# Methicillin Resistant *S. aureus* Severe Infection in 2010

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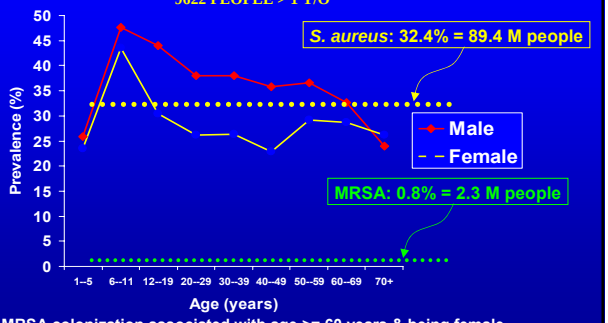
# S. aureus Nasal Colonization

National Health and Nutrition Examination Survey 2001-02

9622 PEOPLE > 1 Y/O




MRSA colonization associated with age >= 60 years & being female

Kuehnert et al, JID 2006; 193:172-9

# Invasive Bacterial Disease Active Bacterial Core Surveillance Cases and US Projections (Klevens et al. JAMA 2007; 298: 1763-71)

National Projections

| | ABC Cases | Cases | Deaths |
|---|---|---|---|
| Group A Streptococcus | 1222 | 11,275 | 1800 |
| Group B Streptococcus | 2116 | 20,375 | 2175 |
| Haemophilus influenzae | 465 | 3750 | 550 |
| Neisseria meningitidis | 215 | 1425 | 175 |
| Streptococcus pneumoniae | 3529 | 40,400 | 5450 |
| MRSA* | 8987 | 94,360 | 18,650 |

Adjusted incidence rate /100,000 ; Cases 31.8, deaths 6.3

**Pulse-Field Gel Electrophoresis Type of MRSA isolates Cultured From Invasive Sites**
**ABC Surveillance, July 2005 – December 2005 (n=864)**

| | Number (%) | | | | |
|---|---|---|---|---|---|
| Pulse-field Type | Hospital-Onset | Health Care-Associated | Community Associated | Unknown | Total |
| USA100 | 160 (74) | 303 (62) | 35 (23) | 2 (15) | 500 (58) |
| USA200 | 5 (2) | 9 (2) | 0 | 0 | 14 (2) |
| USA300 | 34 (16) | 108 (22) | 100 (67) | 10 (77) | 252 (29) |
| USA400 | 1 (<1) | 4 (1) | 1 (<1) | 0 | 6 (<1) |
| USA500 | 9 (4) | 30 (6) | 4 (3) | 0 | 43 (5) |
| USA600 | 1 (<1) | 4 (1) | O | 0 | 5 (<1) |
| USA700 | 0 | 0 | 1 (<1) | 0 | 1 (<1) |
| USA800 | 0 | 6 (1) | 1 (<1) | 0 | 7 (1) |
| USA1000 | 0 | 3 (1) | 2 (2) | 0 | 5 (<1) |
| Iberian | 4 (2) | 6 (1) | 3 (2) | 1 (8) | 14 (2) |
| Non-typeable | 2 (1) | 12 (2) | 3 (2) | 0 | 17 (2) |
| Total | 216 | 485 | 150 | 13 | 864 |

## New Syndromes Associated with Staphylococcal Infection

- **Purpura fulminans** and toxic shock– 5 cases (1 MRSA): produced SEC or TSST-1; 2 also PVL positive [Kravitz et al CID 2005; 40: 941-7]
- **Necrotizing fasciitis** – 14 cases all MRSA, 5 isolates tested –all USA 300 PFGE, SCC mec IV, and PVL, lukD, and lukE positive, no enterotoxins or TSST-1 [Miller et al NEJM 2005; 352: 1445-53.

## "New"Syndromes Associated with Staphylococcal Infection

- **Waterhouse Friderichsen Syndrome. 3 cases; MSSA, 2 MRSA - clonal, all mecIV, PVL+ (Adem et al NEJM 2005;353:1245-51)**
- **Rapidly fatal necrotizing pneumonia especially after influenza like illness**
- **Children with septic thrombophlebitis of the extremities or a "pelvic"syndrome ( septic arthritis, osteomyelitis, pelvic abscess, septic thrombophlebitis)**

## Laboratory Definitions

- MRSA: vancomycin MIC ≤ 2mg/L (was≤ 4)
- VISA: vancomycin MIC 4-16mg/L (was 8-16)
- VRSA: vancomycin MIC ≥ 32mg/L

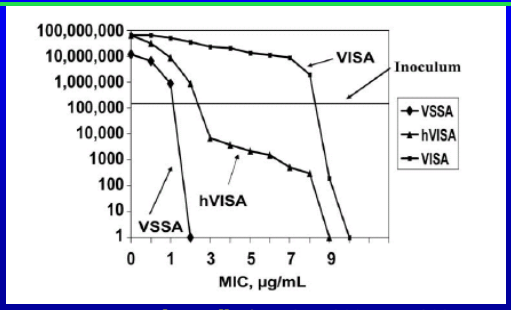
What about hetero-resistant VISA (hVISA)?

- hVISA: MRSA which produce subpopulations (1 in every $10^5$ to $10^6$ colonies) which have MIC for vancomycin of ≥ 4mg/L.

Prototpe is Mu3 isolate from Japan

Tenover et al. Emerg Infect Dis. 2001;7:327-32. Fridkin. CID 2001; 32:108-115.
Ward et al. Med J Aust. 2001;175:480-483..Cosgrove et al. CID 2004; 39:539-545.

## Population Analysis of MRSA Susceptibility to Vancomycin




Tenover and Moellering CID 2007;44:1208

## High Toll of Invasive MRSA Infection Failure to Treat Appropriately

| | Surgical Site Inf | | P Value | Blood Stream Inf | | P Value |
|---|---|---|---|---|---|---|
| | Comm* | Tertiary* | | Comm* | Tertiary* | |
| Effective RX | (N=55) | (N=74) | | (N=246) | (N=318) | |
| Day 1 | 10 (19) | 47 (64) | P 0.001 | 72 (32) | 138 (43) | P 0.005 |
| Day 7 | 33 (60) | 62 (84) | P 0.003 | 145 (59) | 238 (75) | P 0.001 |

Death No Rx 7 d: **Comm 47/101 (46) vs. 31/145 (21) OR 3.2 (1.8-5.5) P<0.001**
**Tertiary 55/80 (69) vs. 56/238 (23) OR 7.4 (4.2-13.1) P<0.001**

*8 community hospitals, 1 tertiary hospital

Kaye, et al., Clin Inf Dis 2008; 46:1568.

## *Delayed Effective Therapy for S. aureus Bacteremia Increases Infection Related Mortality*

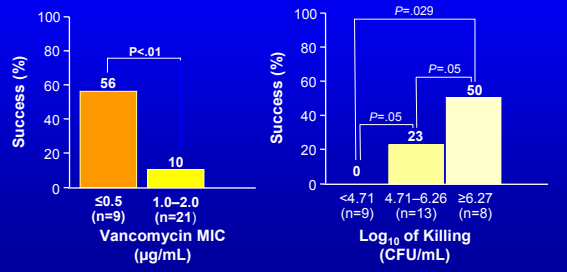
| Outcome | Delayed Rx* | Early Rx | P |
|---|---|---|---|
| Mortality (IRM) | 16/48 (33) | 23/119 (19%) | 0.05 |
| Mortality (adjusted) | OR 3.8 (1.3-11.0) | | 0.01 |
| LOS-SAB (adjusted) | 22.2 d | 14.3 d | 0.05 |
| Mortality: APACHE II > 15.5/High Risk | 86.7 | 44.7 | |
| MRSA associated with delayed Rx 8.3 OR (2.6-16.8) | | | |

*Classification and regression tree analysis: breakpoint of delayed rx = 44.5h.

Lodise, et al., CID 2003; 36:1418-1423.

## Therapeutic Efficacy of Vancomycin in Relation to MIC or Bactericidal Activity

Vancomycin in MRSA Bacteremia







Sakoulas G,. J Clin Microbiol. 2004;42:2398-2402.

## MRSA with High Vancomycin MIC Respond Poorly to Vancomycin Therapy

| | High MIC 1.5-2.0 µg/ml | Low MIC ≤ 1.0 µg/ml |
|---|---|---|
| Clinical response (obtained target) | 24/39 (62) | 34/40 (85)* |
| Clinical response (missed target) | 5/7 (71) | |
| Mortality | 11/51 (22) | 4/44 (9) |

*p=0.02
Target = Vanco free drug conc 4-5 x MIC
Hidayat, et al., Arch Int Med 2006; 166:2138.

## Relationship Between Vancomycin MIC* and Vancomycin Failure in MRSA Bacteremia

| | MIC ≥ 1.5 µg/ml N=66 | MIC < 1.5 µg/ml N=26 | |
|---|---|---|---|
| Mortality 30 d | 12 (18) | 3 (11.5) | |
| Bact > 10 d | 6 (9) | 0 | |
| Relapse < 60 d | 11 (17) | 1 (4) | |
| Overall failure | 24 (36) | 4 (15) | P=.049 |

MIC ≥ 1.5 µg/ml 2.6 (95% CI 1.3-5.4) adj risk ratio failure (also APACHE II, IE, wt > 112 kg)

*E test

Lodise, et al., AAC 2008; 52:3315.

## Clinical Features of Heterogeneous VISA Bacteremia

| | VS-MRSA (N=227) | hVISA (N=27)* | OR (95% CI) | p |
|---|---|---|---|---|
| Duration bacteremia (d) | 2 (1-92) | 12 (0-207) | 1.03 (1.02-1.05) | <0.001 |
| Endocarditis | 8 (4%) | 5 (19%) | 5.37 (1.15-25.01) | 0.032 |
| Osteomyelitis | 16 (7%) | 7 (26%) | 5.62 (1.62-19.51) | 0.007 |
| Emergence Rif resistance | 13 (6%) | 11 (41%) | 8.45 (2.70-26.5) | <0.001 |
| Mortality-attributable | 81 (36%) | 12 (44%) | 1.46 (0.6-3.57) | 0.41 |

*E test macro method
Maor, et al., J Infect Dis 2009; 199:619-624.

## Clinical Features Associated with Heterogeneous VISA (5 of 53, 9.4%)

| | hVISA* | VS-MRSA** | P |
|---|---|---|---|
| High bacterial load | 5/5 (100) | 10/41 (21 | 0.001 |
| Vanco Rx failure | 5/5 (100) | 1/48 (2) | <0.001 |
| Duration bacteremia (d) | | | |
| Mean | 39 ± 32 | 6.4 ± 9 | 0.002 |
| Median (range) | 26 (9-87) | 3.5 (1-7) | |
| Initial vanco ≤ 10 µg/ml | 5/5 (100) | 11/36 (31) | 0.006 |
| Survival months | 4/5 (80) | 31/48 (65) | 0.7 |

*PAP ≥ 0.9 AUC Mu3; MICs 2, 2, 2, 4, 4
**MIC vanco 0.5-2.0 µg/ml, median 1.0 µg/ml

Charles, et al., CID 2004; 38:448-451.

## Bactericidal Activity of Vanco and Dapto Against MRSA with Variable Vancomycin Susceptibility

| | | 2 x MIC* | | 4 x MIC* | |
|---|---|---|---|---|---|
| Phenotype (N) | Agent | ↓CFU | % Cidal | ↓CFU | % Cidal |
| GSSA (10) | V | 1.5 | | 2.3 | 10 |
| | D | 3.8 | 70 | 4.9 | 90 |
| hGISA (10) | V | 2.2 | 20 | 3.4 | 80 |
| | D | 4.3 | 100 | 5.7 | 100 |

V=Vancomycin, D=Daptomycin
*At 24 hrs, cidal = decrease ≥ 3 x log CFU

Wootton, M., et al., AAC 2006; 50:4195-4197.

## Increasing Vancomycin MIC Associated with Reduced Daptomycin Susceptibility

| | MIC µg/ml* | |
|---|---|---|
| Isolate | Vanco | Dapto |
| 1A | 1 | 0.5 |
| 1B | 8 | 2 |
| 2A | 2 | 0.5 |
| 2B | 8 | 2 |
| 3A | 2 | 1 |
| 3B | 4 | 2 |
| 4A | 1 | 0.5-1 |
| 4B | 2 | 2.4 |

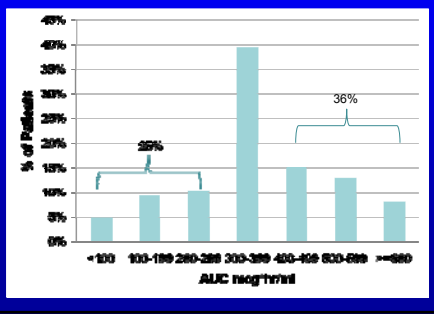
*Agar dilution – before A and after B vancomycin Rx
Pillai, et al., AAC 2007; 51:2223-2225.

## Vancomycin Therapy Guidelines for MRSA

- Dose: Normal renal function 15-20 mg/kg q 8-12 hr, kg = actual body weight (even if obese)
- Levels: Monitor trough levels – most accurate, avoid trough < 10 mcg/ml – selects resistance
- Dose Adjustment: Optimal target AUC/MIC > 400 requires trough conc. 15-20 mcg/ml with MIC ≤ 1.0
- Target Attainment: AUC/MIC not achievable if MIC 2.0 and normal renal function, consider alternative therapy
- Toxicity: Longer infusion time if dose > 1.0 gm, monitor trough and creatinine

Rybak, et al., CID 2009; 49:325-327.

## The Distribution of AUC days 2-3

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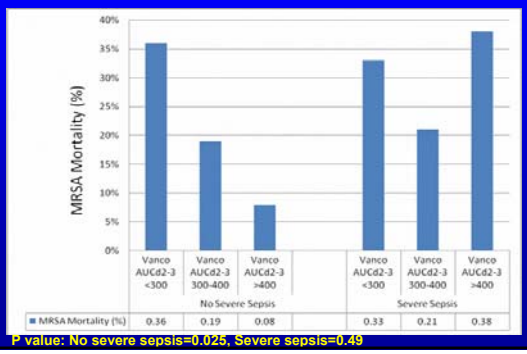
## Mortality by Vancomycin Exposure Stratified by Presence of Severe Sepsis




P value: No severe sepsis=0.025, Severe sepsis=0.49

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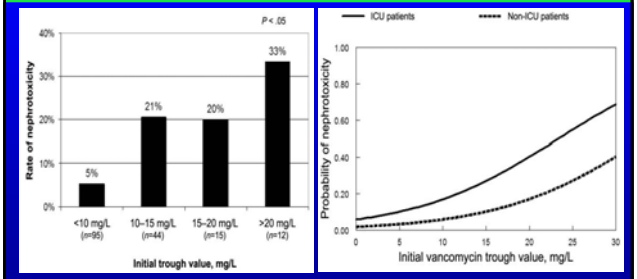
## Larger Vancomycin Doses Associated with Nephrotoxicity

| Group | Nephrotoxicity/Total (%) | |
|---|---|---|
| Vanco ≥ 4 g/d | 9/26 (34.6) | |
| Vanco standard < 4 g/d | 24/220 (10.9) | |
| Linezolid | 2/45 (6.7) | |
| **Variables** | **OR (95% CI)** | **P** |
| Vanco ≥ 4 g/d | 4.4 (1.7-11.8) | 0.003 |
| WT ≥ 101.4 kg | 3.4 (1.5-7.9) | 0.004 |
| Cr Cl ≤ 86.6 ml/min | 3.7 (1.2-11.5) | 0.020 |
| ICU residence | 2.2 (1.1-4.6) | 0.045 |

Lodise, et al., Antimicrob Agents Chemother 2008; 52:1330-1336.

## Vancomycin Nephrotoxicity Correlates with Initial Trough Concentration




Lodise et al Clin Infect Dis 2009;49: 507-14

## Treatment of MRSA Bacteremia or Native Valve IE in Patients with Normal Renal Function

- Vancomycin 15-20 mg/kg (actual body wt) IV q 8-12 h (not > 2 g/dose)
  - If septic, consider loading dose - 25-30 mg/kg
  - Trough conc 15-20 µg/ml (AUC:MIC > 400 if MIC < 1.0)
  - If dose ≥ 1.5 g, infuse over 1.5-2 hrs
  - Monitor trough weekly
  - MIC- E test, MicroScan, BD Phoenix overestimate; Senstitre and Vitek 2 under estimate
- Daptomycin 6 mg/kg IV once daily
  - Consider if vanco MIC ≥ 1.5 µg/ml (cannot achieve AUC:MIC > 400)
  - Some experts advise 8-10 mg/kg IV qd, safe in limited studies
  - FDA approved for SAB and Right sided IE not Left sided IE

No Rifampin or Aminoglycoside

Rybak, et al., CID 2009; 49:325-7.
Fowler, et al., NEJM 2006; 355:653-665.
Figueroa, et al., CID 2009; 49:177-180.
Lodise, et al., AAC 2008; 52:3315-3320.

## Persistent S. aureus Bacteremia: S. aureus and Patient Characteristics

| | Persistent SAB N=84 | Non-Persistent SAB N=152 | OR (95% CI) | P |
|---|---|---|---|---|
| MRSA | 62 (74%) | 58 (38%) | 5.22 (2.63-10.38) | 0.01 |
| CVC/Device present | 64 (76) | 93 (61) | 2.37 (1.11-5.06) | 0.03 |
| Chronic renal failure | 42 (50) | 50 (33) | 2.08 (1.09-3.96) | 0.03 |
| Multiple sites infection | 24 (28) | 7 (4.6) | 3.31 (1.17-9.38) | 0.02 |
| Endocarditis | 20 (23) | 7 (4.6) | 10.30 (2.98-35.64) | 0.01 |
| Vancomycin MIC 1.0 | 56/59 (95) | 49/53 (92%) | | |
| Time to appropriate Rx (d) | 0.82 | 0.69 | | 0.41 |
| Removal of CVC / FB | 33 (52) | 36 (39) | 1.69 (0.84-3.38) | 0.15 |
| Time to remove CVC/FB (d) | 4.94 | 1.64 | | 0.01 |
| Attributable mortality* | 16 (19%) | 1 (0.7%) | 34.82 (4.5-267) | 0.01 |

Vancomycin use not associated with persistent MSSAB *Not significant on multivariable analysis

Hawkins, et al, Arch Int Med 2007; 167:1861-67.

## Approach to Persistent MRSA Bacteremia

- Reassess around day 7 (median duration 7-9 d)
- Search for removal focus of infection
- Assess for vancomycin MIC, hVISA, VISA
- Assess daptomycin MIC
  - Vancomycin may select reduced dapto susceptibility
  - Dapto failure associated with reduced susceptibility
- Vancomycin trough – target attained
- Check dapto dose
- If left IE, consider appropriately timed (quench bacteremia) cardiac surgery
- Patient's clinical status informs Rx change
  - Stable vanco MIC < 2.0 µg/ml
  - Worse regardless susceptibility; critically ill with vanco MIC 2.0 µg/ml

## Options for Antimicrobial Treatment of Persistent MRSA Bacteremia

- **Susceptible to daptomycin:**
  - Daptomycin 10 mg/kg/day* plus
    - Gentamicin 1 mg/kg q 8 h or 5 mg/kg/d
    - Rifampin 300 mg q 8 h or 450 q 12 h po**
    - Both
- **Nonsusceptible to dapto and vancomycin:**
  - Linezolid (in combination Rx)
  - TMP/SMZ (in combination Rx)
  - Quinupristin/dalfopristin

*Not FDA approved dose
**Delay until bacteremia quenched

## Salvage Treatment of Persistent MRSA Bacteremia - Linezolid w / wo Carbapenem

Persistent SAB ≥ 7 d, 35/211 (17%) MRSA, 6/166 (4%) MSSA

| | Vancomycin* N=19 | Linezolid N=16 |
|---|---|---|
| Catheter-related | 11 | 4 |
| Endocarditis | 2 | 1 |
| Bacteremia duration (d) | 11 (7-22) | 13 (7-16) |
| Salvage | | |
| Vanco + Aminogly or Rifampin | 0/12 | --- |
| Linezolid | --- | 7/7 |
| Linezolid + Carbapenem | --- | 7/9 |
| Mortality (S. aureus) | 10/19 (53%) | 2/16 (13%) [p 0.03] |

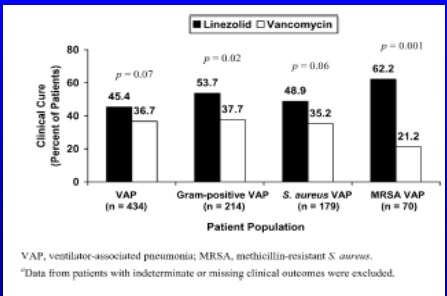
*MIC ≤ 1.0 18/19; conc trough > 10 µg/ml 16 (84%)
Jang, et al., CID 2009; 49:395-401.

## Considerations in the Treatment of MRSA Pneumonia

- Vancomycin penetration into lung is poor; </= 2mcg/ml at 6 hrs after 1gm dose
- Linezold penetration is excellent ; > peak serum level at 12 hrs post dose
- Higher Vancomycin doses and serum conc do not correlate with improved outcome
- Early microbiologic "cure" rates (BAL cult) linezolid (13/23) not superior to vanco (9/19) treated pts

Cruciani J Antimicro Chemother1996;38:865 ; Jefferies Chest 2006;130:947 ; Conte AAC 2002;46:1475; Wunderink Chest 2008;134:1200

## Clinical Cure Rates for VAP - Linezolid vs.Vancomycin with Aztreonam




VAP, ventilator-associated pneumonia; MRSA, methicillin-resistant *S. aureus*.
[a]Data from patients with indeterminate or missing clinical outcomes were excluded.

Kollef et al, Intensive Care Med 2004;30:388

## Treatment of MRSA Pneumonia

- Presentationn could be CAP, HCAP, HAP, VAP
- PK- PD consideration is important
  - Vancomycin (high dose) vs. linezolid
    - Vanco MIC ≤ 0.5 → Vanco high dose at least 15 mg/kg q 12h with trough conc 15-20 mcg/ml
    - Vanco MIC ≥ 1.0 → Linezolid
    - Renal failure / other nephrotoxic Rx → Linezolid
    - Do not use daptomycin

## Clinical Failures in Appropriately Treated MRSA Infections

| Site | Failure/Total (%) | Duration Median Days | Monotherapy (%) |
|---|---|---|---|
| Osteomyelitis* | 37/81 (46) | 42.9 | 55 (68) |
| Bloodstream (no IE) | 5/42 (12) | 25.8 | 32 (76) |
| Pneumonia | 8/45 (18) | 24.3 | 36 (80) |
| Endocarditis | 5/32 (16) | 37.4 | 19 (59) |
| Epidural abs | 5/18 (28) | 40.1 | 12 (67) |
| Joint | 1/23 (4) | 39 | 19 (83) |
| Surg site | 4/15 (27) | 34.6 | 13 (87) |
| Meningitis | 0/1 | 42 | 1 (100) |
| TOTAL | 53/215 (23) | | 157 (73) |

*27/30 hardware removed, OM increase risk failure, vanco 11.6 ± 3.7 µg/ml (75/81)
Limitations – not comparative, vanco dose, MRSA MIC, surgical Rx

Dombrowski J, Winston L: J Infect 2008; 57:110-115.

## Treatment of MRSA Bone and Joint Infection

- Recommendations based on case cohorts
- Vertebral osteomyelitis: (15-20% relapse)
  - Vancomycin, daptomycin (6 mg/kg/d) linezolid (toxicity)
  - Rifampin 300-450 mg PO bid (some experts)
  - Parenteral Rx ≥ 8 weeks
  - Oral consolidation 1-3 mos, rifampin plus 2nd agent
- Non-vertebral osteomyelitis: (20-35% relapse)
  - Rx as vertebral OM
  - Switch after 2-4 wks IV, oral rifampin combination total 8 weeks

## Treatment of MRSA Bone and Joint Infection

- Debride necrotic bone (non-vert), drain abscesses
- Children CA-MRSA (D test neg) if stable no intravasc infection, clindamycin 40 mg/kg/d IV/PO in 3 or 4 divided doses
- Septic arthritis – vancomycin, daptomycin, linezolid
  - Hematogenous: 4-6 wks; direct introduction 3-4 wks
  - Evacuate synovial fluid (arthrotomy hip shoulder) arthroscopy

Livorsi, J Infect 2008; 57:128.
Daver, J Infect 2007; 54:539.
Lamp, Am J Med 2007; 120(10A):513.
Liu C, IDSA Guideline, In Press.

## Summary

- MRSA infections are common and difficult to treat
- Considerations regarding vancomycin use are changing
  - higher dosing targets, increased toxicity
  - PK-PD considerations relevant: MIC >1.0
- Newer drugs may be desirable in selected settings
- Strategies regarding combination therapy and duration of therapy with vancomycin are in evolution