Text BRUCEJONES319 to 22333

# Vancomycin vs Newer Agents for Gram-positive Infections Debate

**George D. Rodriguez, Pharm.D.**
Clinical Pharmacist, The Dr James J Rahal Jr Division of Infectious Diseases
Antimicrobial Stewardship Program Manager
New York-Presbyterian Queens
Assistant Clinical Professor, Pharmacy Sciences
Columbia University School of Nursing
gdr9005@nyp.org
@GeorgeR_IDpharm

**Bruce M. Jones, Pharm.D., BCPS**
Infectious Disease Clinical Pharmacy Specialist
St. Joseph's/Candler Health System, Inc.
Clinical Adjunct Assistant Professor
University of Georgia College of Pharmacy
5353 Reynolds Street
Savannah, GA 31405
jonesbru@sjchs.org
@Bruce_M_Jones

PollEv.com/brucejones319

# Disclosures

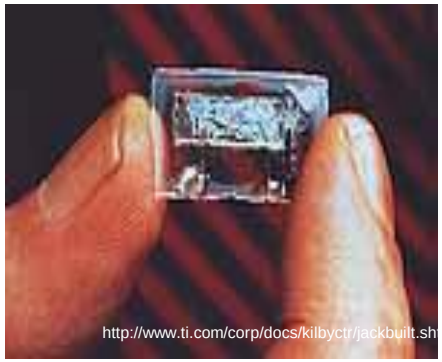
- GDR
  - Speaker's Bureau: Allergan
- BMJ
  - Grant Funding: ALK-Abello, Allergan
  - Consulting: ALK-Abello
  - Speaker's Bureau: Allergan
  - Advisory Board: Cempra, Astellas, Theravance

# Learning Objectives

- Compare the pharmacological differences between vancomycin and recently approved agents for gram positive infections
- Identify clinical opportunities and limitations pertaining to each agent
- Establish a place in therapy within a formulary system that best fits an individual institution

# Marvels of 1958


A. Explorer 1

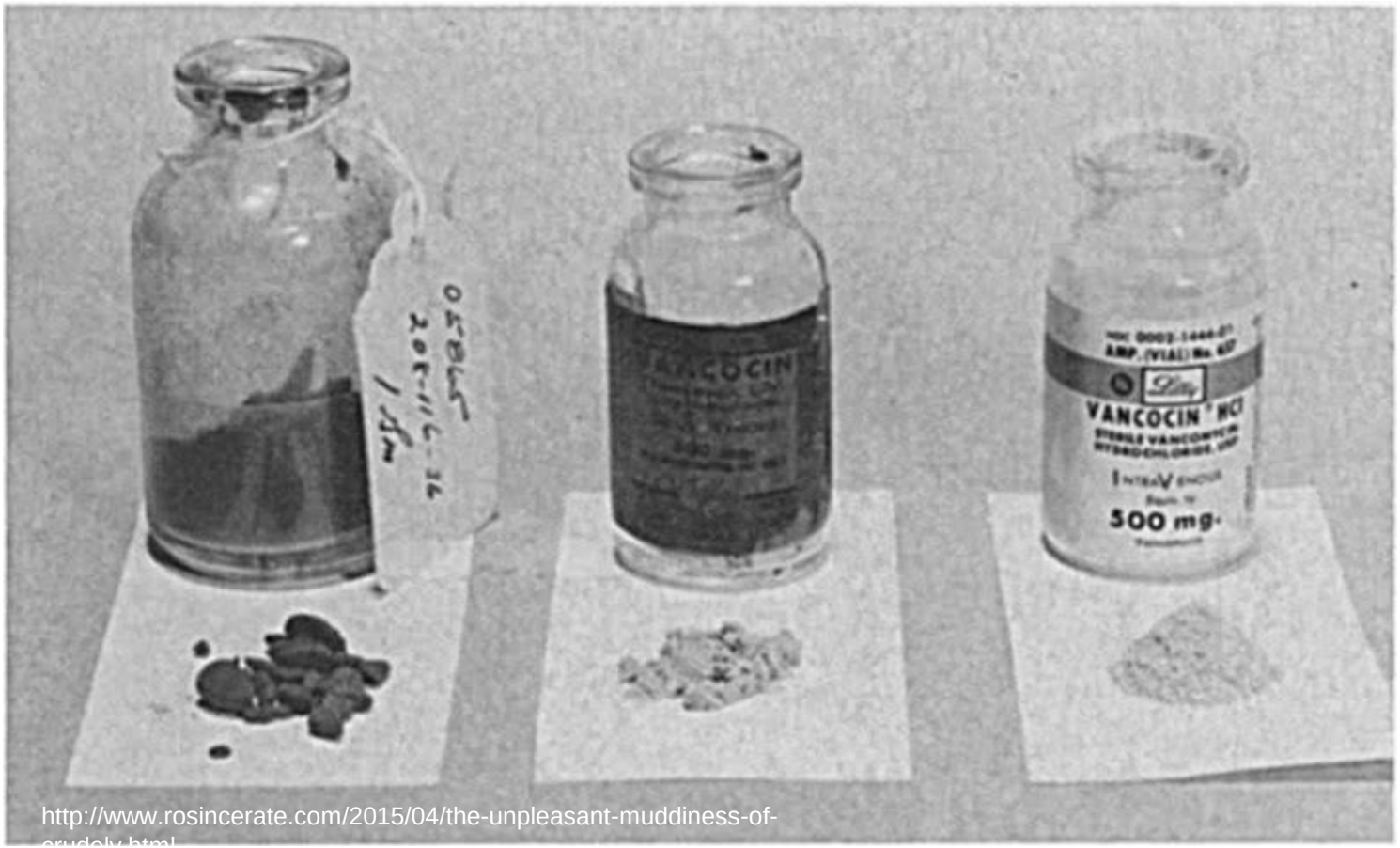



B. Integrated circuit


C. Frank Sinatra and Elvis Presley


D. Hula-Hoop

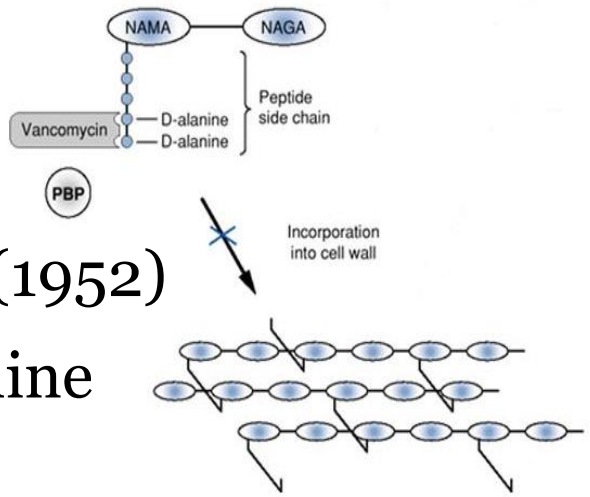
# Marvels of 1958




http://www.rosincerate.com/2015/04/the-unpleasant-muddiness-of-crudely.html

# Vancomycin

http://slideplayer.com/slide/7417455/24/images/29/Mechanism+of+Action+of+Vancomycin.jpg




- Derived from *Streptomyces orientalis* (1952)
- Glycopeptide, binds to D-alanyl-D-alanine precursor
  - Blocks peptidoglycan polymerization and transpeptidation
- Broad gram positive spectrum of activity
- Studied/approved for a wide range of indications
- Often less favored by clinicians due to nephrotoxicity concerns and dosing challenges

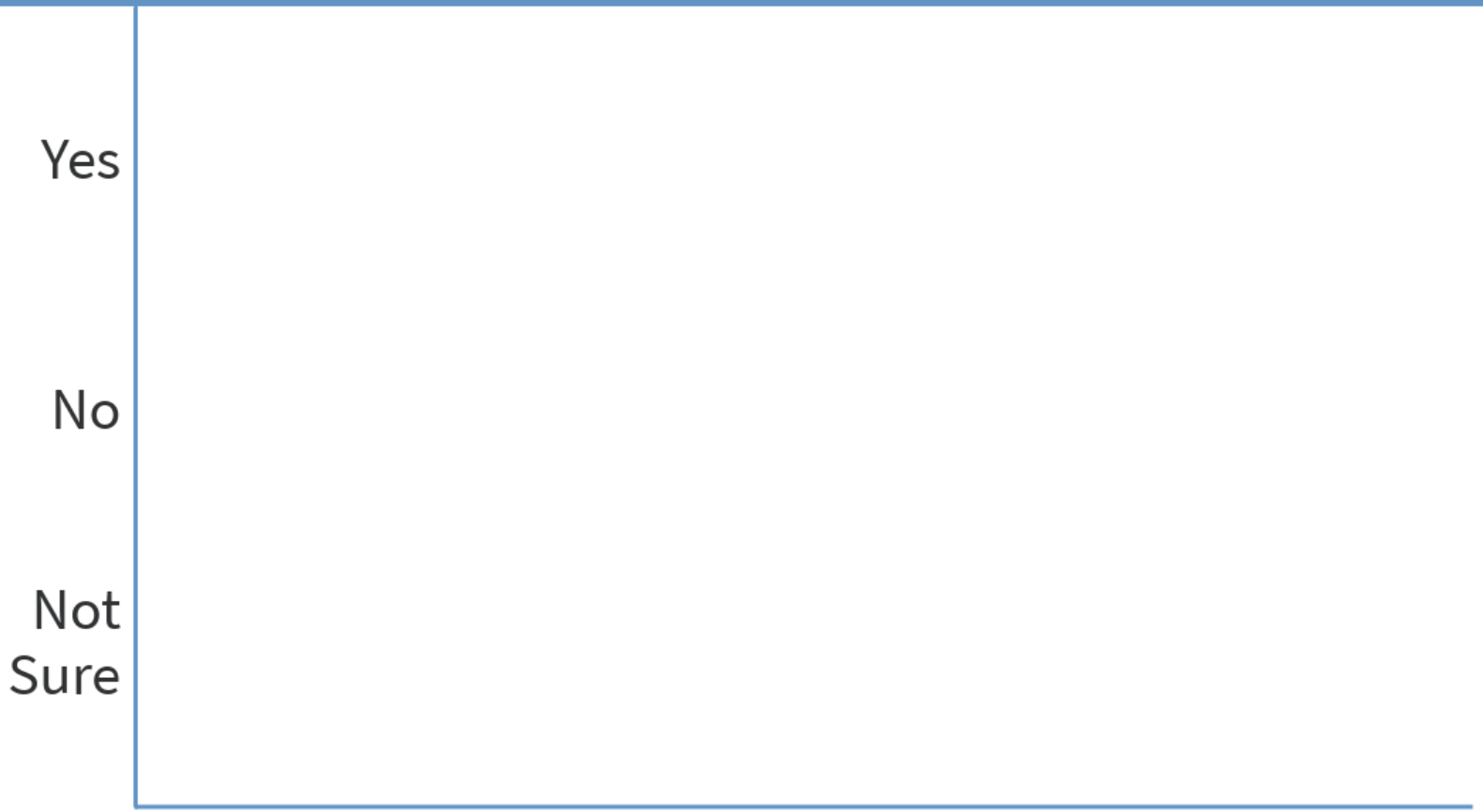
Stryjewski ME. CID 2014;58(s1):s10-9.
Rodvold K. CID 2014;58(s1):s0-7.
Kollef M. CID 2007;45:s191-5.
Levine D. CID 2006;42:s5-12.

# Vancomycin Nephrotoxicity

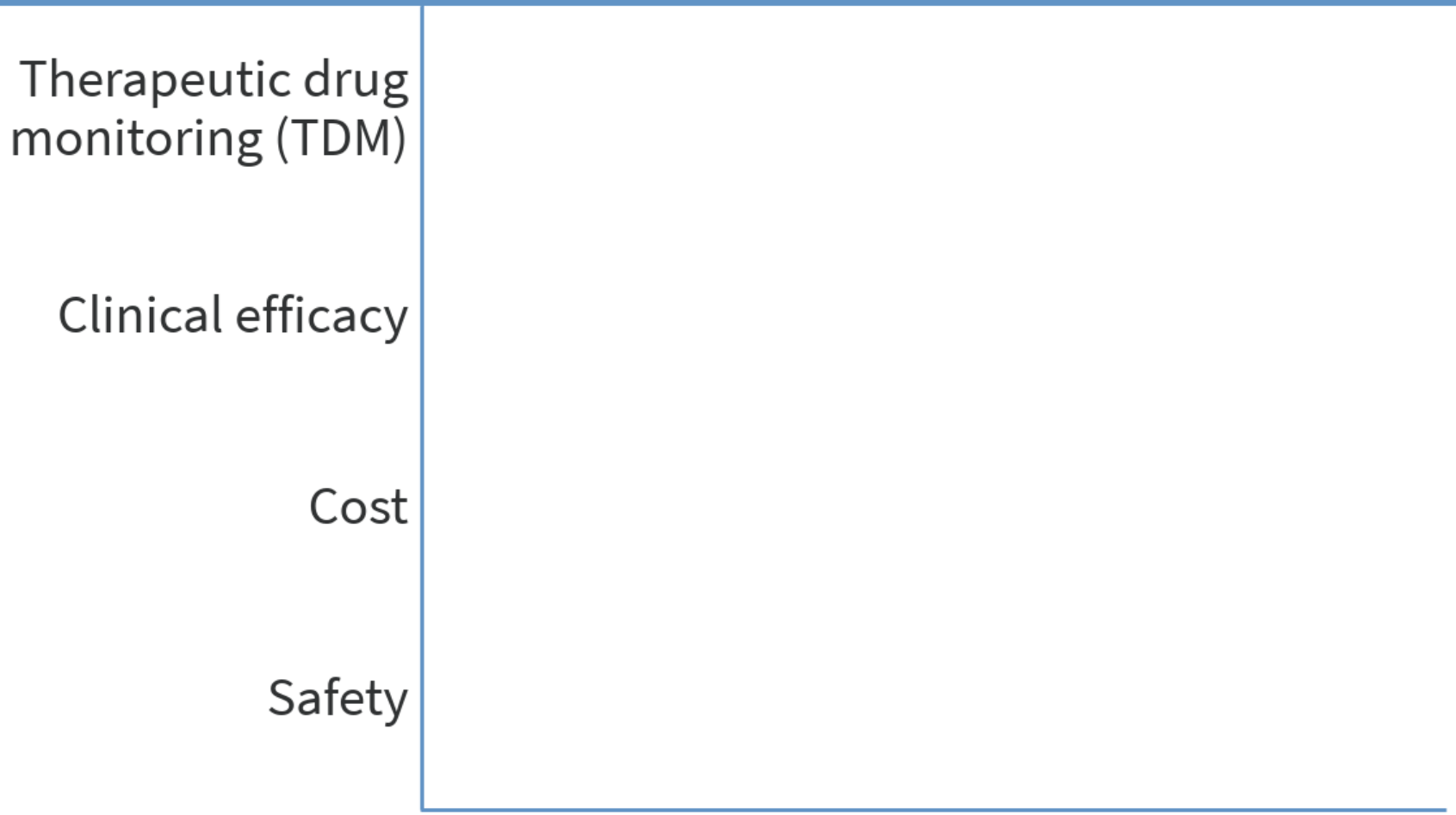
- Mechanism: Oxidative effects → renal tubular ischemia
  - Often reversible
- Variable rates depending on definition
- Many risk factors
- Additive effect seen with piperacillin/tazobactam

Hammond DA. CID 2017;64(5):666-74.
Carreno JJ. Pharmacotherapy 2014;34(12):1259-68.
Elyasi S. Eur J Clin Pharmacol 2012; 68:1243-55.

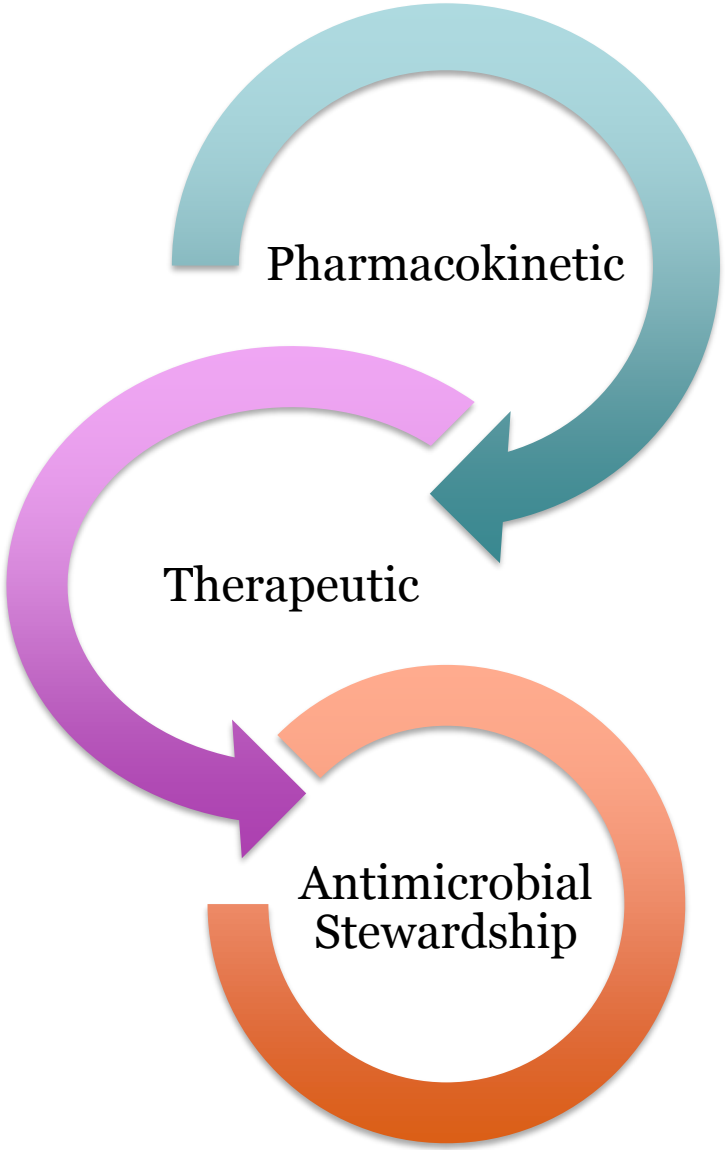
# If given the opportunity (cost not an issue), would you remove vancomycin (for intravenous use) from your institutions' formulary?



# Which of the following factors is most influential when deciding on whether or not to keep vancomycin on formulary?



# Vancomycin Advantages



# Pharmacokinetic Advantages

- Pharmacokinetics
  - Half-life (4 to 6 hours) = easy “turn-off”
  - Dialyzable (~45%)
  - Safety (anaphylaxis)
- Therapeutic drug monitoring (TDM) to individualize dose to patient
- Does not interfere with reagents used for INR and aPTT monitoring
- No CYP 450 enzyme interactions observed

Lodise T. CID 2014; 59(5): 666-75.
Holmes N. AAC 2013; 57(4): 1654-63.
Brown J. AAC 2012; 56(2): 634-8

# Vancomycin Dosing

- PKPD parameter: AUC/$MIC_{BMD}$
  - Goal > 400 for invasive disease (MRSA)
    - Decreased mortality, increased microbiological clearance
- AUC calculations are complicated
  - Vancomycin trough 15-20 mg/mL
- AUC calculators available
- Continuous infusion?


Holmes N. AAC 2013; 57(4): 1654-63.
Brown J. AAC 2012; 56(2): 634-8.
Gawronski KM. Clinical Therapeutics 2013; 35(6): 772-9.
Moise-Broder PA et al. *Clin Pharmacokinet* 2004; 43 (13): 925-42.
Elbarbry F. Eur J Drug Metab Pharmacokinet 2017. 1-10.
Lin H. Critical Care 2016; 20: 205-12.
Pai MP. Advanced Drug Delivery Reviews 2014; 77: 50-7.
Lodise T. CID 2014; 59(5): 666-75

# Therapeutic Advantages

- Empiric MRSA therapy
- Surgical prophylaxis (penicillin allergy)
- Transitions of Care
  - Available on most formularies
- No drug shown to be superior to vancomycin
  - Non-inferiority trials

MRSA, Methicillin-resistant *Staphylococcus aureus*

Kalil AC. CID 2016;63(5):e61-111.
Baddour LM. Circulation 2015;132:1-52.
Bratzler DW. *Am J Health-Syst Pharm*. 2013;70:195–283.
Liu C. CID 2011;52(3):e18-55.

# Antimicrobial Stewardship Advantages

- Narrower spectrum of activity (VRE)
- High barrier to resistance
  - Low prevalence of VRSA (after 60 years of use!)
- Reported outbreaks of resistance to existing MRSA alternatives

VRE, Vancomycin-resistant Enterococcus
VRSA, Vancomycin-resistant *Staphylococcus aureus*

McGuinness WA. YJBM 2017;90:269-81.
Limbago BM. JCM 2014;52(3):998-1002.
Velazquez A. Clin Microbiol Infect 2013;19:1169-72.
Bing G. JAC 2013;68:4-11.

# Long-Term Safety and Expanded Clinical Outcomes Data

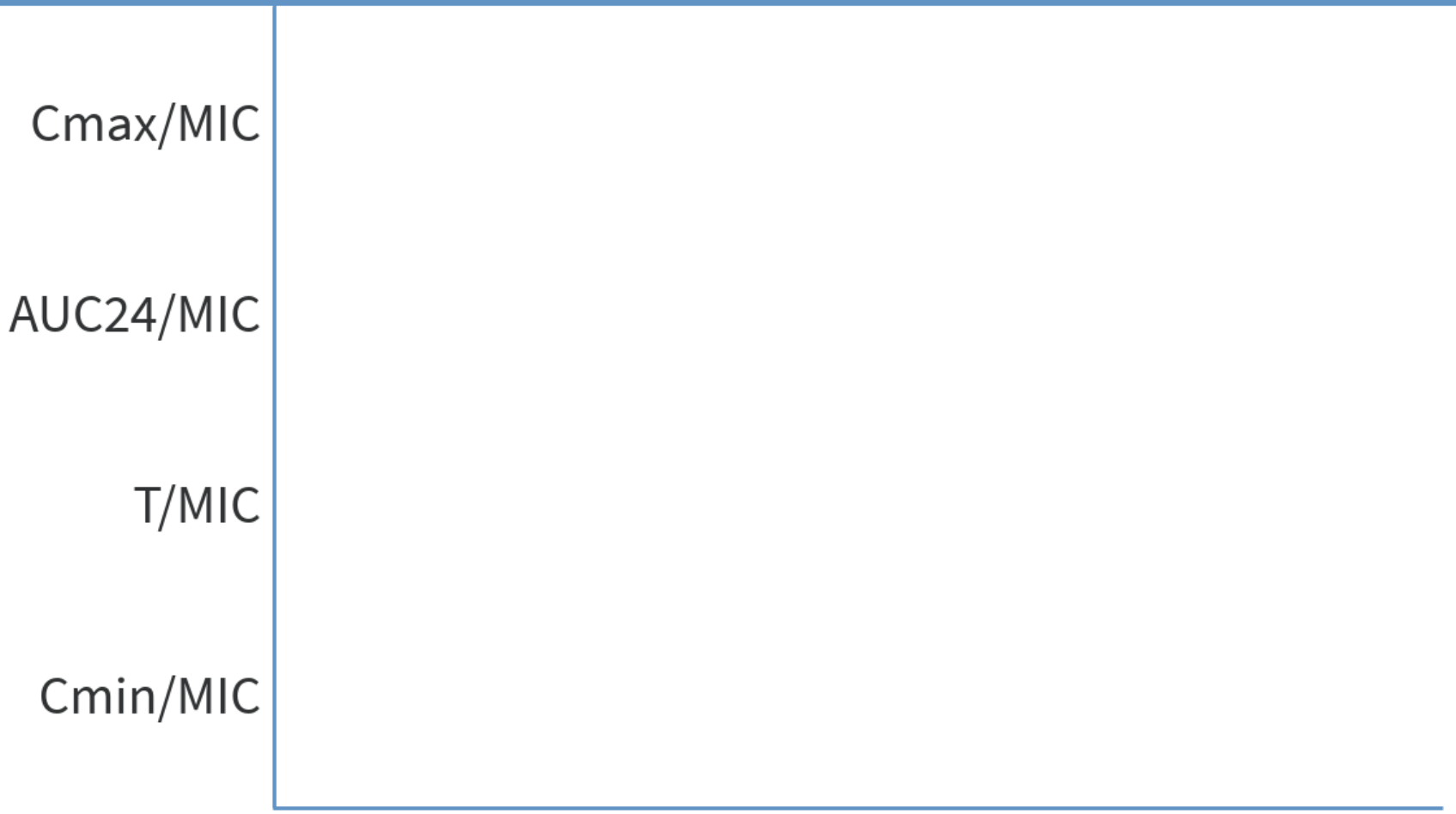
*"… I will not make age an issue of this ~~campaign~~ clinical debate. I am not going to exploit, for ~~political~~ time purposes, ~~my opponent's~~ the youth and inexperience of the new gram positive agents."*

-Ronald Reagan
(debate with Walter Mondale, 1984)

# Conclusion

- Vancomycin still a necessary agent
  - Pharmacokinetics allows for easier turn off
    - Empiric therapy
    - Surgical prophylaxis (penicillin allergy/MRSA colonization)
  - No drug:lab or CYP 450 interactions
  - Narrower spectrum / higher barrier to resistance

# Which PK/PD parameter is the best predictor of vancomycin clinical efficacy?



# Where We Don’t (hopefully) Need Vancomycin

- Most streptococci
- Most enterococci
- MSSA
- Penicillin allergy

https://giphy.com/gifs/reaction-no-the-office-NTddjTZTeOmXK

# Current Challenges for MRSA

- Vancomycin
- Linezolid
  - Bacteriostatic
  - Side effects
  - DDI
- Daptomycin
  - Not an option for pneumonia
  - Dose? 6, 8, 10, 12 mg/kg?
  - Cost
- Tigecycline
  - Black Box Warning for increased all-cause mortality
  - Bacteriostatic
  - Side effects (N/V/D)
- Ceftaroline
  - Cost
  - Niche for CABP?
  - No PO option

# New Antimicrobials

- Gram Positive
  - Delafloxacin (Baxdela®) (2017)
  - Tedizolid (Sivextro®) (2014)
  - Oritavancin (Orbactiv®) (2014)
  - Dalbavancin (Dalvance®) (2014)
  - Telavancin (Vibativ®) (2009,2013)

# Delafloxacin (Baxdela®)

- Indication:
  - ABSSSI
- Class:
  - Anionic bactericidal fluoroquinolone
    - Lower MICs, intracellular penetration, biofilm
- Mechanism of Action:
  - Inhibits bacterial topoisomerase IV and DNA gyrase (topoisomerase II)
  - Activity against gram-negative (including *Pseudomonas aeruginosa)*, atypical, anaerobic, as well as gram-positive (including **MRSA**)


1. https://www.baxdela.com. Accessed 2/12/18.
2. Mogle et al. Clinical review of delafloxacin: a novel anionic fluoroquinolone. *J Antimicrob Chemother*. 2018 Feb 7.

# Delafloxacin (Baxdela®)

- Black Box Warning:
  - Tendinitis and tendon rupture (no cases in trials)
  - Severely exacerbated muscle weakness in patients with myasthenia gravis resulting in death
  - Arthralgia, myalgia, peripheral neuropathy, and central nervous effects such as hallucinations, insomnia, anxiety, depression, and severe headaches
- ADR:
  - Dizziness, confusion, diarrhea, nausea, vomiting, hypersensitivity reactions
  - NO CYP interactions or major drug interactions
  - NO QTc prolongation
  - NO phototoxicity
  - NO glucose abnormalities


1. https://www.baxdela.com. Accessed 2/12/18.
2. Mogle et al. Clinical review of delafloxacin: a novel anionic fluoroquinolone. *J Antimicrob Chemother*. 2018 Feb 7.

# Delafloxacin (Baxdela®)

- Phase III Trials
  - Study 302 - Vancomycin ± aztreonam (IV only)
    Study 303 - Vancomycin ± aztreonam (IV/oral switch on day #4)
  - Early clinical response was shown to be non-inferior to vancomycin
  - Cure and resolution of symptoms at follow-up visit showed comparable success to vancomycin

Early Clinical Response = 48-72h


1. https://www.baxdela.com. Accessed 2/12/18.
2. Mogle et al. Clinical review of delafloxacin: a novel anionic fluoroquinolone. *J Antimicrob Chemother*. 2018 Feb 7.

# Delafloxacin (Baxdela®)

- Take Home Points
  - Fluoroquinolone with MRSA coverage
  - Renal dose adjust based on MDRD instead of Cockroft-Gault
  - Concern for collateral damage
    - DDI (minimal effects of CYP450)
    - Side effects (limited data thus far*)
    - Resistance
  - Niche?


1. https://www.baxdela.com. Accessed 2/12/18.
2. Mogle et al. Clinical review of delafloxacin: a novel anionic fluoroquinolone. *J Antimicrob Chemother*. 2018 Feb 7.

# Tedizolid (Sivextro®)

- Approved June 2014
- Class: Oxazolidinone
- Administration: Oral, IV
- Indications: ABSSSI
- Mechanism
  - Binds 50s subunit to inhibit protein synthesis
- Adverse effects
  - Nausea, headache, diarrhea, vomiting
- Monitoring
  - CBC

https://www.merckconnect.com/sivextro/overview.html. Accessed 2/8/17.

# Tedizolid (Sivextro®)

- Take Home Points
  - More potent version of linezolid
  - Less side effect potential, including DDI
  - Once daily dosing
  - Cost vs. linezolid

https://www.merckconnect.com/sivextro/overview.html. Accessed 2/8/17.

# Oritavancin (Orbactiv®)

- Approved August 2014
- Class: Lipoglycopeptide
- Administration: IV
- Indications: ABSSSI
- Mechanism (Multiple)
  - Inhibition of cell wall synthesis
  - Disruption of membrane leading to depolarization
- Warnings/precautions
  - Use of unfractionated heparin is contraindicated for 5 days after administration
- Adverse Events
  - Headache, nausea, vomiting, diarrhea, abscess (limb and subcutaneous)

http://www.orbactiv.com. Accessed 2/8/17.

# Dalbavancin (Dalvance®)

- Approved May 2014, (1 dose January 2016)
- Class: Lipoglycopeptide
- Administration: IV
- Indications: ABSSSI
- Mechanism
  - Inhibits cell wall peptidoglycan cross-linking, similar to vancomycin
- Warnings/Precautions
  - ALT elevations 3X UNL, diarrhea should be evaluated for CDI, hypersensitivity and skin reactions, infusion related reactions – administer over 30 mins
- Adverse Events
  - Diarrhea, nausea, headaches

https://www.dalvance.com. Accessed 2/8/17.

# Comparison Chart

| | Dalbavancin | Oritavancin |
|---|---|---|
| Cost | ~$4500 | ~$2900 |
| Dose & Administration | 1500mg IV x 1 over 30 min | 1200mg IV x 1 over 3 hrs |
| Storage & Stability | ≤ 48 hrs | ≤ 6 hrs (RT), 12 hrs (RF) |
| Fluid Volume | ≥ 300 ml D5W | ≥ 1000 ml D5W |
| Mechanism of Action | • Preventing cross-linking of peptidoglycans, destabilizing the cell membrane and resulting in bacterial cell death | • Inhibition of cell wall synthesis<br>• Disruption of membrane leading to depolarization<br>• Inhibit RNA synthesis? |
| Drug Interactions | • Not an inhibitor, inducer, or substrate of CYP 450 | • Weak inhibitor CYP2C9 & CYP2C19<br>• Inducer CYP3A4 & CYP2D6<br>• Prolongs aPTT |

Roberts KD, et al. *Pharmacotherapy* 2015;35(10):935–948.

# Dalbavancin & Oritavancin

- Take Home Points
  - Single-dose regimens
  - No TDM
  - No PICC
  - Limited data on other indications
  - Long half life
  - Choose the right patient

1. http://www.orbactiv.com. Accessed 2/8/17.
2. https://www.dalvance.com. Accessed 2/8/17.

# Telavancin (Vibativ®)

- Approved 2009 (cSSTI) 2013 (HABP/VABP)
- Indications: cSSTI, HABP/VABP
- Class:
  - Glycopeptide with concentration-dependent activity against Gram (+) bacteria
- MOA:
  - Stops bacterial cell wall synthesis and disrupts membrane barrier function

https://www.vibativ.com. Accessed 2/8/17.

# Telavancin (Vibativ®)

- Black Box Warning
  - Nephrotoxicity, especially with preexisting disease
  - Increased mortality for CrCl $\leq$ 50 ml/min
  - Use in pregnancy only if potential benefit outweighs risk
- Precautions
  - QTc prolongation, Red-man like syndrome, cross-sensitivity with vancomycin
- Monitor
  - CBC for improvement
  - SCr at baseline and q48-72h after initiation
  - Pregnancy test

https://www.vibativ.com. Accessed 2/8/17.

# Telavancin (Vibativ®)

- Take Home Points
  - Great coverage against MRSA, especially higher MIC against vancomycin
  - Awaiting Phase III data for bacteremia/endocarditis
  - Pros: No therapeutic drug monitoring, once daily dosing (capped dosing?)
  - Cons: Cost, Increased mortality for CrCl <50 ml/min, pregnancy, nephrotoxic

https://www.vibativ.com. Accessed 2/8/17.

# Conclusion

- There are many new agents available for gram-positive infections, namely MRSA
- None definitively replace vancomycin
- Most have a niche and are more desirable than vancomycin depending on infection type and resistance pattern of the organism

# Love / Hate Relationship With New-Agents

Written By: G. Rodriguez

# Delafloxacin (Love)

- Broad spectrum of activity available in oral form
  - Polymicrobial infections
- Well designed clinical trials
- Favorable characteristics vs. other FQ

https://hello.travefy.com/wp-content/uploads/2015/07/central-park-nyc-skyline-beautiful-HR.jpg

McCurdy S. AAC 2017;61(9):1-8.
O'Riordan W. CID 2018 [epub ahead of print]
Kingsley J. AAC ;71:821-9.

# Delafloxacin (Hate)

- Risk > Benefit
  - BBWs
  - *C. difficile* infection associated with FQ use
  - Caution empiric use for MRSA
    - Higher MICs to Levo-R MRSA isolates (breakpoint ≤ 0.25 mcg/mL)

| Organism | Baseline delafloxacin MIC (μg/ml) | *N*1 | No. (%) of subjects with: Eradicated/presumed eradicated infection | Persisted/presumed persisted infection |
|---|---|---|---|---|
| Levofloxacin-susceptible MRSA | | | 36 | 1 |
| | 0.004 | 3 | 3 (100.0) | 0 |
| | 0.008 | 30 | 29 (96.7) | 1 (3.3) |
| | 0.015 | 3 | 3 (100.0) | 0 |
| | 0.06 | 1 | 1 (100.0) | 0 |
| Levofloxacin-nonsusceptible MRSA | | | 70 | 1 |
| | 0.12 | 32 | 32 (100.0) | 0 |
| | 0.25 | 36 | 35 (97.2) | 1 (2.8) |
| | 0.5 | 2 | 2 (100.0) | 0 |
| | 4 | 1 | 1 (100.0) | 0 |

McCurdy S. AAC 2017;61(9):1-8.

# Tedizolid (Love)

- Excellent points
- Many argue thrombocytopenia
- Recent literature to support safety > 6 days
  - Phase III ABSSSI trial in Japan
  - Case reports
    - MRSA Suppression therapy
    - CNS Nocardiosis (6 month treatment)
    - Nontuberculous Mycobacterial infections
    - Renal insufficiency vs. linezolid

Nigo M. CID 2018 [epub ahead of print]
Matin A. International Journal of Antimicrobial Agents 2017;49:488-92.
Yuste JR. JAC 2017;72(2):625-28.
Khatchatourian L. JAC;72(7):2135-36.
Si S. Infect Dis Clin Pract 2017;25(2):105-7.
Kim T. Open Forum Infectious Dis 2016;3(1):577.

# Dalbavancin and Oritavancin (Love/Hate)

- Prolonged half-life, gift or curse?
- Gift
  - Compliance
  - Logistics
- Curse
  - Prolonged exposure (low concentrations)
  - Protein binding (D >90%, O 85%)
    - Resistance?
      - Dalbavancin-resistant MRSA urinary isolate identified
- Oritavancin should be conserved for VRE

Werth BJ. Clinical Microbiology and Infection 2018(24):429e1-e5.

# Telavancin (Love/Hate)

- Advantages
  - Option for HA-MRSA pneumonia
  - Once-daily dosing, no TDM required
  - Useful in the OPAT setting as an alt alternative agents
- Disadvantages
  - Dosing unclear
  - Tolerability
  - Inappropriately priced

Rodriguez GD. OFID 2017;4(s1):s337.

# Conclusion

- New agents offer many advantages (love)…

  … but not without collateral (hate)
- None of the agents should replace vancomycin as first line therapy (particularly in MRSA)
- Consider an algorithmic approach to optimize care on an individual level

# Gram Positive Stewardship

- You are going on a very long hike (clinical practice)
- You bring a supply of water for the journey (new agents)
- Do not drink all of your water during the first 5 minutes
- Save it for when you really need it!

# Issues with Vancomycin

- Overall Activity
- Weight-based Dosing
- TDM (AUC/MIC or troughs)
  - Narrow therapeutic index
  - Nephrotoxicity
- Resistance
  - Issues with automated testing


1. Rybak et al. *Am J Health Syst Pharm*. 2009; 66: 82-98.
2. https://www.wine-searcher.com/find/mississippi+mud+black+tan+beer+new+york+usa.

# What is the biggest current issue you see with vancomycin?

Toxicity

Dosing

Resistance

Better Antibiotics Available

# Activity

- Weak overall activity
- Cidal….Somewhat
- Poor tissue penetration
  - High Molecular Weight (1449 Daltons)
  - Hydrophilic
  - ELF concentration in the lung ~14% of serum
- Can we just overcome this by giving more drug more often to hit goal troughs of 15-20 mg/L?

Deresinski S. *Clin Infect Dis*. 2007; 44:1543-8.

# Weight-based Dosing

I said Super size them fries!

https://www.funnyjunk.com/funny_pictures/563245

# Weight-based Dosing

- Loading Doses? 20mg/kg? 25-30mg/kg?
- How have you standardized maintenance doses?
- Infusion reactions

Rybak et al. *Am J Health Syst Pharm*. 2009; 66: 82-98.

# Therapeutic Drug Monitoring

- Narrow Therapeutic Index
  - Most patients targeted at 15-20 mg/L
    - Improves penetration
    - Increases chance of hitting AUC:MIC of 400
    - Improves clinical outcomes
- Nephrotoxicity
  - Conflicting data on monotherapy
  - More and more data with combination of piperacillin/tazobactam

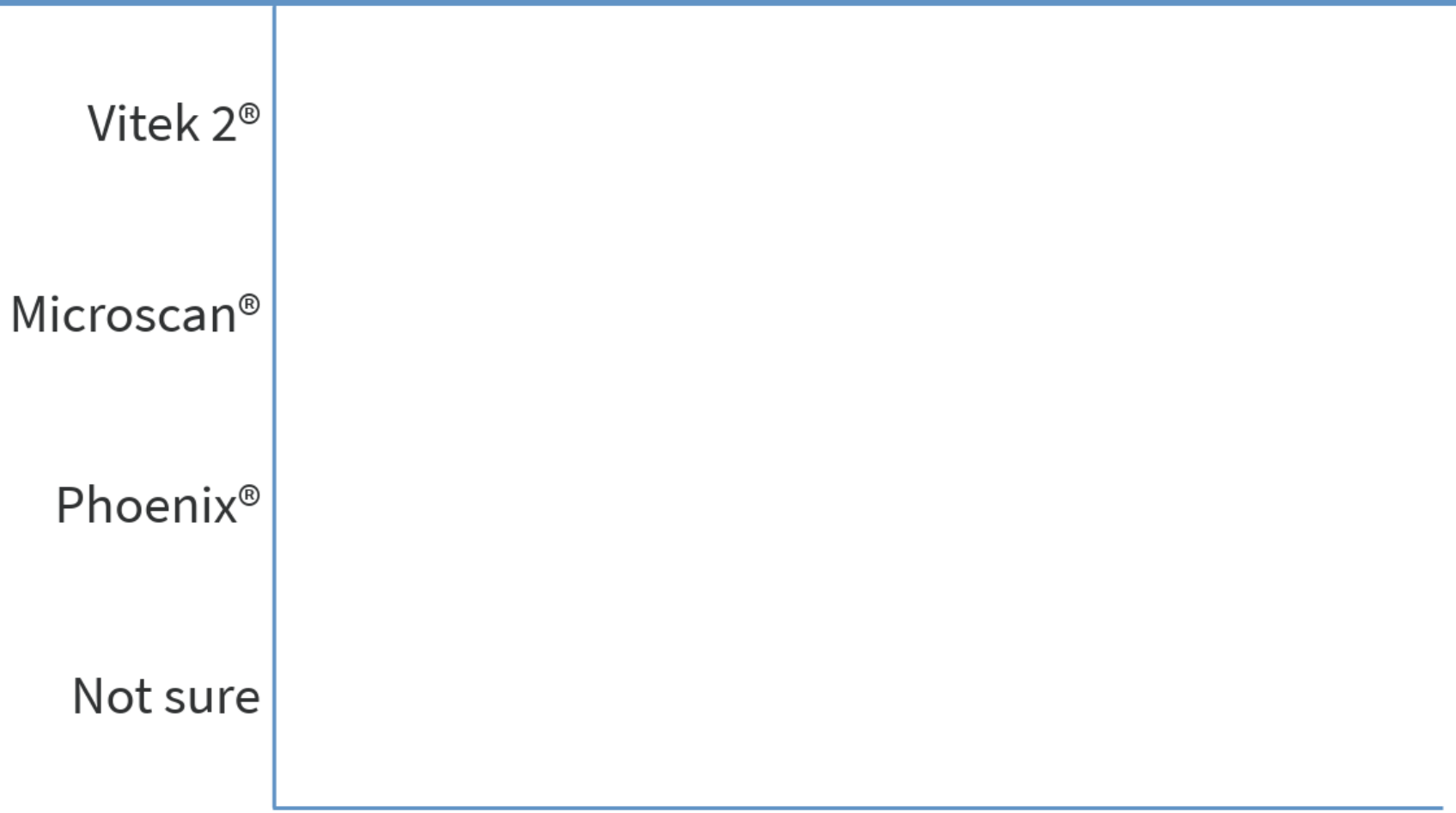
Rybak et al. *Am J Health Syst Pharm*. 2009; 66: 82-98.

# Resistance

- 13/16 peer-reviewed publications on MRSA with a higher MIC to vancomycin treated with vancomycin showed worse clinical outcomes
- Attributed to non-optimal AUC/MIC
- A 5 year study from 2000-2004 with 6,002 isolates showed *S. aureus* isolates with MIC of 1 to be significantly higher (70.4% vs 19.9%)
- This same study also showed a trend of higher rates of isolates with MIC $\geq$ 2

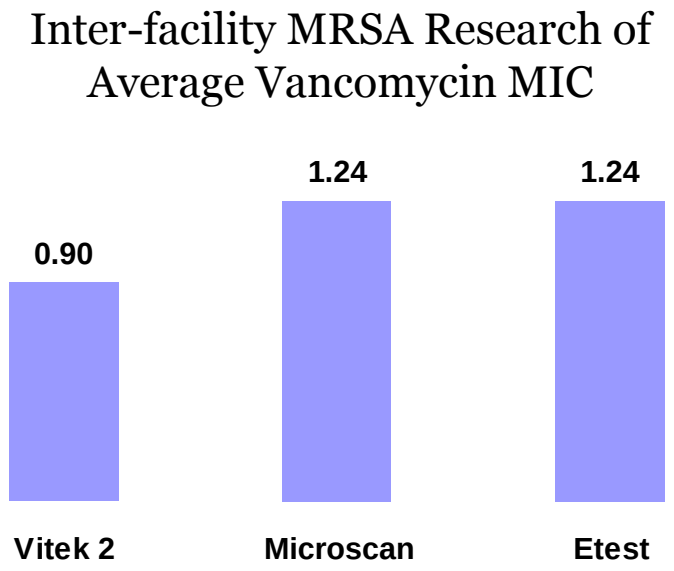

1. Holland TL and Fowler VG. *J Infect Dis*. 2011; 204:329-331
2. Wang et al. *J. Clin. Microbiol*. 2006; 3883-3886.

# What automated testing system do you currently use for antibiotic susceptibility testing?



# Issues With Automated Testing

- Within our city-wide stewardship program we evaluated Vancomycin MICs at two health systems
- Vitek 2 testing showed consistently lower MICs than both Microscan and Etest
- Higher rates of MIC = 2 on Microscan




| N=99 | Vitek 2 | Microscan | Etest |
|---|---|---|---|
| Mode MIC | 1 | 1 | 1.5 |
| MIC = 2 | N=1 | N=24 | N=5 |

# Questions???

**George D. Rodriguez, Pharm.D.**
Clinical Pharmacist, The Dr James J Rahal Jr Division of Infectious Diseases
Antimicrobial Stewardship Program Manager
NewYork-Presbyterian Queens
Assistant Clinical Professor, Pharmacy Sciences
Columbia University School of Nursing
gdr9005@nyp.org
@GeorgeR_IDpharm

**Bruce M. Jones, Pharm.D., BCPS**
Infectious Disease Clinical Pharmacy Specialist
St. Joseph's/Candler Health System, Inc.
Clinical Adjunct Assistant Professor
University of Georgia College of Pharmacy
5353 Reynolds Street
Savannah, GA 31405
jonesbru@sjchs.org
@Bruce_M_Jones