase mortality in severe renal impairment	Red man syndrome with rapid infusion rates	Hypersensitivity infusion site reactions False elevations in aPTT and INR
Storage	Store at 2-8°C (35-46°F) Excursions: 25°C (77°F)	Store at 25°C (77°F) Excursions: 15-30°C (59-86°F) Reconstituted: room temperature for up to 48 hours	Store at 20-25°C (68-77°F) Excursions: 15-30°C (59-86°F) Reconstituted: room temperature for 6 hours; use within 12 hours when refrigerated

Vibativ (telavancin) [package insert; Dalvance (dalbavancin) [package insert]; Orbactiv (oritavancin) [package insert]

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Medication Dispensing Errors

Causes	Impact	Prevention
• Expired product • Incorrect drug, preparation, strength, rate, dose • Known allergen, contraindication	• Prolonged hospital stays • Elevated healthcare costs • Increased mortality risk	• Medication reconciliation • Barcode identification of medications • Encourage error reporting

Tariq RA, et al. In: *StatPearls*.; Ciapponi A, et al. *Cochrane Database Syst Rev*. 2021;11(11):CD009985.

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Question 3

You see a label print for oritavancin. What would be an appropriate dosing you would expect to see?

A. 1200 mg IV once

B. 1200 mg IV every 12 hours

C. 1200 mg IV every 24 hours

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Summary

1. Enterococci have become increasingly resistant to vancomycin in the US, which has increased number of VRE cases, mortality, and healthcare costs

2. Appropriate use of antibiotics is important for improving patient outcomes and decreasing rates of resistance

3. If VRE has significant resistance to other antibiotics, linezolid and daptomycin are the preferred agents

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Thank You!

Questions?

dbiello@uchc.edu | jzhao@uchc.edu

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