IS IT TIME TO REPLACE VANCOMYCIN?

A discussion stemming from patient cases

AMMI Canada – CACMID Annual Conference
April 17, 2015
Charlottetown, PEI

Faculty

PRESENTERS

- **Andrew E. Simor, M.D., FRCPC,**
  Chief, Department of Microbiology
  Chief, Division of Infectious Diseases
  Sunnybrook Health Sciences Centre
  Senior Scientist, Sunnybrook Research Institute
  Professor, Departments of Laboratory Medicine & Pathobiology, and Medicine
  University of Toronto, Toronto, ON

- **Daniel J. G. Thirion, B.Pharm., M.Sc. (Pharmacy), Pharm.D., FCSHP**
  Clinical Full Professor, Faculty of Pharmacy, Université de Montréal
  Pharmacist, Royal Victoria Hospital/McGill University Health Centre
  Montreal, QC

Disclosure

- Daniel J. G. Thirion, Pharm.D., FCSHP
  - None to declare

Learning Objectives

1. Describe the current evidence supporting the use of vancomycin for treatment of complicated MRSA infections
2. Describe the limits of using vancomycin

Properties of the Ideal Antibiotic to Treat MRSA Infections

- Rapid bactericidal killing
- Excellent tissue penetration
- Consistent pharmacokinetics and pharmacodynamics that allow for predictable dosing
- Low potential for development of resistance on treatment
- Low side effect profile
- Demonstrated clinical and microbiological efficacy

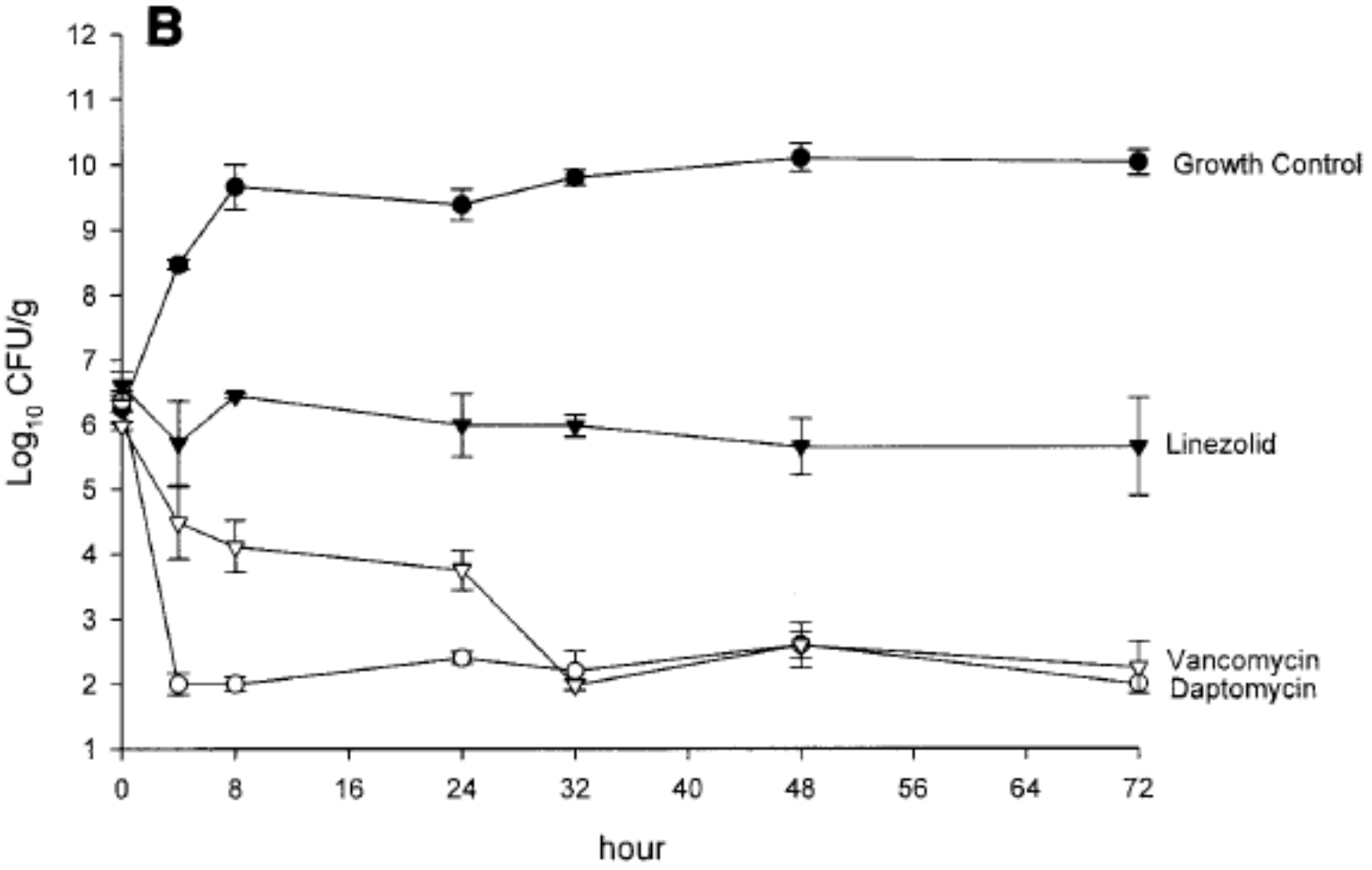
Vancomycin Under the Microscope

- Do we understand the vanco? (*in vitro*)
- Resistance (visa, hvisa, mic creep)
- Vanco levels? (Pk)
- Pharmacodynamics
- Clinical failures?
- Dosing (loading dose)

Vancomycin MICs

	NCCLS (previous)	CLSI
S	≤4 µg/mL	≤2 µg/mL
I	8-16 µg/mL	4-8 µg/mL
R	>32 µg/mL	≥ 16 µg/mL

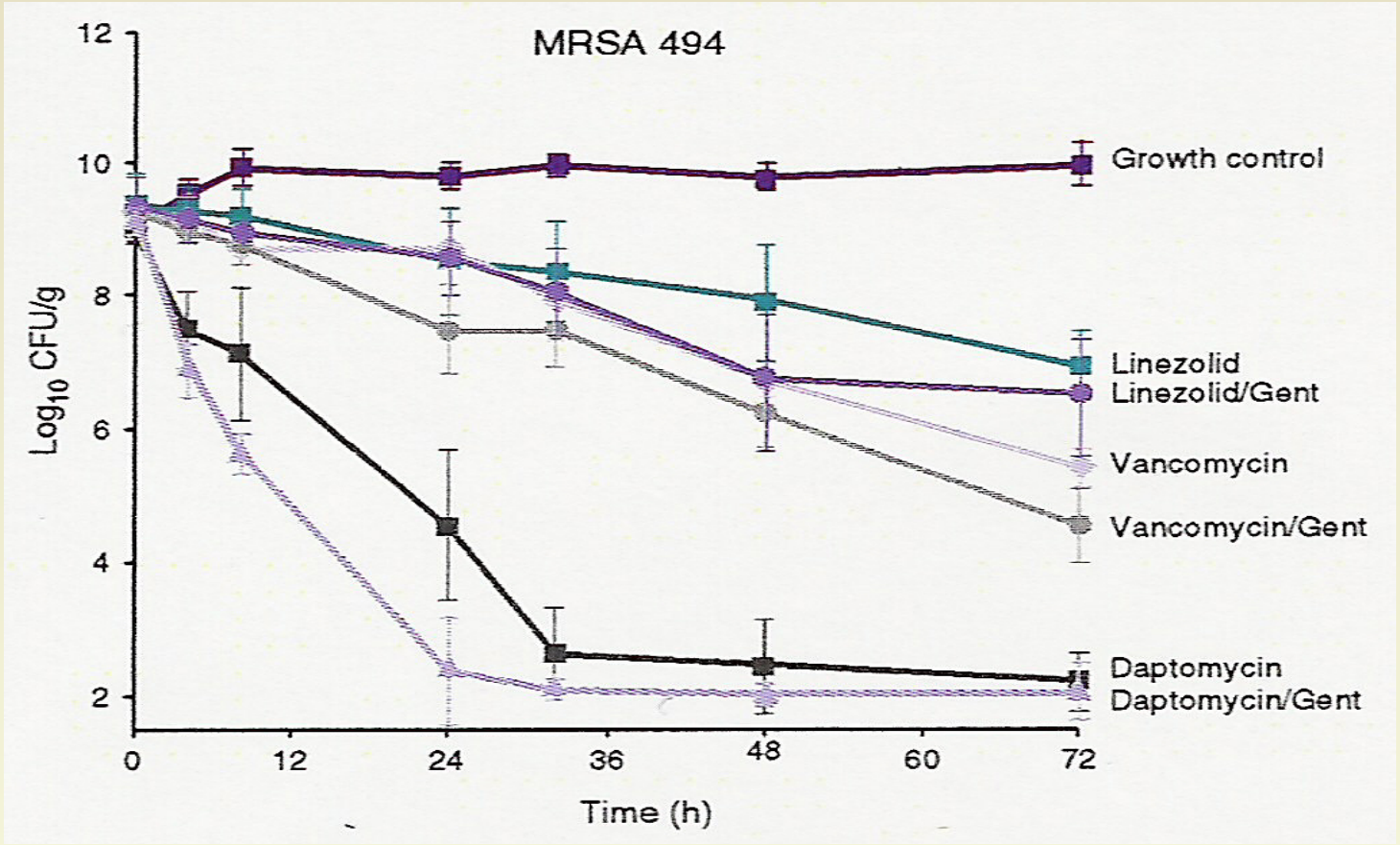
IMPACT OF MODERATE VS HIGH-INOCULUM MRSA ON ACTIVITIES OF ANTIMICROBIALS



MODERATE INOCULUM

Laplante K, et al. AAC 2004;48:4665

IMPACT OF MODERATE VS HIGH-INOCULUM MRSA ON ACTIVITIES OF ANTIMICROBIALS



HIGH INOCULUM

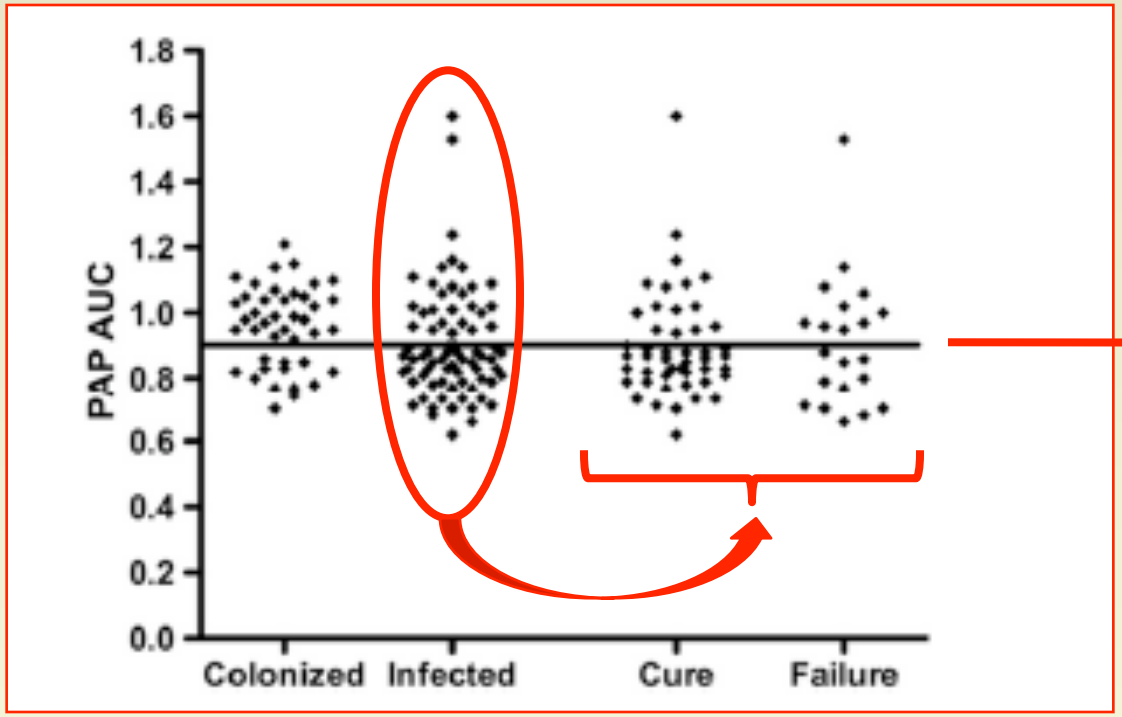
Laplante K, et al. AAC 2004;48:4665

Vancomycin Resistance in *S. aureus* is rare in Canada

- VISA
  - Intermediate susceptible, 8-16 ug/mL
  - Thickened cell wall
- VRSA
  - Vancomycin resistant, 1st reported 2002
  - *van*A gene
- hVISA
  - Subpopulation of susceptible *S. aureus* (MRSA) that may express intermediate resistance

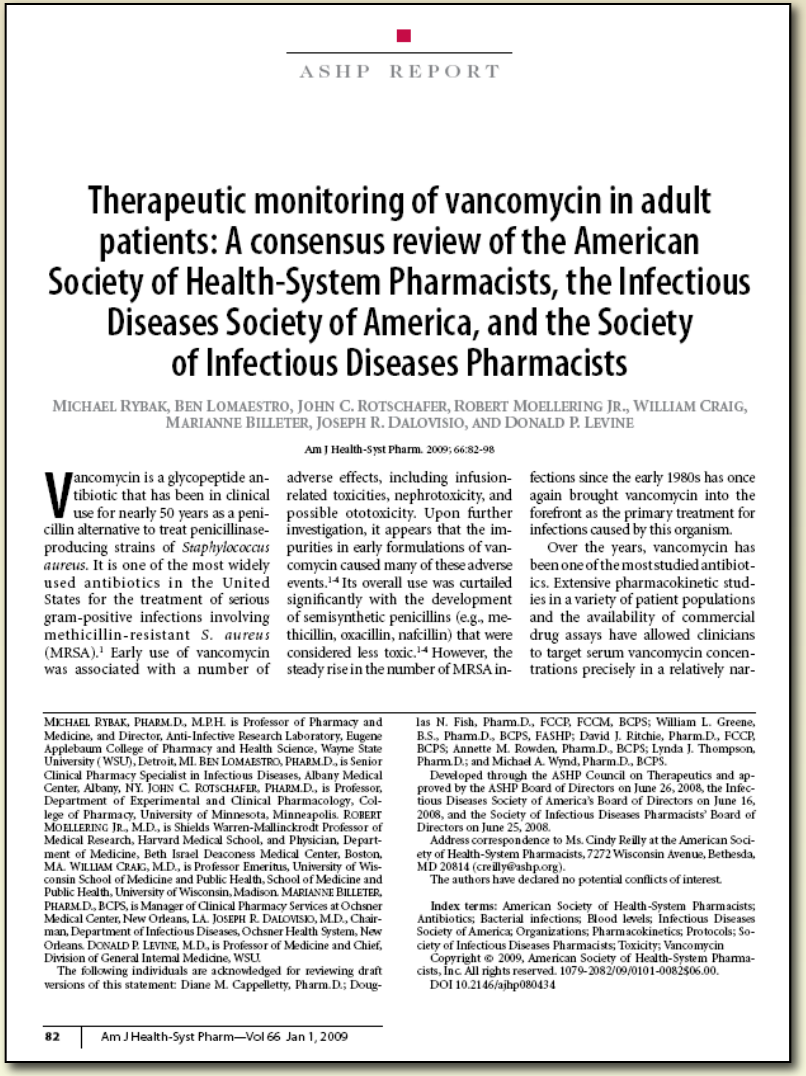
hVISA may not be Clinically Relevant

- Outcomes of hVISA-MRSA compared to vanco susceptible MRSA: prospective evaluation



Horne KC et al. Antimicrob Agents Chemother 2009;53:3447-52

Understanding vancomycin TDM



ASHP REPORT

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

MICHAEL RYBAK, BEN LOMAESTRO, JOHN C. ROTSCHAFER, ROBERT MOELLERING JR., WILLIAM CRAIG, MARIANNE BILLETER, JOSEPH R. DALOVISIO, AND DONALD P. LEVINE

Am J Health-Syst Pharm. 2009; 66:82-98

Vancomycin is a glycopeptide antibiotic that has been in clinical use for nearly 50 years as a penicillin alternative to treat penicillinase-producing strains of *Staphylococcus aureus*. It is one of the most widely used antibiotics in the United States for the treatment of serious gram-positive infections involving methicillin-resistant *S. aureus* (MRSA).[1] Early use of vancomycin was associated with a number of adverse effects, including infusion-related toxicities, nephrotoxicity, and possible ototoxicity. Upon further investigation, it appears that the impurities in early formulations of vancomycin caused many of these adverse events.[1-4] Its overall use was curtailed significantly with the development of semisynthetic penicillins (e.g., methicillin, oxacillin, nafcillin) that were considered less toxic.[1-4] However, the steady rise in the number of MRSA infections since the early 1980s has once again brought vancomycin into the forefront as the primary treatment for infections caused by this organism.

Over the years, vancomycin has been one of the most studied antibiotics. Extensive pharmacokinetic studies in a variety of patient populations and the availability of commercial drug assays have allowed clinicians to target serum vancomycin concentrations precisely in a relatively nar-

MICHAEL RYBAK, PHARM.D., M.P.H. is Professor of Pharmacy and Medicine, and Director, Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Science, Wayne State University (WSU), Detroit, MI. BEN LOMAESTRO, PHARM.D., is Senior Clinical Pharmacy Specialist in Infectious Diseases, Albany Medical Center, Albany, NY. JOHN C. ROTSCHAFER, PHARM.D., is Professor, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis. ROBERT MOELLERING JR., M.D., is Shields Warren-Mallinckrodt Professor of Medical Research, Harvard Medical School, and Physician, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA. WILLIAM CRAIG, M.D., is Professor Emeritus, University of Wisconsin School of Medicine and Public Health, School of Medicine and Public Health, University of Wisconsin, Madison. MARIANNE BILLETER, PHARM.D., BCPS, is Manager of Clinical Pharmacy Services at Ochsner Medical Center, New Orleans, LA. JOSEPH R. DALOVISIO, M.D., Chairman, Department of Infectious Diseases, Ochsner Health System, New Orleans. DONALD P. LEVINE, M.D., is Professor of Medicine and Chief, Division of General Internal Medicine, WSU.

The following individuals are acknowledged for reviewing draft versions of this statement: Diane M. Cappelletty, Pharm.D.; Douglas N. Fish, Pharm.D., FCCP, FCCM, BCPS; William L. Greene, B.S., Pharm.D., BCPS, FASHP; David J. Ritchie, Pharm.D., FCCP, BCPS; Annette M. Rowden, Pharm.D., BCPS; Lynda J. Thompson, Pharm.D.; and Michael A. Wynd, Pharm.D., BCPS.

Developed through the ASHP Council on Therapeutics and approved by the ASHP Board of Directors on June 26, 2008, the Infectious Diseases Society of America's Board of Directors on June 16, 2008, and the Society of Infectious Diseases Pharmacists' Board of Directors on June 25, 2008.

Address correspondence to Ms. Cindy Reilly at the American Society of Health-System Pharmacists, 7272 Wisconsin Avenue, Bethesda, MD 20814 (creilly@ashp.org).

The authors have declared no potential conflicts of interest.

Index terms: American Society of Health-System Pharmacists; Antibiotics; Bacterial infections; Blood levels; Infectious Diseases Society of America; Organizations; Pharmacokinetics; Protocols; Society of Infectious Diseases Pharmacists; Toxicity; Vancomycin

DOI 10.2146/ajhp080434

TDM of Vancomycin

- 15-20 mg/kg/dose ABW IV q8-12h in normal renal function (BII)
- Loading dose of 25-30 mg/kg (ABW) in seriously ill patients (CIII)
- 1 g IV q12h acceptable for SSTI and normal renal function, non obese (BII)
- Monitor trough levels (not peaks) (BII)
- Aim for 15-20 mg/L (BII)

Liu C et al. Clin Infect Dis. 2011:epub;1-38.

Target Pharmacodynamics is Known

- Associated with AUC24/MIC $\geq$ 400
- Clinical and bacteriologic response superior when threshold is reached (p=0.0046)
  - More rapid bacterial eradication (p=0.0402)
  - Relationship between time to bacterial eradication and time to improvement in pneumonia score (p<0.0001)

Moise-Broder PA, et al. Clin Pharmacokinet 2004;43:925-42

Newer Alternative Agents

Antibiotic	Class	NOC Year
Quinupristin-Dalfopristin	Streptogramin	1999
Linezolid	Oxazolidinone	2001
Tigecycline (black box by FDA)	Glycylcycline	2006
Daptomycin	Lipopeptide	2007
Ceftobiprole (rejected by FDA)	Cephalosporin	2008

Vancomycin on Trial

- Approved for use in 1958
- Increasing and now extensive use since 1960s
- Is there an alternative that has appropriately demonstrated superiority?
- Does resistance preclude the use of vancomycin in Canada?
- Is there an alternative that has a demonstrated better safety profile?
- Is there a more reasonable economic way of doing things?

Daptomycin vs Vancomycin/Gent for MRSA Bacteremia or Right-Sided Endocarditis

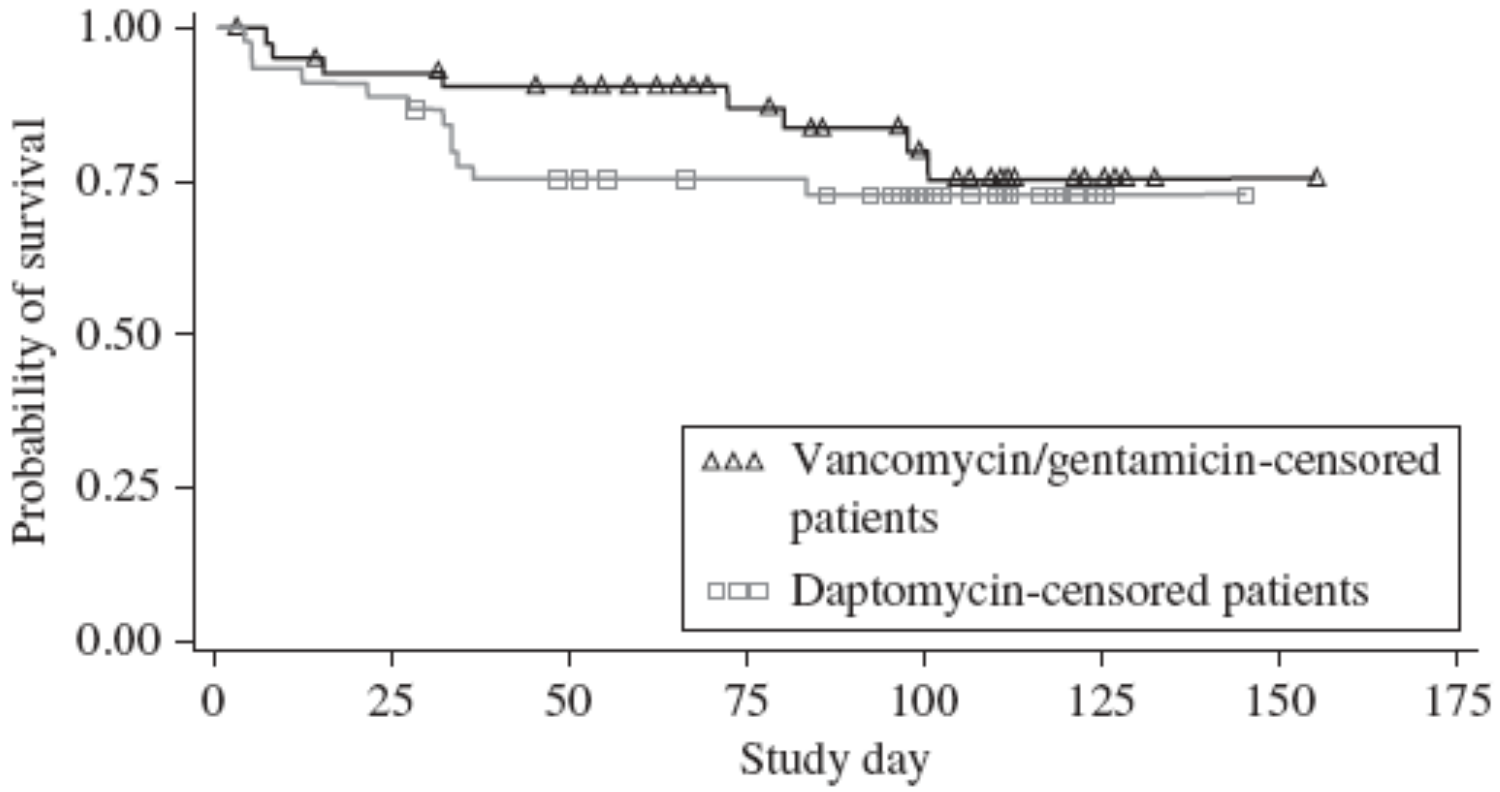


Figure 1. The Kaplan–Meier plot of overall survival. Wilcoxon $P = 0.25$, log-rank $P = 0.42$.

Rehm SJ, et al. J Antimicrob Chemother 2008;62:1413-21

"Cross-resistance" with Vancomycin and Daptomycin

- Membrane permeability is compromised

Table 1. Effect of increasing vancomycin MICs on daptomycin susceptibility for *Staphylococcus aureus* isolates.

Vancomycin MIC, μg/mL	No. (%) of isolates	
	Daptomycin MIC ≤1 μg/mL	Daptomycin MIC ≥2 μg/mL
≤2	812 (97)	30 (3)
4	11 (20)	43 (80)
8–16	1 (7)	15 (93)
≥32	5[a] (100)	0 (0)

NOTE. $P < .0001$; χ^2 test for trend.

[a] Five *S. aureus* isolates with vanA-mediated resistance.

However, vanA-mediated resistance does not seem to impact dapto susceptibility

Patel JB et al. Clin Infect Dis 2006;42:1652-3
Huang YT et al. J Clin Microbiol 2008;46:1132
Tenover FC et al. Int J Antimicrob Ag 2009;33:564
Bennett JW et al. Diagn Microbiol Infect Dis 2008;60:437

Facts about nosocomial pneumonia (NP)

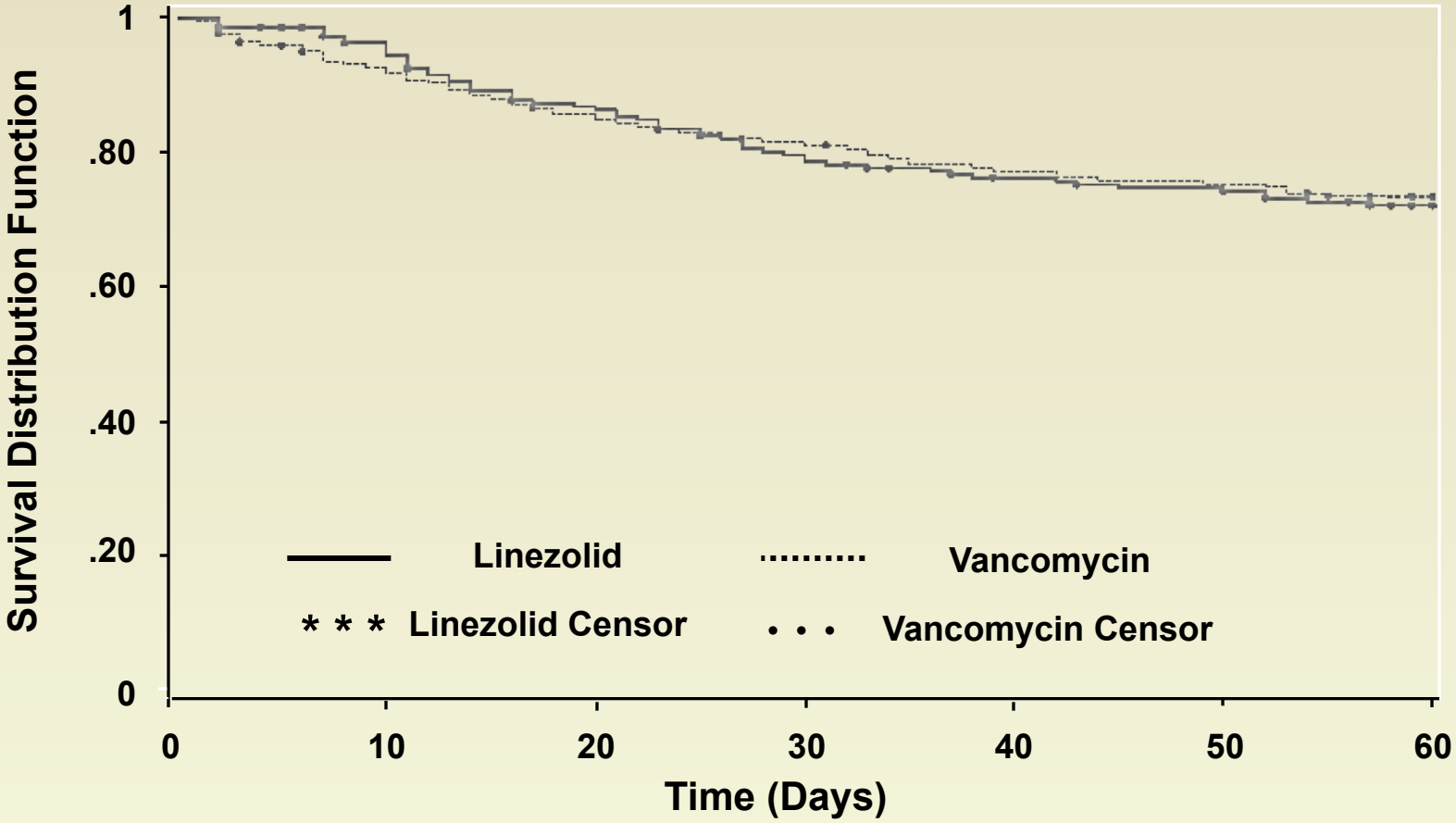
- Mortality rates in NP vary depending on the patient population, with HAP mortality as high as 30% to 60%, lower in clinical drug trials 18-25%, higher in epidemiological trials

- Mortality in VAP varies from 24% to 60%, with the higher mortality rates occurring when VAP is accompanied by acute lung injury (ALI) or adult respiratory distress syndrome (ARDS).

- The majority of deaths that occur during or after an episode of NP are commonly related to the underlying medical conditions rather than being directly attributable to NP

Leroy et al. Treat Respir Med. 2004;3:123-31.
Edis EC, et-al. Respiration. 2009;78:416-422.
Connelly SM, et-al. Am J Infect Control. 2009;37:143-9.)
Fagon J,et-al . Am J Respir Crit Care Med. 2000 ;161(3 Pt 1):753-62.
Fagon JY & Chastre J.. Eur Respir J Suppl. 2003 Aug;42:77s-83s.
Markowicz P, et-al.. ARDS Study Group. Am J Respir Crit Care Med. 2000 161:1942-8.

Linezolid vs Vanco in MRSA pneumonia
Mortality: Kaplan-Meier Plot – 60 Days: ITT



94 subject deaths (15.7%) in linezolid arm
100 subject deaths (17.0%) in vancomycin arm

Wunderink RG, et al. CID 2012;54:621

Vancomycin Trough Levels - HA-MRSA Pneumonia

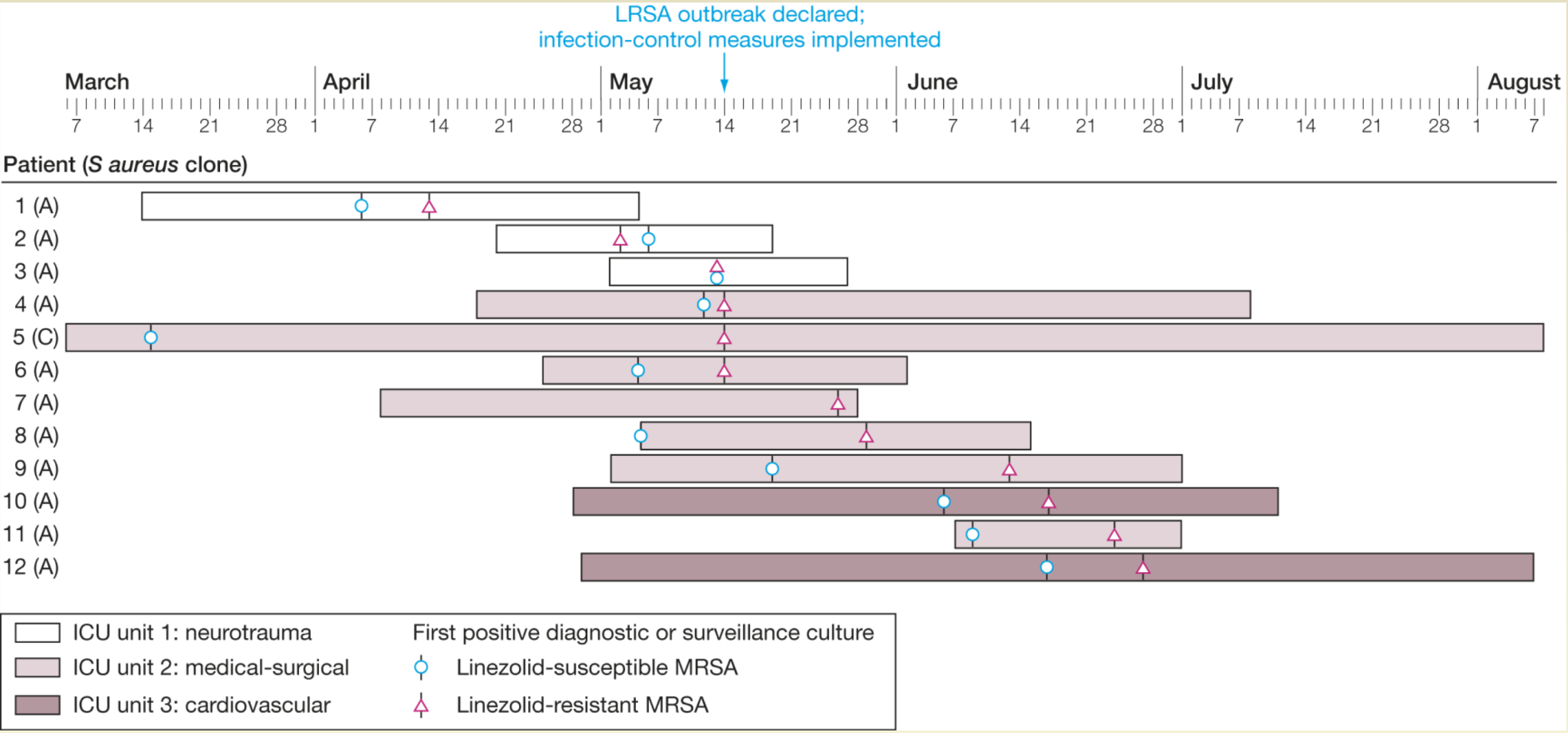
Table 2. Clinical Success Rates in the Per-Protocol Population at End of Study, by Patient Subgroup

Vancomycin trough levels (day 3)			
0–7.9 μg/mL	…	17/35 (48.6)	
8–12.3 μg/mL	…	17/37 (46.0)	
12.4–17.4 μg/mL	…	15/33 (45.5)	
>17.4 μg/mL	…	15/33 (45.5)	
Vancomycin MIC			
<1 μg/mL	10/16 (62.5)	7/14 (50.0)	−22.8 to 47.8
1 μg/mL	77/122 (61.5)	64/134 (47.8)	1.6 to 25.8
≥2 μg/mL	3/8 (37.5)	7/13 (53.8)	−59.5 to 26.8

Trial not designed to evaluate vancomycin troughs

Wunderink RG, et al. CID 2012;54:621

Emergence of resistance with linezolid



Garcia MS, et al. JAMA 2010;303:2260

Canadian Guidelines for HAP/VAP

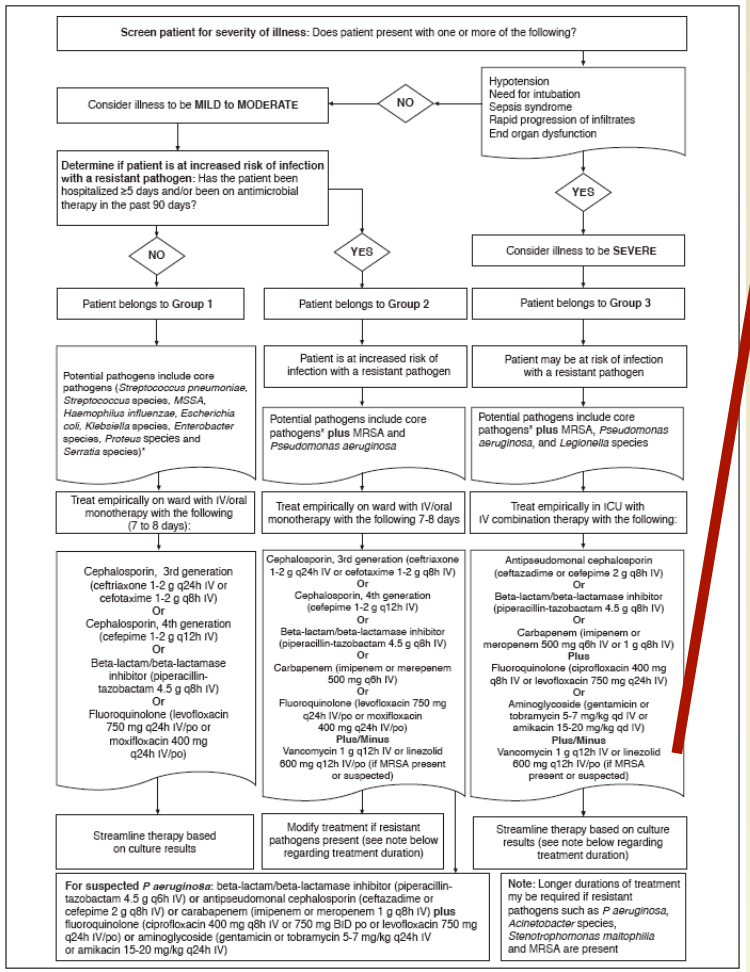


Figure 6) *Treatment algorithm for hospital-acquired pneumonia. BID Twice daily; ICU Intensive care unit; IV Intravenous; MRSA Methicillin-resistant* Staphylococcus aureus; *MSSA Methicillin-susceptible* S aureus; *q Every; po By mouth*

Vancomycin 1g q12 h or linezolid 600 mg q12h IV/po (if MRSA present or suspected)

« Additional studies are warranted to advise clinicians of the optimal agents and dosages for treating *P aeruginosa* and MRSA HAP and VAP. »

Rotstein C et al. Can J Infect Dis Med Microbiol 2008;19:19-53

Safety: Choose your Poison

- RCT-open label trial: MRSA infections (pneumonia, SSTIs, sepsis) in Japan

AE	Linezolid, $n = 100$	Vancomycin, $n = 51$
Total no. of patients reported (%)	55 (55.0)	22 (43.1)
Total (%)		
laboratory test abnormal	6 (6.0)	0 (0.0)
diarrhoea	10 (10.0)	1 (2.0)
liver function abnormal	6 (6.0)	4 (7.8)
renal function abnormal*	1 (1.0)	5 (9.8)
nausea	6 (6.0)	0 (0.0)
vomiting	5 (5.0)	0 (0.0)
anaemia*	13 (13.0)	1 (2.0)
leucopenia	7 (7.0)	0 (0.0)
thrombocytopenia*	19 (19.0)	1 (2.0)
hyponatraemia	7 (7.0)	0 (0.0)
rash	2 (2.0)	3 (5.9)

*$P < 0.05$ (χ^2 test).

- V: Reversible nephrotoxocity
- L: Reversible hematological abnormalities
- L: longer exposure neurotoxicity

Kohno S, et al. J Antimicrob Chemother 2007;60:1361-9

Safety Monitoring

- Vancomycin
  - Nephrotoxicity
  - DI: nephrotoxic meds
- Daptomycin
  - LFTs, CK
  - DI: statins, rhabdomyolisis
- Linezolid
  - Plts
  - DI: MOAI, SSRIs

Closing Position

- Require appropriate demonstration (studies) to satisfy criteria of superior efficacy and equivalent or superior safety
- Require epidemiology of severe infections caused by MRSA (local)
- Require outcomes data on severe infections according to vancomycin dosing and MIC (international)