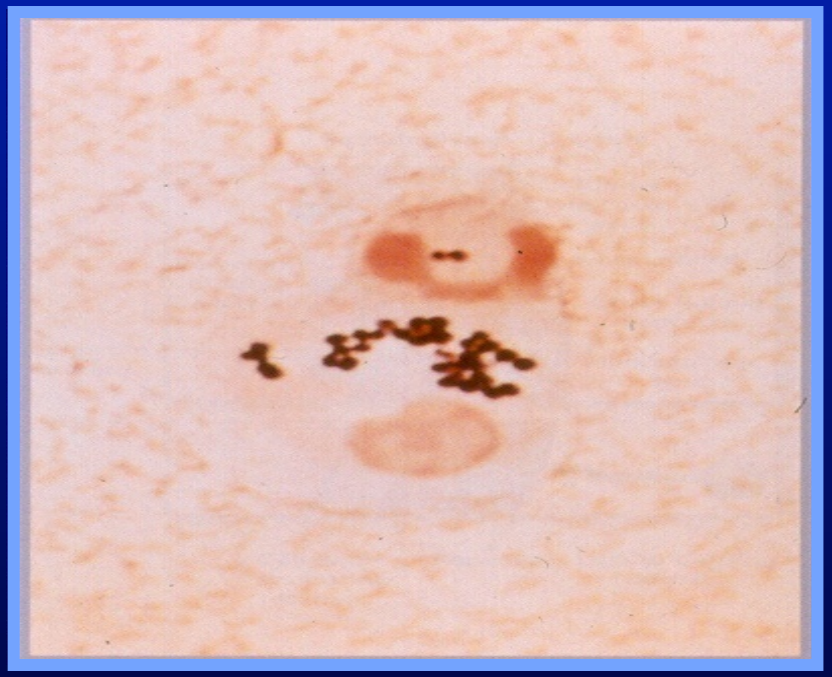
Treatment of Serious MRSA Infections: What Alternatives to Vancomycin Should Be Considered?



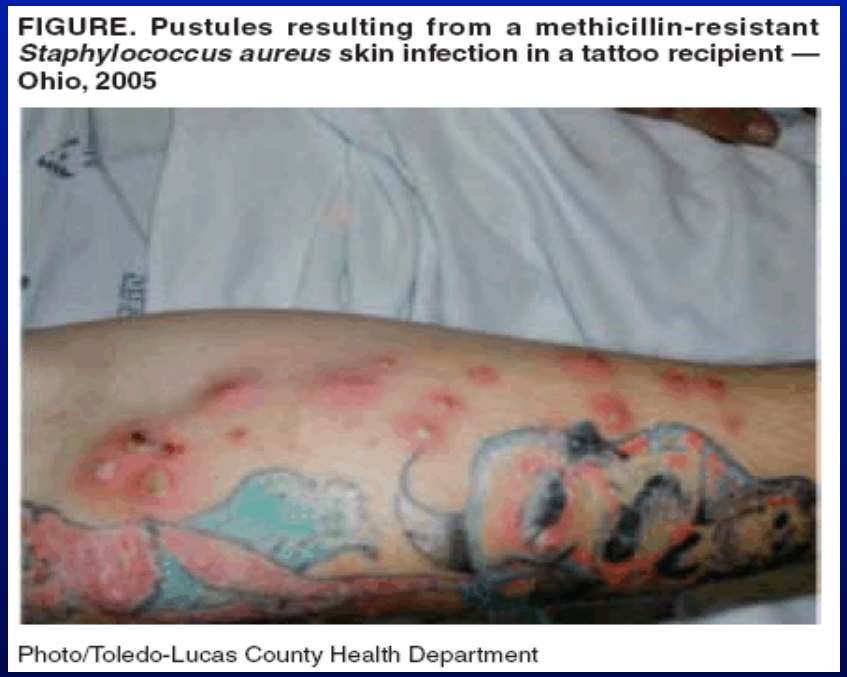


FIGURE. Pustules resulting from a methicillin-resistant *Staphylococcus aureus* skin infection in a tattoo recipient — Ohio, 2005

Photo/Toledo-Lucas County Health Department

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Disclosures

I have received grants, and served as a consultant on Advisory Boards for:

- Cubist Pharmaceuticals Canada, Inc.
- Merck Pharmaceuticals Canada, Inc.
- Pendopharm
- Pfizer Canada, Inc.
- Sunovion Pharmaceuticals Canada, Inc.

Objectives

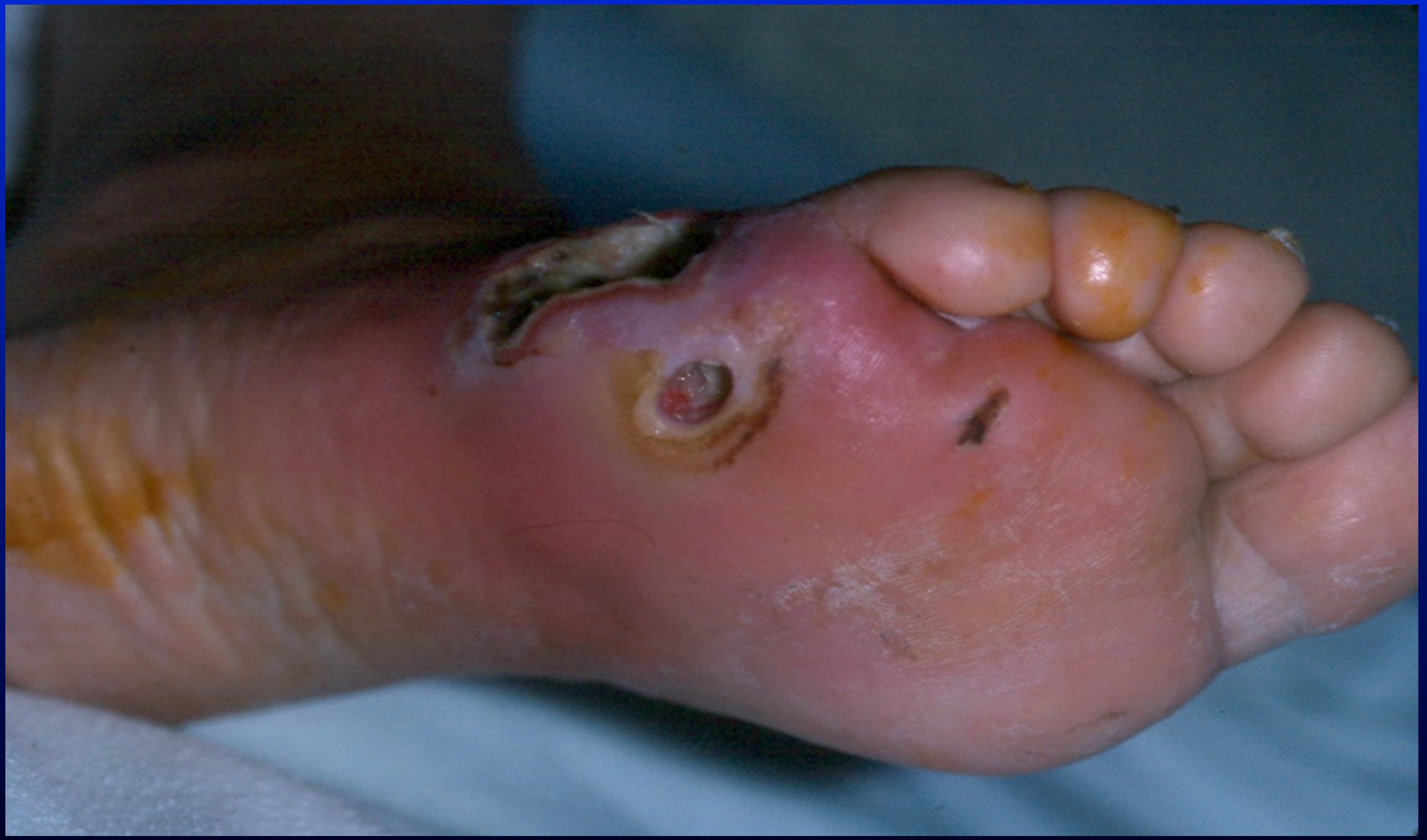
- To review current epidemiology of MRSA pneumonia and MRSA bloodstream infection in Canada;
- Discuss why alternative treatments to vancomycin may be considered

Case History (1a)

- 54 y.o. male diabetic hospitalized with 1 week history of an infected left foot plantar wound
- Past Hx: IDDM, nephropathy (hemodialysis), neuropathy
- 7 days pain, erythema, swelling left foot; 2 days fever, chills

Case History (1b)

- 36.7°C, 130/80, 84/min
- systolic murmur at apex, no stigmata of endocarditis; chest clear
- left plantar ulcers with purulence and surrounding cellulitis



Case History (1c)

- Hgb 107, WBC 10.8
- serum creatinine 415 µmol/L
- foot ulcer culture – MRSA, GBS
  blood culture – MRSA

Case History (1d)

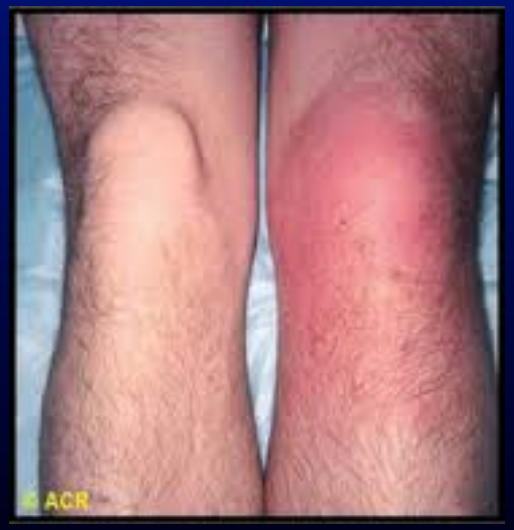
- IV vancomycin started
  (dose adjusted for renal failure)
- plantar ulcer debrided
- dialysis catheter removed, re-sited

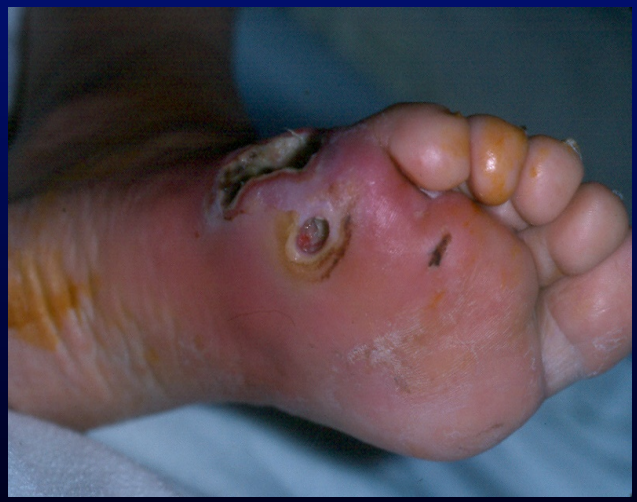
Case History (1e)

- after 7 days, minimal change in appearance of lower limb cellulitis; left knee swollen; repeat blood cultures still growing MRSA; a left knee aspirate also grew MRSA
- vancomycin trough = 22 mg/L
- vancomycin MIC (Etest) = 1.5 µg/ml

What would you do now?

Echocardiogram?
Debridement/better source control?
New dialysis catheter?
Add gentamicin or rifampin?
Change antibiotics?





Case History (2a)

- 75 y.o. male with asthma, hospitalized Feb. 20 with 4 days of fever, dyspnea, increasing cough, hemoptysis
- Hgb 124; WBC 9.1; creatinine 173 µmol/L
- CXR: consolidation RUL,
  subsegmental opacity LUL

Case History (2b)

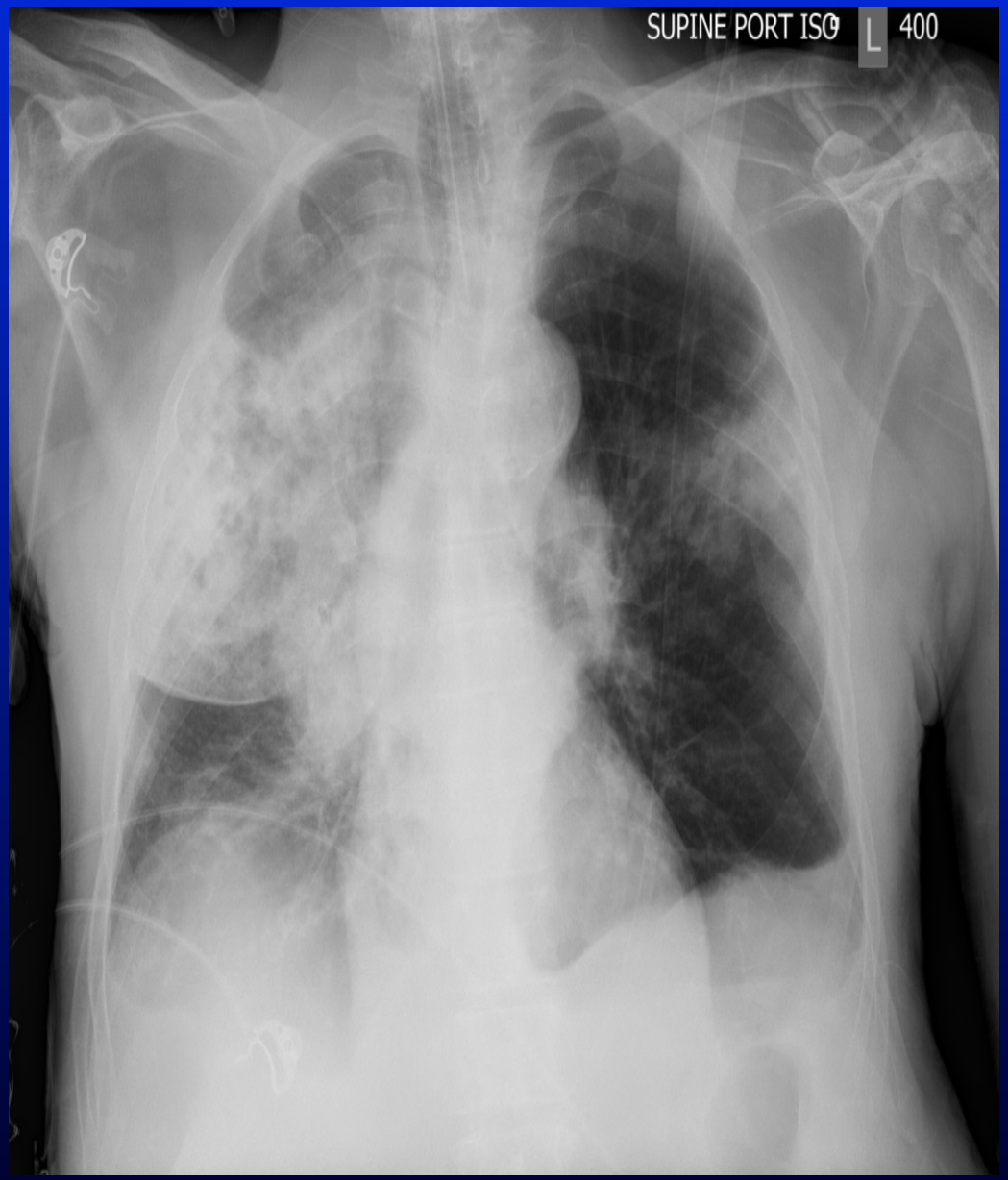
Feb. 20: resp distress; admit to ICU
Rx: ceftriaxone, azithromycin

Feb. 21: MT swab – influenza A (H3N2)
Rx: oseltamivir

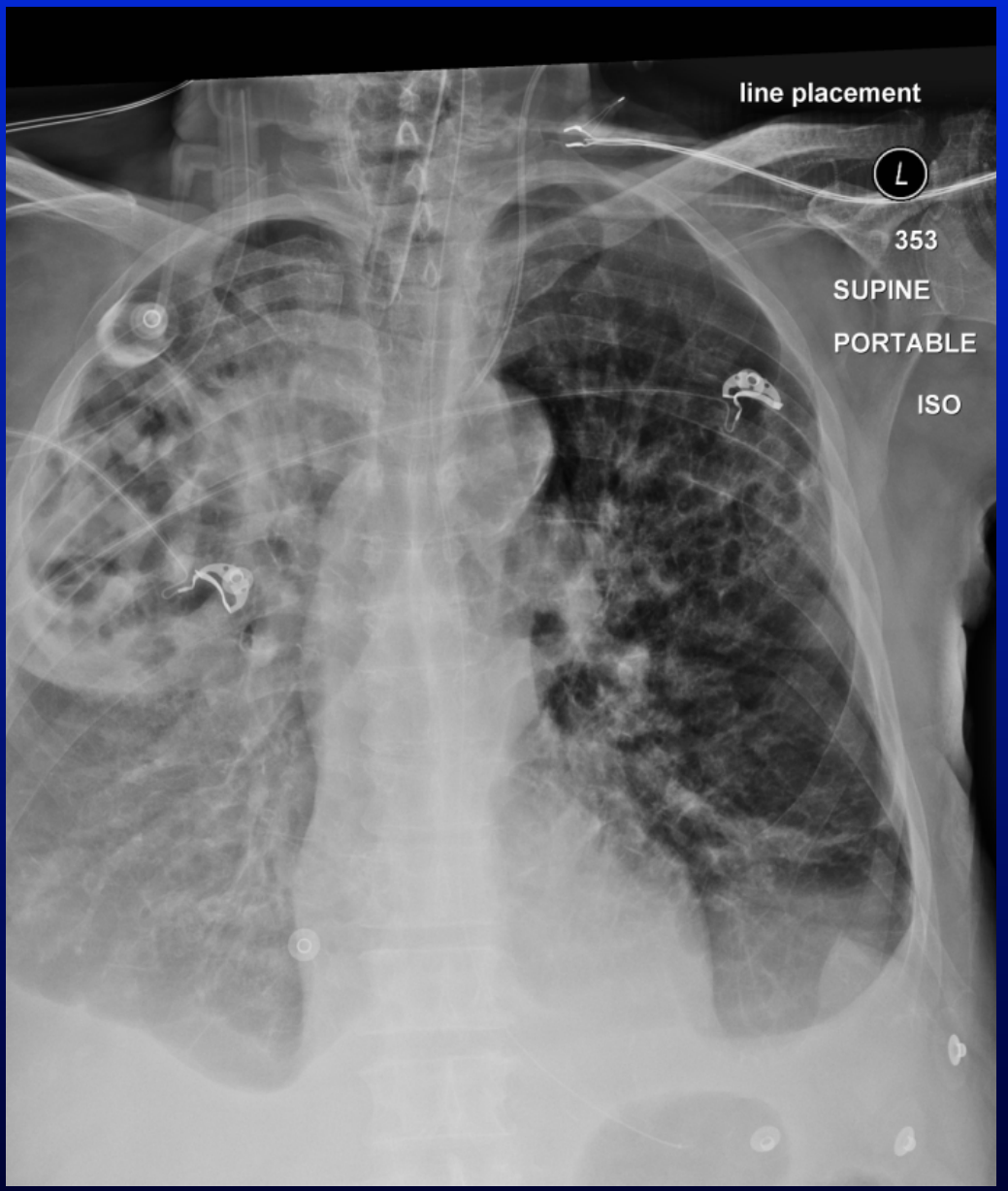
Feb. 22: blood, sputum – MRSA
Rx: vancomcyin, ceftriaxone

Case History (2c)

- Feb. 24: repeat blood cultures neg
  Vanco trough level 19.1 mg/L
- Feb. 25: progressive resp failure
  hypoxemia, ↓ LOC, WBC 20.5
  creatinine 246 µmol/L
  Vanco trough level 22.9 mg/L
  CXR – necrotizing pneumonia

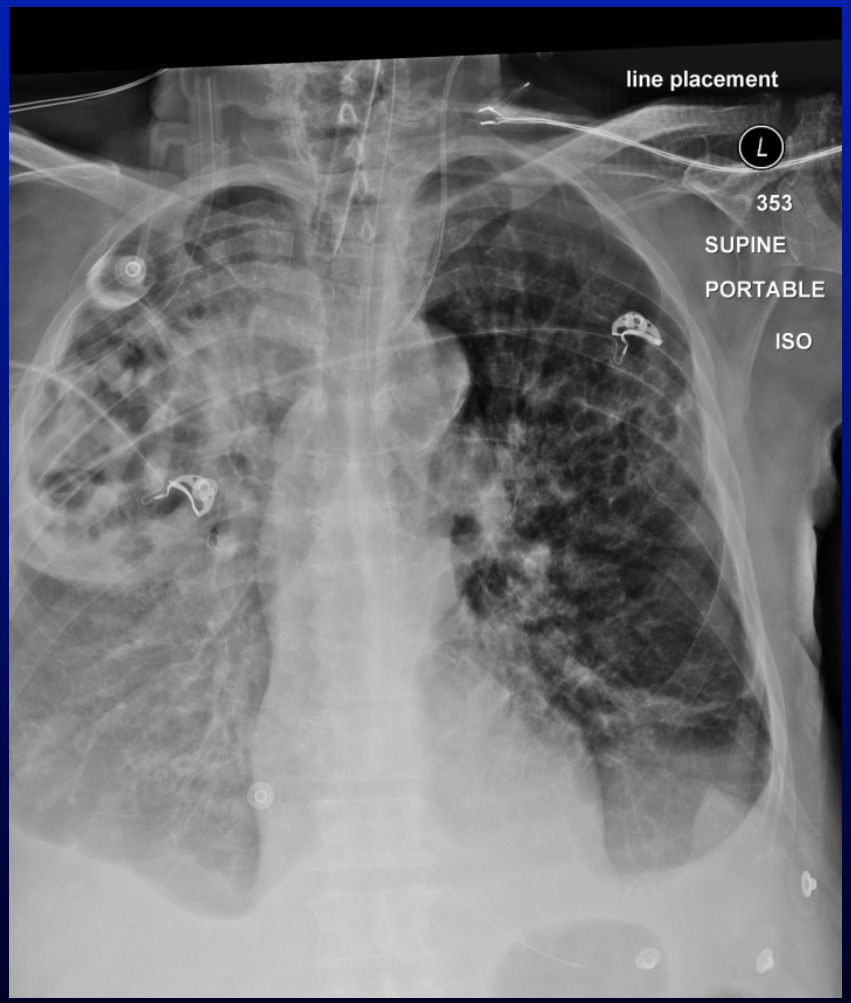


Feb. 20, 2015



Feb. 25, 2015

What would you do now?



- Continue current treatment?
- Add another drug?
- Change Vanco to another drug?

MRSA-Related Mortality

Infection	Mortality (%)
MRSA Bacteremia*	20-35
MRSA Pneumonia†	25-60

* Cosgrove, Clin Infect Dis 2003; Melzer, Clin Infect Dis 2003; Wyllie, BMJ 2006

† DeRyke, Chest 2005; Zahar, Clin Infect Dis 2005; Tadros, PLoS ONE 2013

MRSA Bloodstream Infections

Location	MRSA as a % of *S. aureus* bacteremias
Ontario*	17
Quebec†	15
Canada (CANWARD)§	24

* QMPLS, 2012; †Institut National de Santé Publique du Québec, 2013; § Adam, Diagn Microbiol Infect Dis 2011

MRSA Bacteremia in Canadian Hospitals, 2008-12

- Incidence: 0.45/1,000 admissions
- 30-day all-cause mortality: 23.8%
- variables associated with mortality:
  - Age > 65 yrs (OR 3.3, 95% CI 1.4-7.9)
  - Pneumonia (OR 2.3, 95% CI 1.4-3.7)
  - Failure to receive appropriate therapy within 24 hrs (OR 3.2, 95% CI 2.1-4.9)

Simor, IDSA 2013

MRSA Pneumonia in Canadian Hospitals

- 1-yr surveillance; 11 hospitals
- Incidence: 0.34/1,000 admissions
- 72% HAP (13% VAP); 28% CAP
- 23% had associated bacteremia; 32% required transfer to ICU

Tadros, PLoS ONE 2013

MRSA Pneumonia in Canadian Hospitals

- 30-day all-cause mortality: 28%
- Mortality was not associated with initial treatment, PFGE type, PVL, or initial vancomycin trough levels
- Higher mortality associated with Vancomycin MIC > 1.5 µg/ml
  (OR 2.5; 95% CI, 1.00-6.28; *p*=0.05)

Tadros, PLoS ONE 2013

Treatment of Serious MRSA Infections

Vancomycin has long been considered to be the treatment of choice.

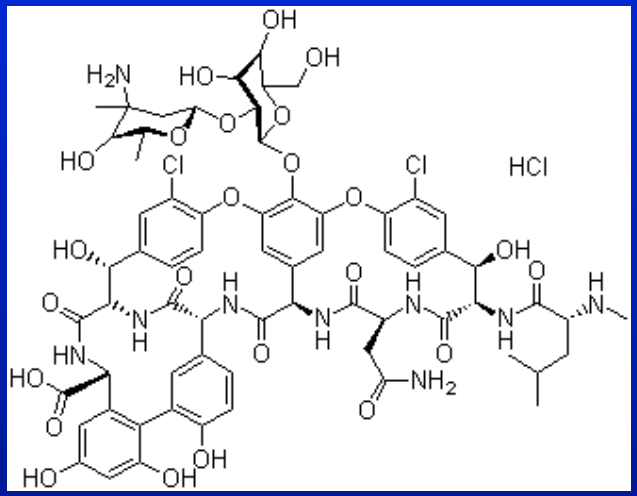
But .....

Treatment of Serious MRSA Infections

- Problems with vancomycin

- Potential advantages of newer antimicrobial agents

Vancomycin

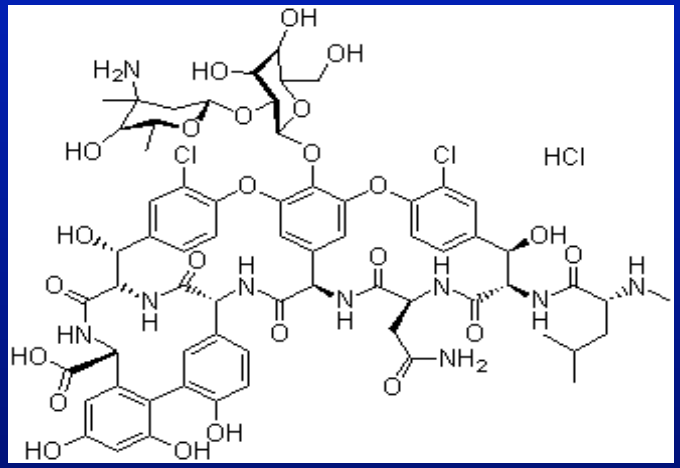


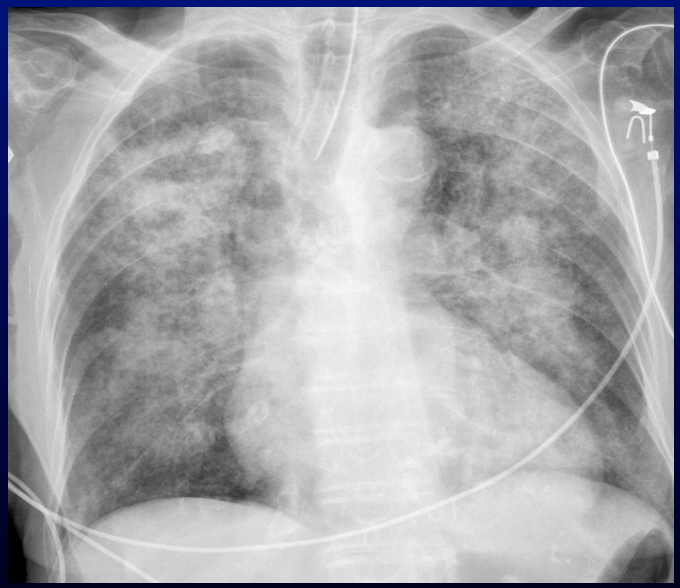
- less rapidly bactericidal
- less effective in clinical trials
  (Lodise, Antimicrob Agents Chemother 2007;
  Kim, Antimicrob Agents Chemother 2008)
- toxicity; need for TDM
- may induce resistance

Vancomycin and the Lung

- poor penetration in the lung; low levels of drug in epithelial lining fluid

  (Cruciani, J Antimicrob Chemother 1996; Lodise, Antimicrob Agents Chemother 2011)



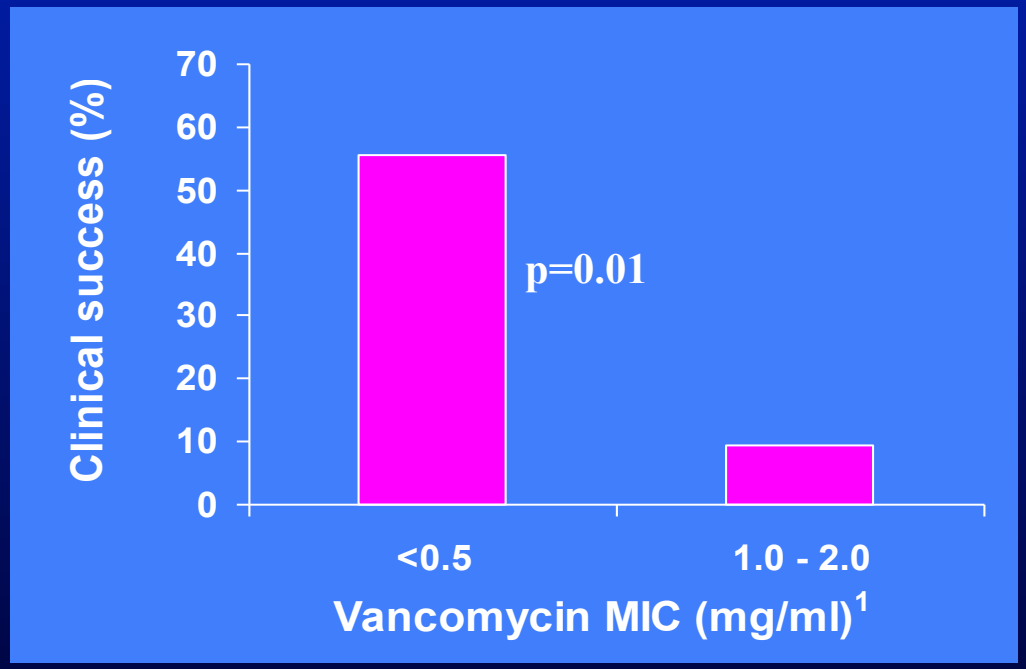


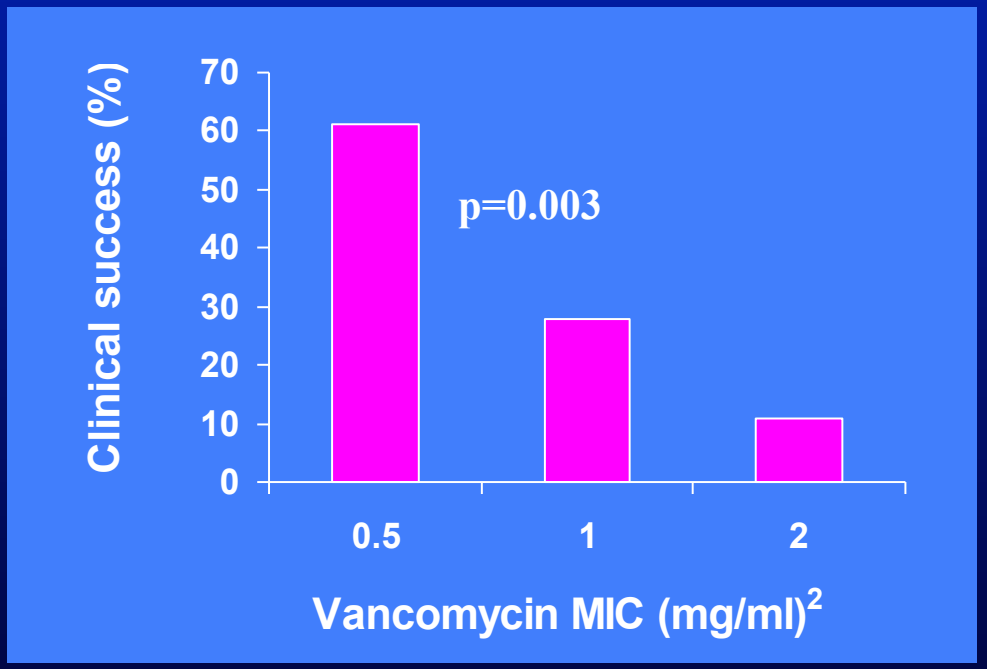
Vancomycin Susceptibility Breakpoints in Staphylococci

MIC (µg/ml)	Interpretation
≤2	Susceptible
4-8	Intermediate
≥16	Resistant

CLSI

Vancomycin MICs and Treatment Outcome in MRSA Bacteremia



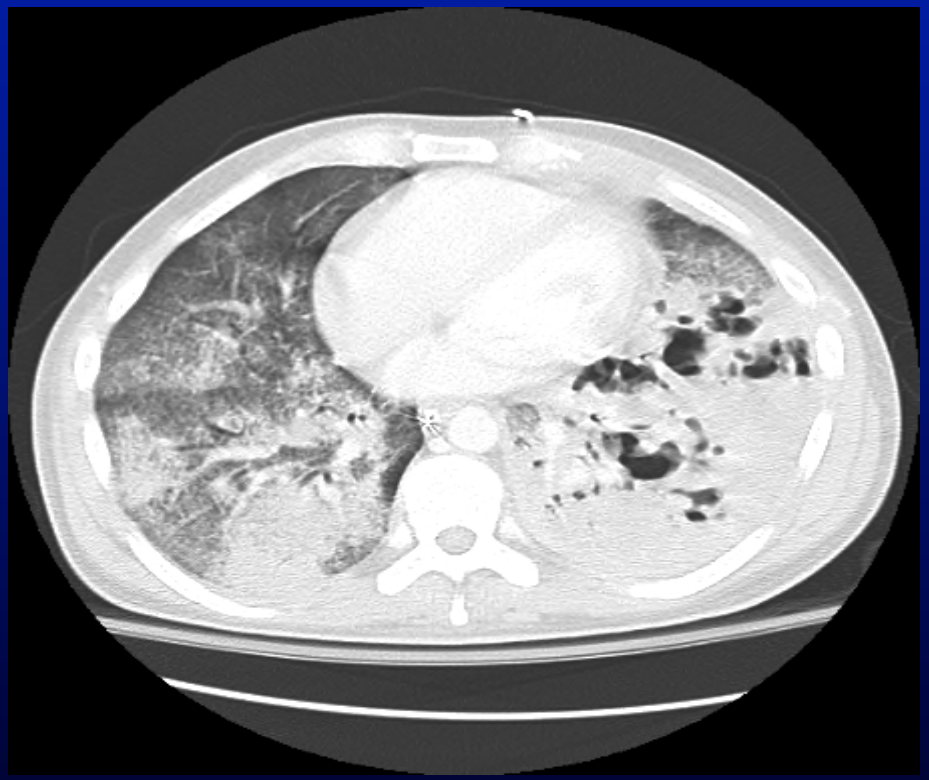


[1] Sakoulas, J Clin Microbiol 2004

[2] Moise-Broder, Clin Infect Dis 2004

MRSA Pneumonia Outcome

Mortality increased with vancomycin MIC > 1.5 µg/ml



Haque, Chest 2010;
Choi, Intensive Care Med 2011;
Tadros, PLoS ONE 2013

Vancomycin MIC and MRSA Infection Outcome

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	13	37	11	28	6.5%	0.84 [0.30, 2.31]
Choi et al (15)	4	34	6	36	4.6%	0.67 [0.17, 2.60]
Haque et al (19)	41	115	10	43	7.9%	1.83 [0.82, 4.08]
Hidayat et al (21)	12	51	4	44	5.3%	3.08 [0.91, 10.37]
Holmes et al (23)	28	94	16	105	8.8%	2.36 [1.18, 4.71]
Lalueza et al (32)	2	13	14	50	3.6%	0.47 [0.09, 2.38]
Liao et al (34)	13	40	46	137	8.3%	0.95 [0.45, 2.02]
Lodise et al (36)	12	66	3	26	4.7%	1.70 [0.44, 6.61]
Musta et al (43)	60	206	7	36	7.4%	1.70 [0.71, 4.10]
Neuner et al (45)	39	186	1	10	2.5%	2.39 [0.29, 19.42]
Schweizer et al (50)	46	341	3	20	5.1%	0.88 [0.25, 3.13]
Soriano et al (52)	37	130	6	38	6.9%	2.12 [0.82, 5.49]
Takesue et al (53)	33	97	62	662	10.4%	4.99 [3.04, 8.18]
van Hal et al (54)	38	117	73	236	10.6%	1.07 [0.67, 1.73]
Wang et al (55)	13	26	27	97	7.3%	2.59 [1.07, 6.30]
Total (95% CI)		**1553**		**1568**	**100.0%**	**1.64 [1.14, 2.37]**
Total events	391		289			

Heterogeneity: Tau² = 0.27; Chi² = 34.07, df = 14 (P = .002); I² = 59%
Test for overall effect: Z = 2.65 (P = .008)

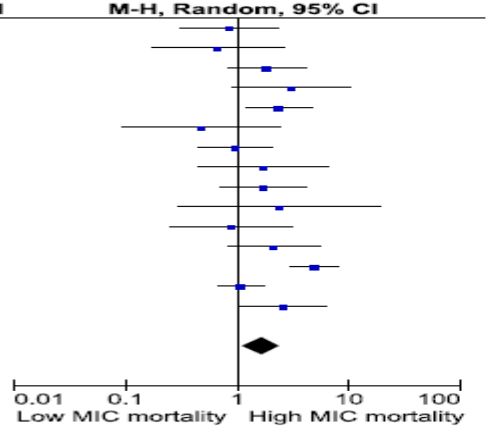


Figure 2. Forest plot (using Mantel-Haenszel analysis) of events denoting methicillin-resistant *S. aureus* mortality (irrespective of source of infection and minimum inhibitory concentration [MIC] methodology used) comparing high vancomycin MIC (≥1.5 µg/mL) with low MIC (<1.5 µg/mL) infections. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

Study or Subgroup	High MIC≥1.5µg/mL Events	Total	Low MIC<1.5µg/mL Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	14	37	12	28	10.9%	0.81 [0.30, 2.21]
Choi et al (15)	12	34	10	36	10.8%	1.42 [0.51, 3.91]
Ferry et al (17)	9	24	9	28	9.7%	1.27 [0.40, 3.98]
Hidayat et al (21)	20	51	7	44	11.0%	3.41 [1.27, 9.12]
Hsu et al (25)	17	45	4	38	9.3%	5.16 [1.56, 17.11]
Lalueza et al (32)	3	13	17	50	7.7%	0.58 [0.14, 2.40]
Lodise et al (36)	6	66	0	26	2.7%	5.69 [0.31, 104.78]
Moise et al (41)	11	14	5	20	6.5%	11.00 [2.16, 56.09]
Moise-Broder et al (42)	23	25	22	38	6.8%	8.36 [1.72, 40.68]
Takesue et al (53)	34	97	85	662	15.9%	3.66 [2.28, 5.89]
Yoon et al (58)	14	18	17	45	8.8%	5.76 [1.63, 20.41]
Total (95% CI)		**424**		**1015**	**100.0%**	**2.69 [1.60, 4.51]**
Total events	163		188			

Heterogeneity: Tau² = 0.38; Chi² = 22.59, df = 10 (P = 0.01); I² = 56%
Test for overall effect: Z = 3.75 (P = 0.0002)

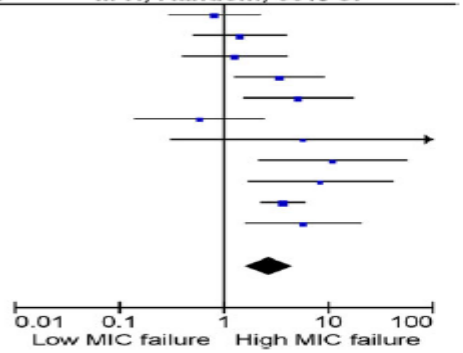


Figure 5. Forest plot (using Mantel-Haenszel analysis) of events denoting *S. aureus* vancomycin treatment failure (irrespective of definition, source of infection and minimum inhibitory concentration [MIC] methodology used) comparing high vancomycin MIC (≥1.5 µg/mL) with low MIC (<1.5 µg/mL) infections. Squares indicate point estimates, and the size of the square indicates the weight of each study. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; MIC, minimum inhibitory concentration.

van Hal, Clin Infect Dis 2012

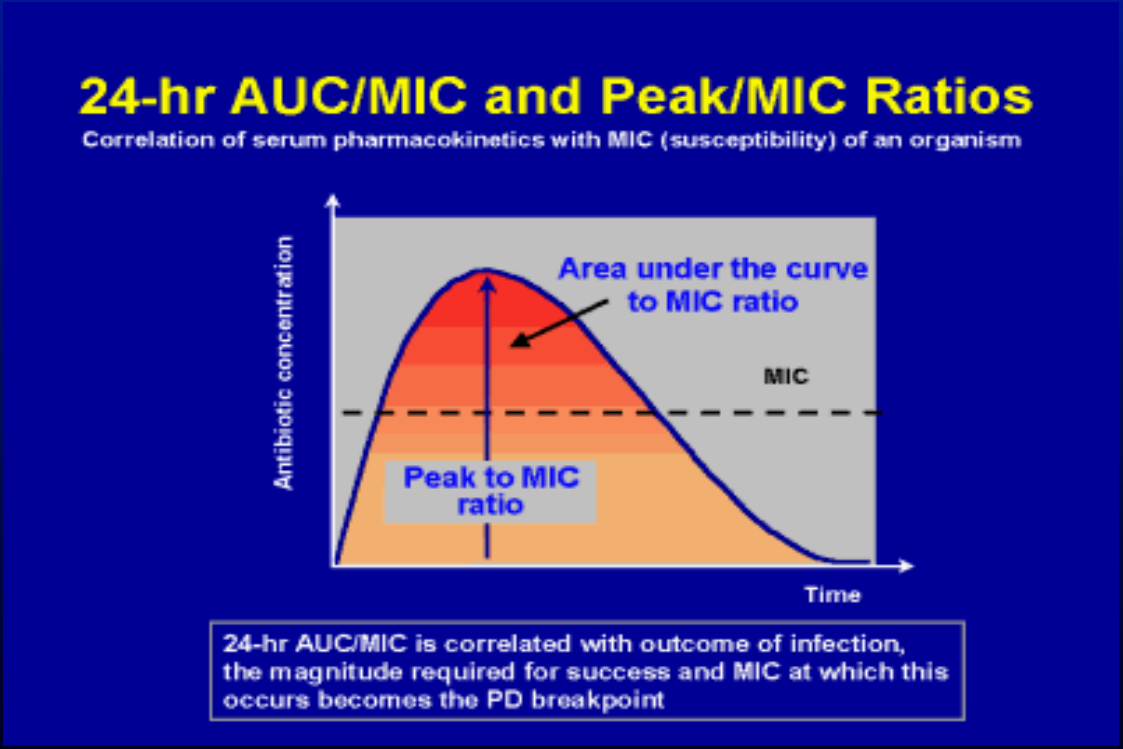
How Common are Higher Vancomycin MICs in MRSA in Canada?

- no VRSA and very few VISA in Canada as of April 2015
- < 4% of MRSA have vancomycin MIC = 2 µg/ml

Simor, Antimicrob Agents Chemother 2010;
Zhanel, Diagn Microbiol Infect Dis 2011

Vancomycin Pharmacodynamics

- vancomycin efficacy best predicted by AUC:MIC ratio

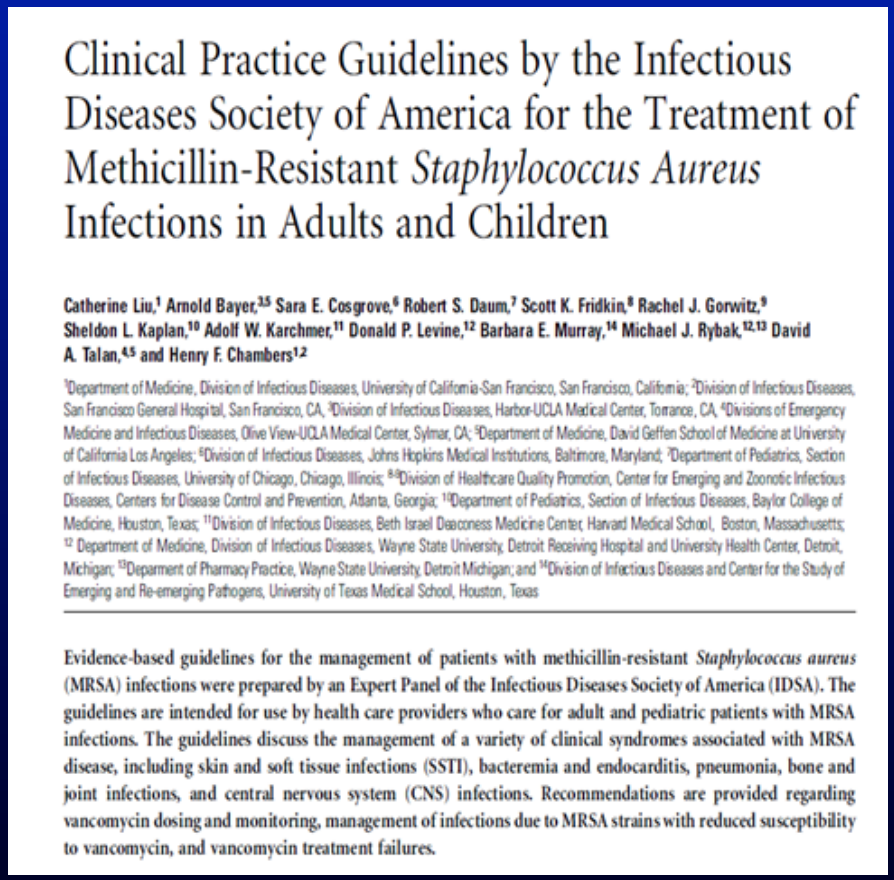


Vancomycin Pharmacodynamics

- 1 study in patients with *S. aureus* pneumonia suggested AUC/MIC ≥ 400 associated with better outcome
  (Moise-Broder, Clin Pharmacokinet 2004)
- AUC/MIC ≥ 400 requires Vanco trough 15-20 µg/ml, but is not achievable if Vanco MIC ≥ 2 µg/ml (Mohr, Clin Infect Dis 2007)

Vancomycin and Treatment Failure

- higher vancomycin MICs associated with worse outcome
- recommendations to use higher Vanco doses (target trough: 15-20 µg/ml)



Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

[1]Department of Medicine, Division of Infectious Diseases, University of California-San Francisco, San Francisco, California; [2]Division of Infectious Diseases, San Francisco General Hospital, San Francisco, CA; [3]Division of Infectious Diseases, Harbor-UCLA Medical Center, Torrance, CA; [4]Divisions of Emergency Medicine and Infectious Diseases, Olive View-UCLA Medical Center, Sylmar, CA; [5]Department of Medicine, David Geffen School of Medicine at University of California Los Angeles; [6]Division of Infectious Diseases, Johns Hopkins Medical Institutions, Baltimore, Maryland; [7]Department of Pediatrics, Section of Infectious Diseases, University of Chicago, Chicago, Illinois; [8,9]Division of Healthcare Quality Promotion, Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [10]Department of Pediatrics, Section of Infectious Diseases, Baylor College of Medicine, Houston, Texas; [11]Division of Infectious Diseases, Beth Israel Deaconess Medicine Center, Harvard Medical School, Boston, Massachusetts; [12] Department of Medicine, Division of Infectious Diseases, Wayne State University, Detroit Receiving Hospital and University Health Center, Detroit, Michigan; [13]Deparment of Pharmacy Practice, Wayne State University, Detroit Michigan; and [14]Division of Infectious Diseases and Center for the Study of Emerging and Re-emerging Pathogens, University of Texas Medical School, Houston, Texas

Evidence-based guidelines for the management of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections were prepared by an Expert Panel of the Infectious Diseases Society of America (IDSA). The guidelines are intended for use by health care providers who care for adult and pediatric patients with MRSA infections. The guidelines discuss the management of a variety of clinical syndromes associated with MRSA disease, including skin and soft tissue infections (SSTI), bacteremia and endocarditis, pneumonia, bone and joint infections, and central nervous system (CNS) infections. Recommendations are provided regarding vancomycin dosing and monitoring, management of infections due to MRSA strains with reduced susceptibility to vancomycin, and vancomycin treatment failures.

Liu, Clin Infect Dis 2011

Vancomycin Levels and Toxicity

Higher vanco troughs are not always associated with better outcome; vanco-induced nephrotoxicity associated with higher trough levels

Study or Subgroup	Receipt of NTs Events	Total	no NTs Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	26	55	90	233	14.0%	1.42 [0.79, 2.57]
Cano et al. (22)	16	29	7	159	12.4%	26.73 [9.32, 76.63]
Hidayat et al. (13)	10	11	17	84	8.4%	39.41 [4.71, 329.47]
Kralovicova et al. (31)	31	134	19	64	13.7%	0.71 [0.36, 1.39]
Lodise et al. (36)	6	21	55	145	12.6%	0.65 [0.24, 1.79]
McKamy et al. (38)	18	24	24	143	12.6%	14.88 [5.35, 41.36]
Minejima et al. (39)	37	169	6	58	12.9%	2.43 [0.97, 6.10]
Prabaker et al. (43)	21	31	174	317	13.4%	1.73 [0.79, 3.78]
Total (95% CI)		**474**		**1203**	**100.0%**	**3.30 [1.30, 8.39]**
Total events	165		392			

Heterogeneity: $Tau^2 = 1.54$; $Chi^2 = 60.99$, $df = 7$ ($P < 0.00001$); $I^2 = 89\%$

Test for overall effect: $Z = 2.50$ ($P = 0.01$)

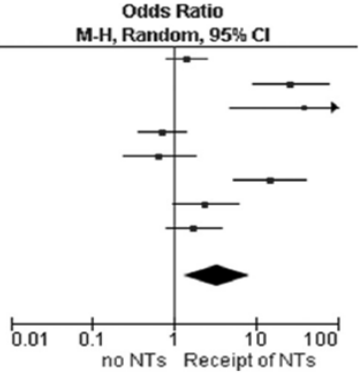


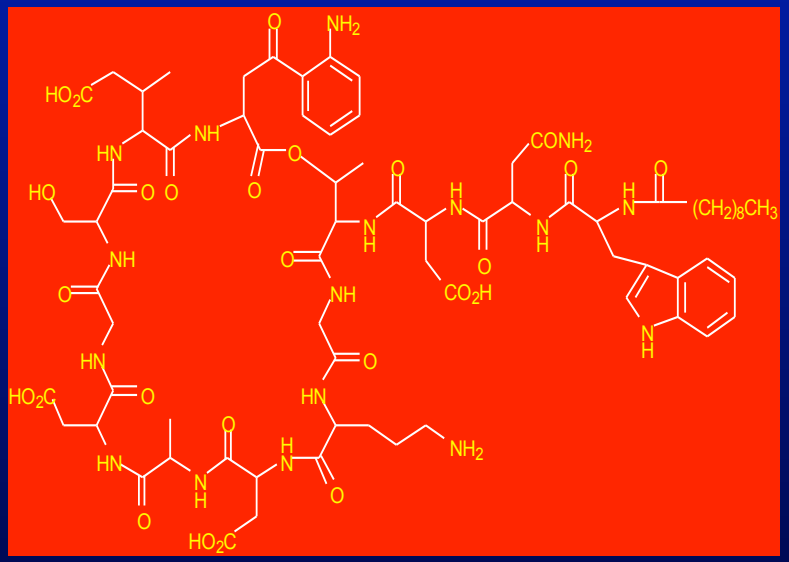
FIG 5 Forest plot (using Mantel-Haenszel [M-H] analysis) of events denoting nephrotoxicity associated with vancomycin, comparing rates for patients receiving and not receiving concomitant nephrotoxins at the time of diagnosis. Squares indicate point estimates, and the size of the square indicates the weight of each study. NT, nephrotoxins.

(van Hal, Antimicrob Agents Chemother 2013)

Alternatives to Vancomcyin

- Daptomycin
- Linezolid
- Ceftaroline
- Lipoglycopeptides (telavancin, dalbavancin, oritavancin)
- New oxazolidinone (tedizolid)

Daptomycin



Indications:

- SSTI (Gram-positive)
- BSI/right-sided endocarditis (*S. aureus*)

Off-label use:

- Endocarditis
- Osteomyelitis, PJI
- VRE infections
- CNST infections

Treatment of MRSA Bacteremia and Infective Endocarditis

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Liu, Clin Infect Dis 2011

Daptomycin vs Standard Therapy for *S.aureus* Bacteremia

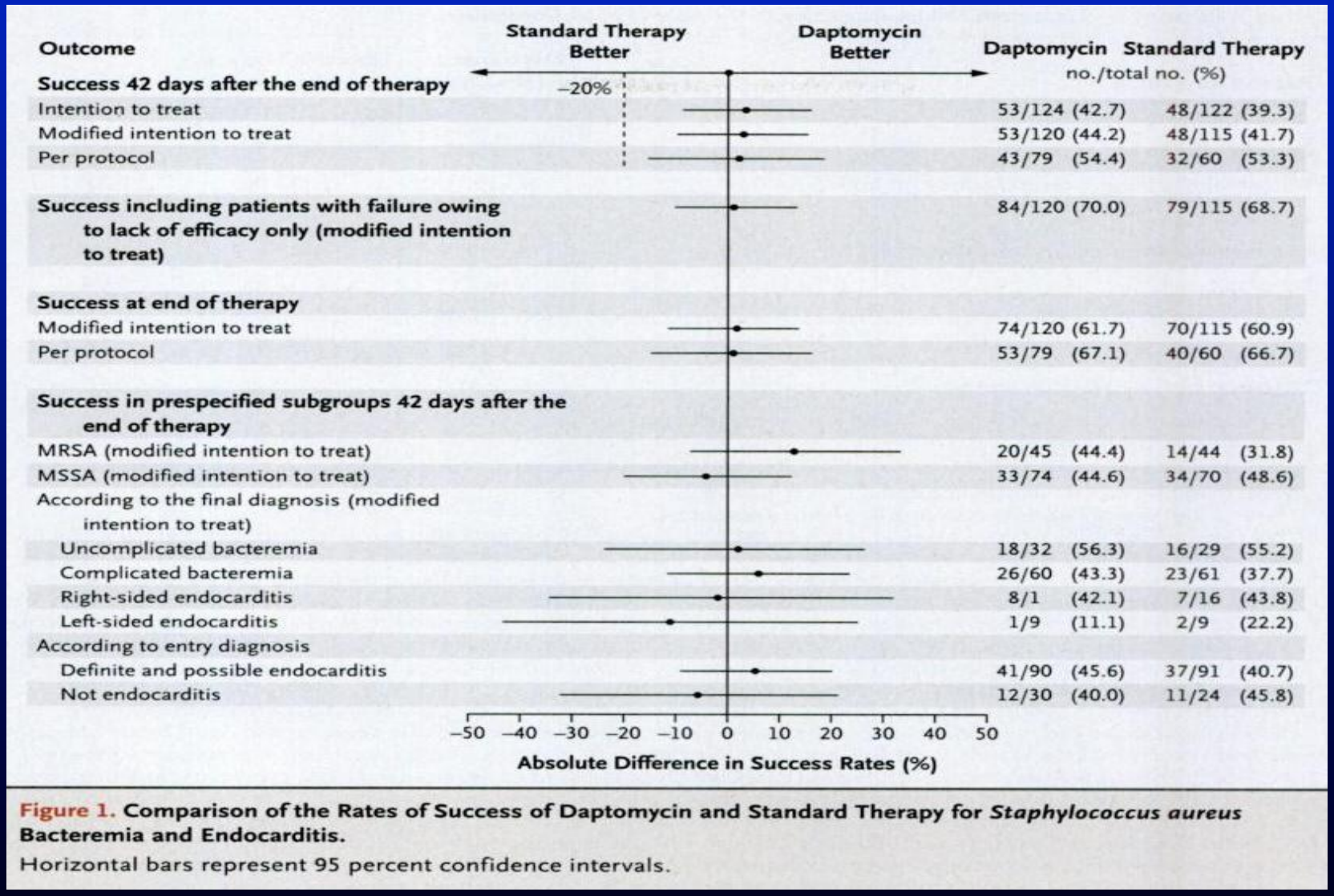
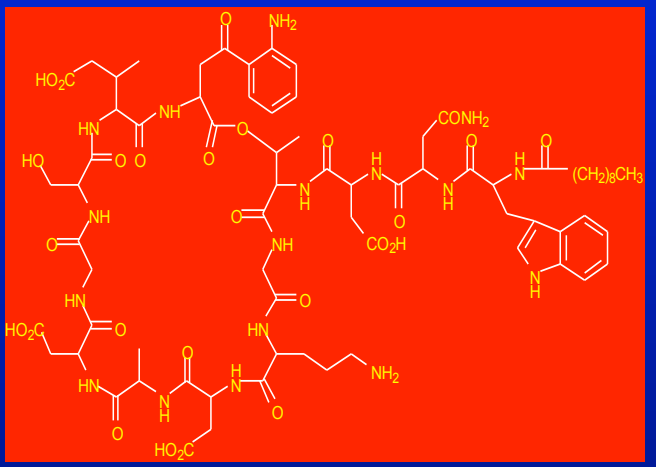


Figure 1. Comparison of the Rates of Success of Daptomycin and Standard Therapy for *Staphylococcus aureus* Bacteremia and Endocarditis.

Horizontal bars represent 95 percent confidence intervals.

Fowler, N Engl J Med 2006

Daptomycin



- Daptomycin treatment failures associated with reduced susceptibility (Fowler, N Engl J Med 2006)
- Daptomycin has concentration-dependent killing (Benvenuto, Antimicrob Agents Chemother 2005)
- Perhaps efficacy improved using higher doses (6-10 mg/kg/day)

Safety of High-Dose Intravenous Daptomycin Treatment: Three-Year Cumulative Experience in a Clinical Program

D. A. Figueroa,[1] E. Mangini,[2] M. Amodio-Groton,[3] B. Vardianos,[1] A. Melchert,[1] C. Fana,[2] W. Wehbeh,[2] C. M. Urban,[2] and S. Segal-Maurer[2]

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(See the editorial commentary by Cosgrove and Corey on pages 181–3)

Background. There are limited safety data for high-dose and long-term daptomycin treatment (>6mg/kg administered for ≥14 days). We present our experience in 61 patients.

Methods. We performed a retrospective chart review for all patients treated with daptomycin at New York Hospital Queens (Flushing) from 1 January 2004 through 30 April 2007; patients were identified through a computerized hospital pharmacy database.

Results. Sixty-one patients (29 male and 32 female patients; mean age, 66.6 years) received a mean dose of 8 mg/kg of daptomycin for a median of 25 days (range, 14–82 days). Twelve patients (with bone and skin and soft-tissue infections) did not have an identified microbiologic isolate. Gram-positive infections included bloodstream infection with or without infective endocarditis ($n = 32$), skin and soft-tissue infection ($n = 14$), bone and joint infection ($n = 9$), and intra-abdominal infection ($n = 5$), and unidentified infection ($n = 1$). Prosthetic devices were removed from 11 of 20 patients. Grade 1 adverse events occurred in 22 patients and did not lead to daptomycin discontinuation. Fifty-eight patients underwent creatine phosphokinase (CPK) analysis (34 patients had paired CPK analyses at the beginning of and during therapy, and 13 patients had random CPK analysis performed during treatment). Three patients had constitutional and/or musculoskeletal symptoms accompanying CPK levels >10 times upper limit of normal (grade 3). All occurred after 24 days of treatment and improved after daptomycin treatment was discontinued. Two of 3 patients were morbidly obese (body mass index grade III).

Conclusions. Daptomycin treatment was well tolerated at a mean dose of 8 mg/kg for a median duration of 25 days. The incidence of symptomatic CPK level elevation was within the range reported with lower doses of daptomycin and/or for shorter treatment durations.

Safety of high dose daptomycin

Figueroa, Clin Infect Dis 2009

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Journals.ASM.org

High-Dose Daptomycin Therapy for Left-Sided Infective Endocarditis: a Prospective Study from the International Collaboration on Endocarditis

Manuela Carugati,[a,d] Arnold S. Bayer,[b] Josè M. Miró,[c] Lawrence P. Park,[d] Armenio C. Guimarães,[e] Athanasios Skoutelis,[f] Claudio Q. Fortes,[g] Emanuele Durante-Mangoni,[h] Margaret M. Hannan,[i] Francisco Nacinovich,[j] Nuria Fernández-Hidalgo,[k] Paolo Grossi,[l] Ru-San Tan,[m] Thomas Holland,[d] Vance G. Fowler, Jr.,[d] Ralph G. Corey,[d] Vivian H. Chu,[d] on behalf of the International Collaboration on Endocarditis

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The use of daptomycin in Gram-positive left-sided infective endocarditis (IE) has significantly increased. The purpose of this study was to assess the influence of high-dose daptomycin on the outcome of left-sided IE due to Gram-positive pathogens. This was a prospective cohort study based on 1,112 cases from the International Collaboration on Endocarditis (ICE)–Plus database and the ICE-Daptomycin Substudy database from 2008 to 2010. Among patients with left-sided IE due to *Staphylococcus aureus*, coagulase-negative staphylococci, and *Enterococcus faecalis*, we compared those treated with daptomycin (cohort A) to those treated with standard-of-care (SOC) antibiotics (cohort B). The primary outcome was in-hospital mortality. Time to clearance of bacteremia, 6-month mortality, and adverse events (AEs) ascribable to daptomycin were also assessed. There were 29 and 149 patients included in cohort A and cohort B, respectively. Baseline comorbidities did not differ between the two cohorts, except for a significantly higher prevalence of diabetes and previous episodes of IE among patients treated with daptomycin. The median daptomycin dose was 9.2 mg/kg of body weight/day. Two-thirds of the patients treated with daptomycin had failed a previous antibiotic regimen. In-hospital and 6-month mortalities were similar in the two cohorts. In cohort A, median time to clearance of methicillin-resistant *S. aureus* (MRSA) bacteremia was 1.0 day, irrespective of daptomycin dose, representing a significantly faster bacteremia clearance compared to SOC (1.0 versus 5.0 days; $P < 0.01$). Regimens with higher daptomycin doses were not associated with increased incidence of AEs. In conclusion, higher-dose daptomycin may be an effective and safe alternative to SOC in the treatment of left-sided IE due to common Gram-positive pathogens.

Safety and efficacy of high dose daptomycin for treatment of endocarditis

Carugati, Antimicrob Agents Chemother 2013

Daptomycin for MRSA BSI with High Vancomycin MIC

Early Use of Daptomycin Versus Vancomycin for Methicillin-Resistant *Staphylococcus aureus* Bacteremia With Vancomycin Minimum Inhibitory Concentration >1 mg/L: A Matched Cohort Study

Kyle P. Murray,[1] Jing J. Zhao,[1] Susan L. Davis,[3] Ravina Kullar,[3] Keith S. Kaye,[2] Paul Lephart,[4] and Michael J. Rybak[1,2,3]

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(See the Editorial Commentary by Weston and Boucher on pages 1570–2.)

Background. Recent reports have described decreased effectiveness with vancomycin treatment for methicillin-resistant *Staphylococcus aureus* bacteremia (MRSAB) when the vancomycin minimum inhibitory concentration (MIC) is >1 μg/mL.

Methods. This matched, retrospective cohort study compared the clinical effectiveness of daptomycin with that of vancomycin for the treatment of MRSAB with vancomycin MICs >1 μg/mL. The primary outcome was clinical failure, defined as a composite of 30-day mortality or bacteremia persisting for ≥7 days.

Results. One hundred seventy patients were matched 1:1 with respect to the antimicrobial administered. In the daptomycin group, all patients received <72 hours of vancomycin (median, 1.7 days [interquartile range, 1.1–2.3 days]) prior to switching to daptomycin. The rate of clinical failure at 30 days was significantly lower in the daptomycin arm compared to the vancomycin arm (20.0% vs 48.2%; $P < 0.001$). Both 30-day mortality and persistent bacteremia were significantly lower in the daptomycin group compared to the vancomycin group (3.5% vs 12.9% [$P = .047$] and 18.8% vs 42.4% [$P = .001$], respectively). Logistic regression confirmed the association between vancomycin treatment and increased risk of clinical failure (adjusted odds ratio, 4.5; 95% confidence interval, 2.1–9.8).

Conclusions. This is the first matched study comparing early daptomycin versus vancomycin for the treatment of MRSAB when the vancomycin MIC is >1 μg/mL. Treatment with daptomycin resulted in significantly improved outcomes, including decreased 30-day mortality and persistent bacteremia. These results support the practice of switching early from vancomycin to daptomycin for the treatment of MRSAB when the vancomycin MIC is >1 μg/mL.

Keywords. vancomycin; daptomycin; methicillin-resistant *Staphylococcus aureus*; bacteremia.

Table 3. Variables Associated With Clinical Failure at 30 Days in Multivariate Analysis

	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Vancomycin treatment group	3.7 (1.9–7.4)	<.001	4.5 (2.1–9.8)	<.001
ICU admission	4.4 (2.2–8.9)	<.001	5.8 (2.7–12.8)	<.001
Intravenous drug use	2.8 (1.4–5.4)	.002	3.0 (1.4–6.3)	.004

Table 2. Patient Outcomes

	DAP (n = 85)	VAN (n = 85)	*P* Value
Clinical failure[a]	17 (20.0%)	41 (48.2%)	<.001
Mortality at 30 d	3 (3.5%)	11 (12.9%)	.047
Persistent bacteremia	16 (18.8%)	36 (42.4%)	.001

Murray, Clin Infect Dis 2013

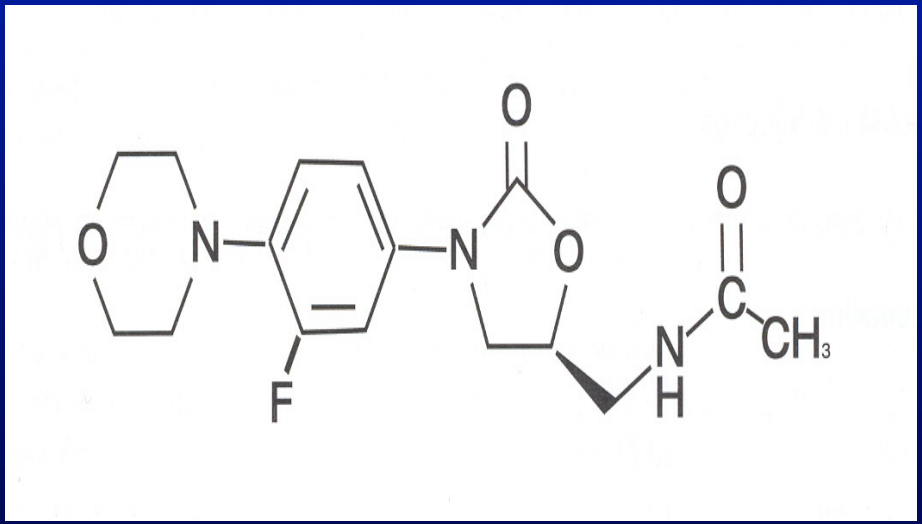
Potential Benefits of Treatment with Daptomycin (1)

- Efficacy equivalent to that of Vanco for treatment of SSTI and Staph BSI
  (Arbeit, Clin Infect Dis 2004; Fowler, N Engl J Med 2006)
- Efficacy for treatment of MRSA BSI (incl. endocarditis) as salvage therapy or if higher vanco MIC
  (Moise, Lancet Infect Dis 2009; Moore, Clin Infect Dis 2012; Murray, Clin Infect Dis 2013; Carugati, Antimicrob Agents Chemother 2013)

Potential Benefits of Treatment with Daptomycin (2)

- Safety, even at higher doses (10 mg/kg/day) (Figueroa, Clin Infect Dis 2009)
- Once-daily; no need for therapeutic drug monitoring; safe in patients with renal failure (Mueller, Pharmacotherapy 2011)
- Resistance is rare

Linezolid



Indications:

- SSTI (Gram-positive)
- CAP/HAP (incl. MRSA)
- VRE infections

Off-label use:

- Osteomyelitis, PJI
- Febrile neutropenia

IDSA Clinical Practice Guidelines for Treatment of MRSA Pneumonia

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus Aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

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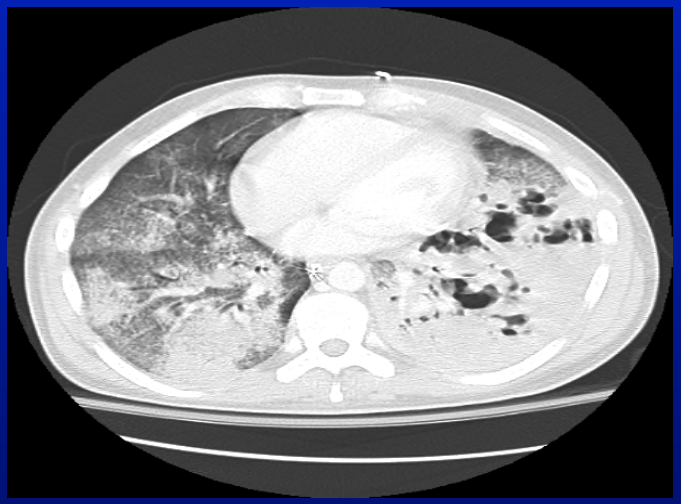
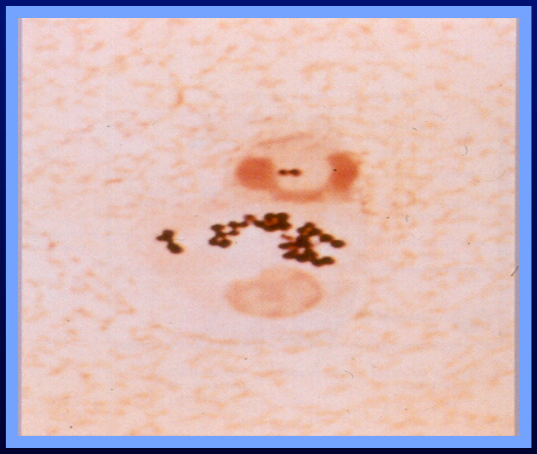
Evidence-based guidelines for the management of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections were prepared by an Expert Panel of the Infectious Diseases Society of America (IDSA). The guidelines are intended for use by health care providers who care for adult and pediatric patients with MRSA infections. The guidelines discuss the management of a variety of clinical syndromes associated with MRSA disease, including skin and soft tissue infections (SSTI), bacteremia and endocarditis, pneumonia, bone and joint infections, and central nervous system (CNS) infections. Recommendations are provided regarding vancomycin dosing and monitoring, management of infections due to MRSA strains with reduced susceptibility to vancomycin, and vancomycin treatment failures.





Liu, Clin Infect Dis 2011

Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

Richard G. Wunderink,[1] Michael S. Niederman,[2] Marin H. Kollef,[3] Andrew F. Shorr,[4] Mark J. Kunkel,[5] Alice Baruch,[5,a] William T. McGee,[6] Arlene Reisman,[5] and Jean Chastre[7]

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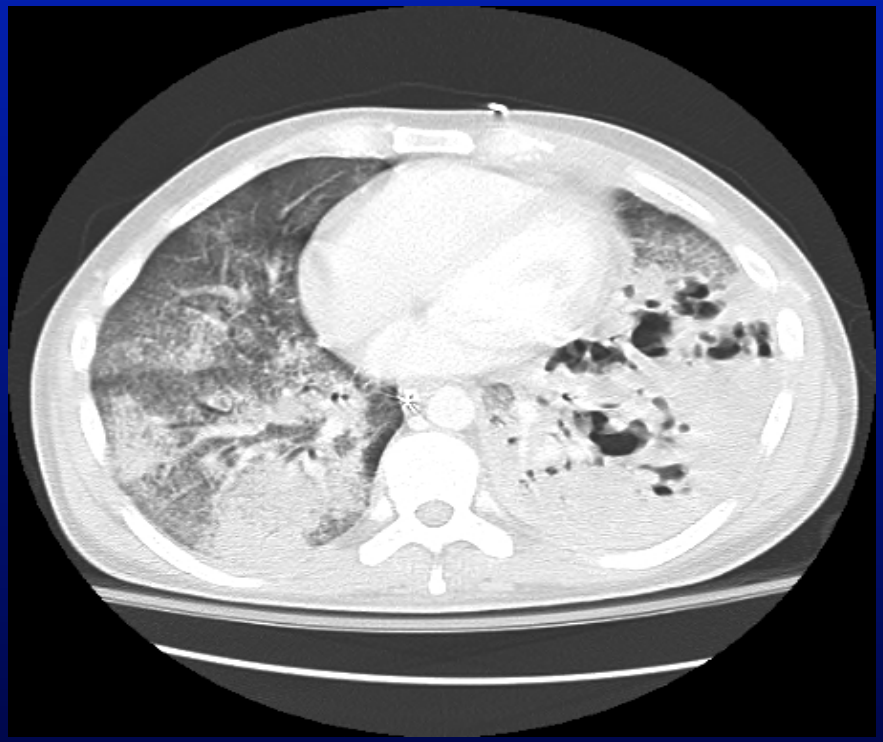
Background. Post hoc analyses of clinical trial data suggested that linezolid may be more effective than vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial pneumonia. This study prospectively assessed efficacy and safety of linezolid, compared with a dose-optimized vancomycin regimen, for treatment of MRSA nosocomial pneumonia.

Methods. This was a prospective, double-blind, controlled, multicenter trial involving hospitalized adult patients with hospital-acquired or healthcare–associated MRSA pneumonia. Patients were randomized to receive intravenous linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours) for 7–14 days. Vancomycin dose was adjusted on the basis of trough levels. The primary end point was clinical outcome at end of study (EOS) in evaluable per-protocol (PP) patients. Prespecified secondary end points included response in the modified intent-to-treat (mITT) population at end of treatment (EOT) and EOS and microbiologic response in the PP and mITT populations at EOT and EOS. Survival and safety were also evaluated.

Results. Of 1184 patients treated, 448 (linezolid, n = 224; vancomycin, n = 224) were included in the mITT and 348 (linezolid, n = 172; vancomycin, *n* = 176) in the PP population. In the PP population, 95 (57.6%) of 165 linezolid-treated patients and 81 (46.6%) of 174 vancomycin-treated patients achieved clinical success at EOS (95% confidence interval for difference, 0.5%–21.6%; $P = .042$). All-cause 60-day mortality was similar (linezolid, 15.7%; vancomycin, 17.0%), as was incidence of adverse events. Nephrotoxicity occurred more frequently with vancomycin (18.2%; linezolid, 8.4%).

Conclusions. For the treatment of MRSA nosocomial pneumonia, clinical response at EOS in the PP population was significantly higher with linezolid than with vancomycin, although 60-day mortality was similar.

‘ZEPHyR’ Study



Wunderink, Clin Infect Dis 2012

Linezolid vs Vancomycin for HA-MRSA Pneumonia

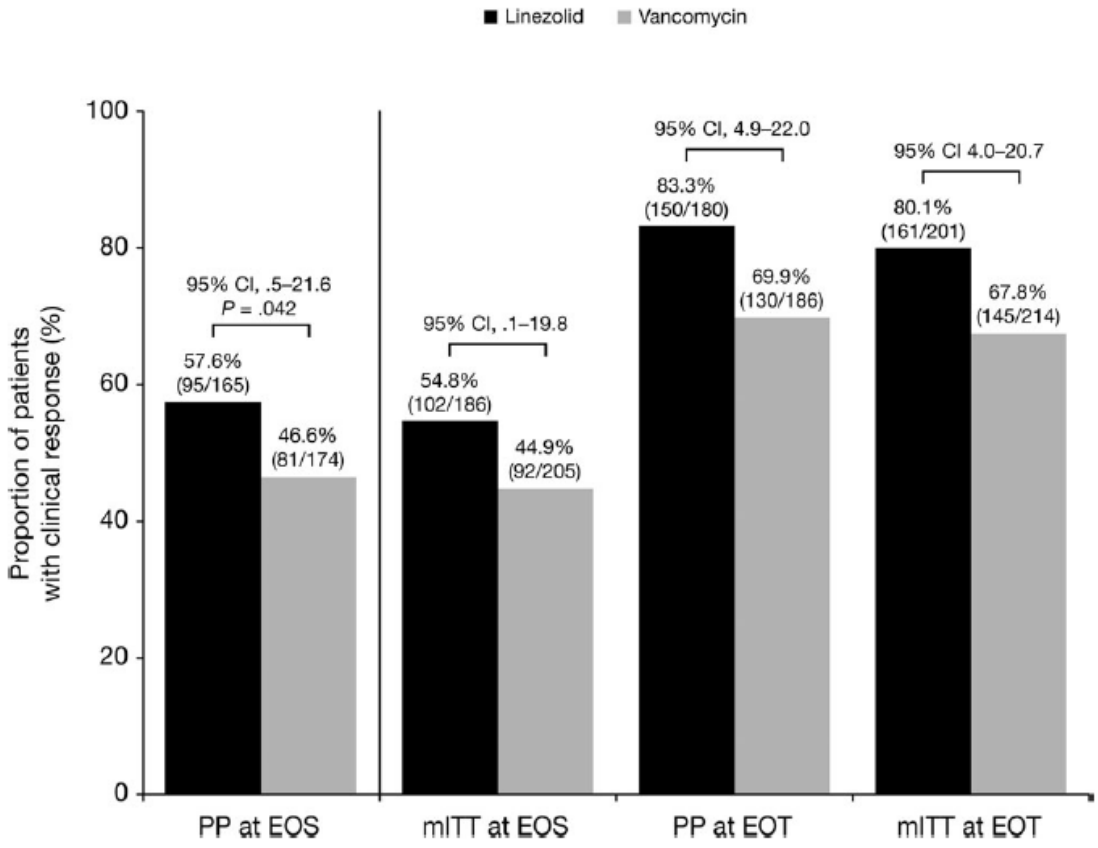


Figure 2. Clinical response rates in per-protocol (PP) and modified intent-to-treat (mITT) patients at end-of-study (EOS) and end of therapy (EOT). *P* values and 95% confidence intervals (CI) are included for the differences between treatment groups in the primary end point.

Wunderink, Clin Infect Dis 2012

Linezolid vs Vancomycin for HA-MRSA Pneumonia

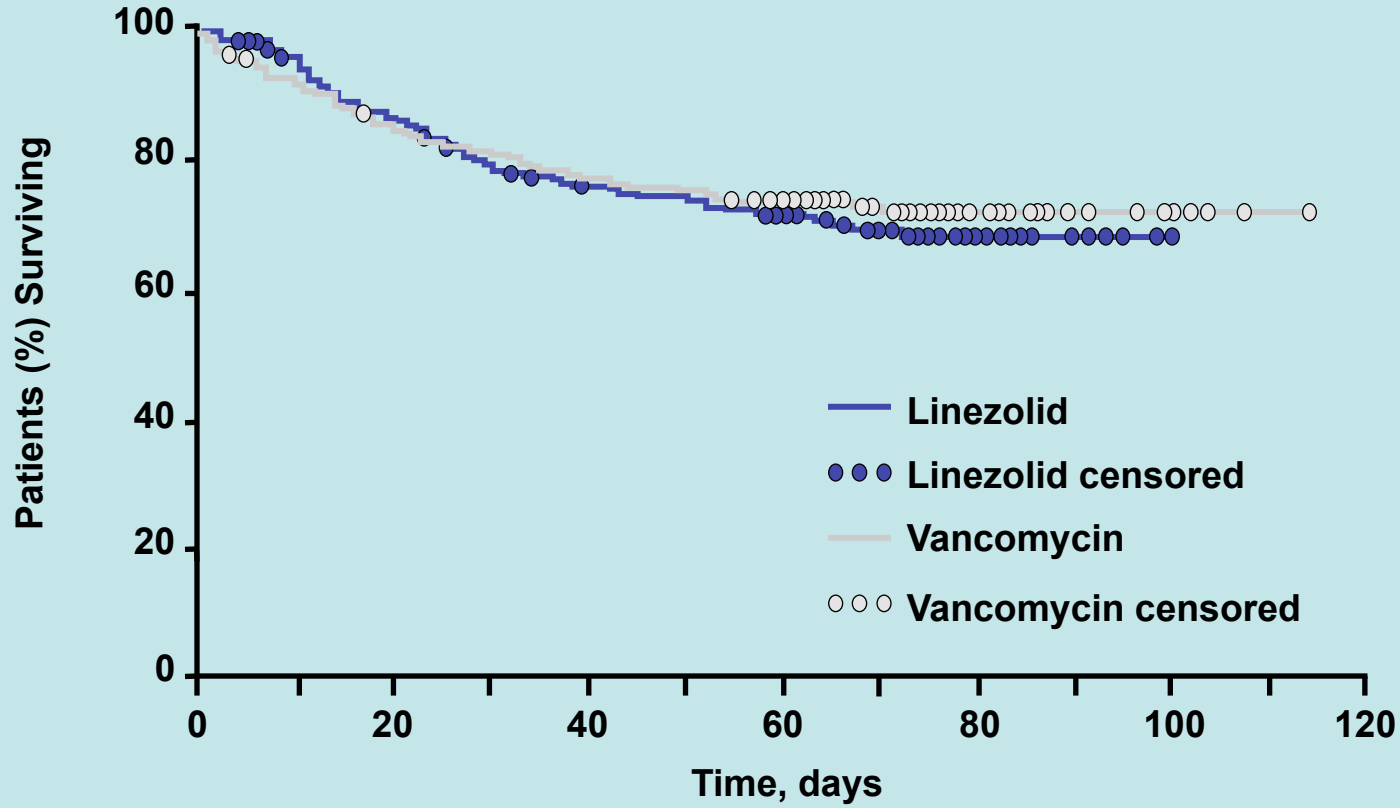
Linezolid treatment was associated (in mITT population) with:

- **better clinical response (54.8% vs. 44.9%)**
- **fewer days in hospital (17.9 vs. 18.6)**
- **less renal failure (4.0% vs. 15.8%)**

Wunderink, Clin Infect Dis 2012

60-Day Survival

- Comparable all-cause 60-day follow up mortality rates
  - ITT population, linezolid arm, 15.7%; vancomycin arm, 17.0%
  - MITT population, linezolid arm, 28.1%; vancomycin arm, 26.3%



Wunderink, Clin Infect Dis 2012

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

Higher Vanco troughs on day 3, not associated with better outcomes

Wunderink, Clin Infect Dis 2012

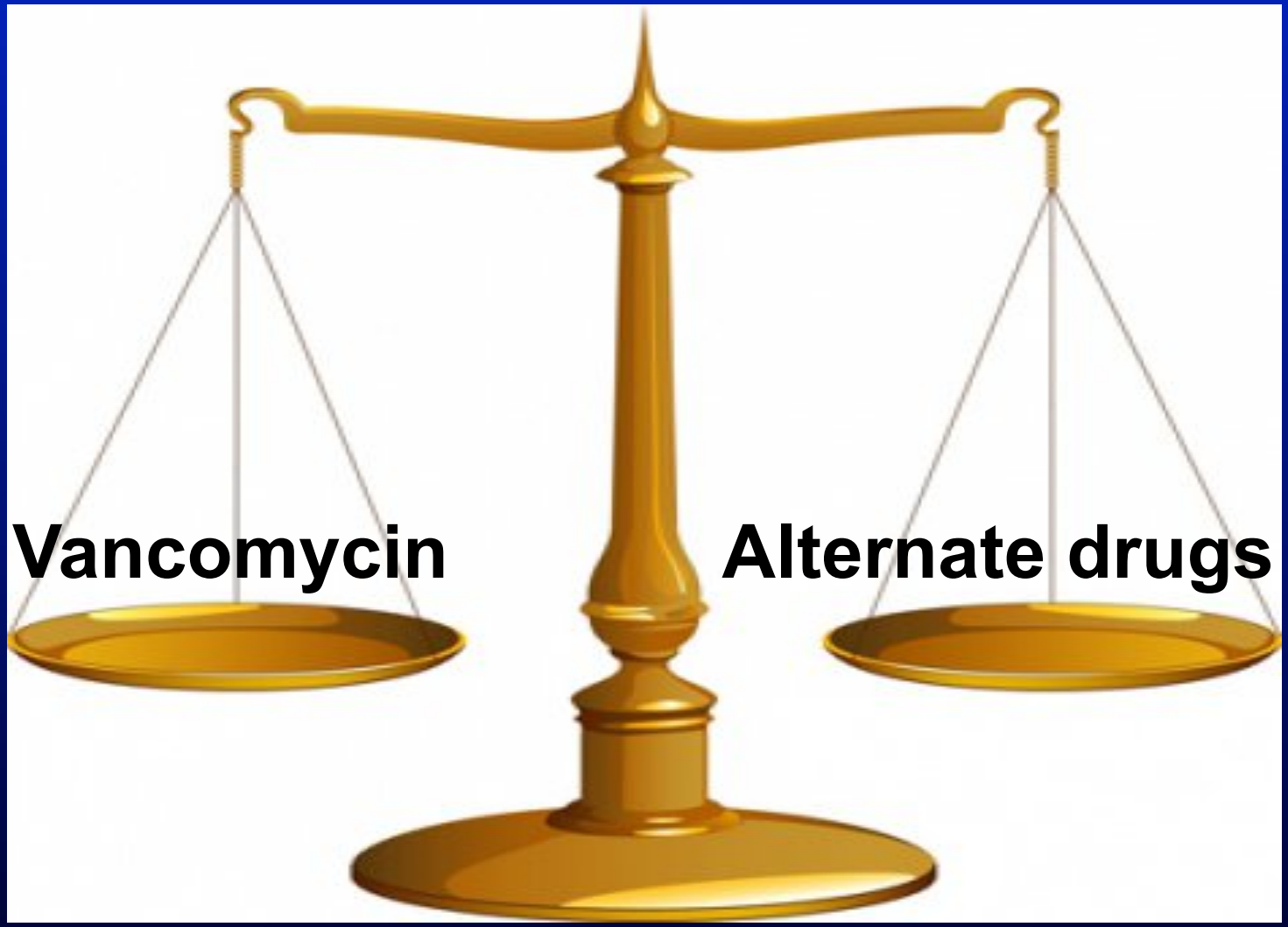
Potential Benefits of Treatment with Linezolid (1)

- Efficacy equivalent to that of Vanco for treatment of SSTI (Stevens, Clin Infect Dis 2002; Weigelt, Antimicrob Agents Chemother 2005)
- Superior efficacy for treatment of HA-MRSA pneumonia (incl. VAP) (Wunderink, Clin Infect Dis 2012)

Potential Benefits of Treatment with Linezolid (2)

- Safety with short (< 14 days) treatment
- No dose adjustment with renal failure and no need for TDM
- Resistance is rare

Which to Use?



Is It Time to Replace Vancomycin in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections?

Sebastiaan J. van Hal[1,2] and Vance G. Fowler Jr[3,4]

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For more than 4 decades, vancomycin has been the antibiotic of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Recently, infections due to isolates with high but susceptible vancomycin minimum inhibitory concentrations have been associated with additional treatment failures and patient mortality. These poorer outcomes may in part be explained by the inability of attaining appropriate vancomycin levels in these patients. However, assumptions that these poor outcomes are solely due to failure to achieve optimal serum levels of vancomycin are premature. The availability of effective alternatives further erodes the position of vancomycin as first-line therapy. The emergence of resistance and cost considerations, however, favor a more measured approach when using alternative antimicrobials. Collectively, the current available data suggest that the optimal therapy for MRSA infections remains unclear. In the absence of further data, the Infectious Diseases Society of America guidelines remain relevant and inform clinicians of best practice for treating patients with MRSA infections.

van Hal, Clin Infect Dis 2013