# Infective Endocarditis Considerations in 2010

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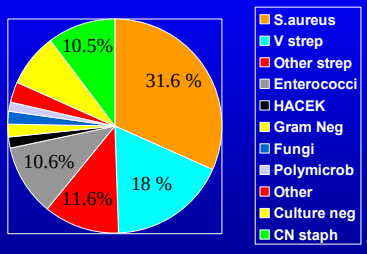
## Causes of Endocarditis: International Collaborative on Endocarditis – 1779 Cases, 39 Centers 2000-2003




Fowler et al JAMA 2005;293:3012-21

## Impact of TEE vs TTE on Diagnosis of Endocarditis (Modified Duke Criteria)

Reviewed 114 Episodes TTE & TEE*

| | Definite | Possible | Rejected |
|---|---|---|---|
| TTE | 52 | 50 | 12 |
| TEE | 74 | 30 | 10 |

*Native valves 80, prosthetic valves 34

Roe, et al., Amer Heart J 2000; 139:945-951.

## Impact of TEE vs TTE on Diagnosis of Endocarditis (Modified Duke Criteria)

- ***Changes***
  - 22 possible IE patients to definite (10 PV)
  - 2 rejected IE patients to possible (2 PV)
  - 11% of NVE, 34% of PVE
- ***Impact:***
  - Other than PVE, major impact of TEE vs. TTE is not on the decision to RX as IE, major effect is to shift to definite from possible when clinical features are intermediate clinical likelihood. Little impact with no clinical evidence of IE (in screening)

Roe, et al., Amer Heart J 2000; 139:945-951.

## Echocardiographic Diagnosis of Prosthetic Valve Endocarditis*

| | Number of Valves (%) | | | |
|---|---|---|---|---|
| | Transthoracic | | Transesophageal | |
| Prosthesis Type and Position (Number Studied) | Non-Diagnostic | Diagnostic | Non-Diagnostic | Diagnostic |
| Aortic position (34) | 16 | 18 (53) | 5 | 29 (85) |
| Bioprosthesis (12) | 6 | 6 (50) | 1 | 11 (92) |
| Mechanical valve (22) | 10 | 12 (55) | 4 | 18 (82) |
| Mitral position (37) | 32 | 5 (14) | 4 | 33 (89) |
| Bioprosthesis (10) | 8 | 2 (25) | 2 | 8 (80) |
| Mechanical valve (27) | 24 | 3 (11) | 2 | 25 (93) |

*Patients had pathoanatomic or clinically confirmed (von Reyn criteria) PVE

Daniel WG, et al., Am J Cardiol 1993; 71:210-215.
Morguet AJ, et al., 1995; 20:390-398.

## Source of *S. aureus* Bacteremia in Patients With/Without Endocarditis

| Source of Infection | All Pts. (n=103) | IE (n=26) | No IE (n=77) | Excluded Pts. (n=109) |
|---|---|---|---|---|
| No focus | 6 | 3 | 4 | 35 |
| Deep tissue infection | 28 | 7 | 21 | 35 |
| Vascular catheter | 69 | 16 | 53 | 40 |
| Nosocomial | 61 | 17 | 44 | 68 |
| Community acquired | 38 | 8 | 30 | 36 |
| Nursing home | 4 | 1 | 3 | 4 |

Fowler et al. JACC. 1997; 30: 1072.

## Treatment for Native Valve Endocarditis Due to Penicillin-Susceptible Viridans Streptococci and *Streptococcus bovis* (MIC < 0.1 µg/ml)

| Antibiotic | Dosage and Route | Duration (wk) |
|---|---|---|
| • Aqu penicillin G | 12-18 million U/24 h IV either continuously or every 4 h in 6 equally divided doses | 4 |
| • Ceftriaxone | 2 g once daily IV or IM | 4 |
| • Aqu penicillin G<br>*or*<br>Ceftriaxone<br>*plus*<br>Gentamicin | 12-18 million U/24 h IV either continuously or every 4 h in 6 equally divided doses<br>2 g once daily IV or IM<br>1 mg/kg IM or IV every 8 h or 3mg/kg IV qd single dose | 2<br><br>2<br><br>2 |

Baddour et al AHA Scientific Statement. Circ. 2005:111:e394-e433

## Contraindications to Short Course Treatment of IE Caused by Penicillin-Susceptible Viridans Streptococci/S. bovis

- Isolate with MIC Pen >/= 0.1µg/ml, HLR gent
- NVE with cardiac or CNS complications
- PVE (short course not effective – ↑relapses)
- Intra or extra cardiac abscess/focal infection
- VIII nerve dysfunction
- Reduced renal function (Cr Cl < 20 mL/min)
- Visual impairment (severe)
- Non –viridans streptococci, *Gemella, Abriotrophia, Granulicatella* species

## *Treatment of Native Valve Endocarditis Due to Streptococci Relatively Resistant to Penicillin G (MIC > 0.1 µg/ml And < 0.5 µg/ml)*

| Antibiotic | Dosage and Route | Duration (wk) |
|---|---|---|
| ➢Aqueous penicillin G | 24 million U/24 h IV either continuously or every 4-6 h in divided doses | 4 |
| | or | |
| Ceftriaxone | 2g/24 h IV in single dose | 4 |
| | plus | |
| Gentamicin | 1mg/kg IM or IV every 8 h | 2 |
| ➢Vancomycin | 30 mg/kg per 24 h IV in 2 equally divided doses, not to exceed 2g/24 h unless serum levels are monitored | 4 |

Treat Abiotrophia and Granulicatella spp. and Gemella with enterococcal Rx (can use ceftriaxone) although series suggest maybe cult neg by 14 days .

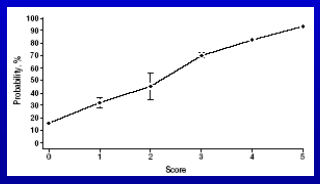
Baddour et al AHA Scientific Statement. Circ. 2005;111:e394-e433

## Predictive Model of Complicated *S. aureus* Bacteremia From 724 Episodes 1994-99

Table 4. Reduced Prognostic Model of Complicated *Staphylococcus aureus* Bacteremia*

| Variable | Odds Ratio (95% Confidence Interval) | P Value |
|---|---|---|
| Community acquired† | 3.10 (1.96-4.87) | <.001 |
| Skin examination findings suggesting the presence of acute systemic infection | 2.04 (1.30-3.18) | .002 |
| Positive follow-up blood culture result‡ | 5.58 (3.93-7.93) | <.001 |
| Persistent fever at 72 h | 2.23 (1.56-3.12) | <.001 |

| Variable | Points |
|---|---|
| Skin findings | 1 |
| Fever at 72h | 1 |
| Community-acquired | 1 |
| Bacteremia at 48-96h | 4 |

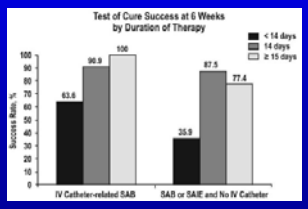



Fowler, et al., Arch Intern Med 2003; 163:2066-2072

## Duration of Therapy for Catheter Associated *S. aureus* Bacteremia

46 patients with IV catheter associated S. aureus bacteremia[17]
- negative TEE, no foci of infection

189 patients non-catheter associated S. aureus bacteremia or endocarditis




Boucher H. et al Abstract L-1205 46th ICAAC (San Francisco, CA)

## Duration of Therapy for MRSA or MSSA Bacteremia

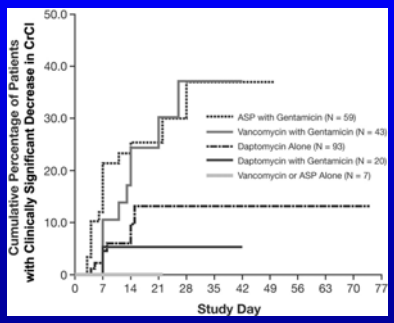
- Uncomplicated bacteremia: ≥ 2 weeks
  - A. Catheter related – if removed
  - B. R/O IE (Need a TEE ideally)
  - C. No device implants
  - D. F/U cults 2-4 d neg
  - E. Defervesce ≤ 72 h
  - F. No metastatic infection
- Complicated bacteremia: 4-6 weeks

## *Treatment for Endocarditis Due to Methicillin-Susceptible Staphylococci in the Absence of Prosthetic Material*

| Antibiotic | Dosage and Route | Duration (wk) |
|---|---|---|
| Nafcillin or oxacillin | 2g IV every 4 h | 4-6 |
| With optional addition of gentamicin | I mg/kg IM or IV every 8 h | 3-5 days |
| Cefazolin (or other first generation cephalosporins in equivalent doses) | 2g IV every 8 h | 4-6 |
| With optional addition of gentamicin | I mg/kg IM or IV every 8 h | 3-5 days |

Baddour et al AHA Scientific Statement. Circ. 2005;111:e394-e433

## Time to Clinically Significant Decrease in Creatinine Clearance Among Patients in the *S. aureus* Bacteremia Trial Daptomycin vs. Comparator




**Vanc/ASP rx median 5 days (1-13d) GENT@ 2.1mg/Kg**

**Dapto rx median 2 day (1-12d) GENT @ 3.1mg/ Kg.**

**Overall: 27/122 (27%) any Gent vs 8/100 (8%) no GENT had decrease CrCl (P=.005)**

ASP= antistaph penicillin

Cosgrove SE et al Clin Infect Dis 2009; 48(6):713-721

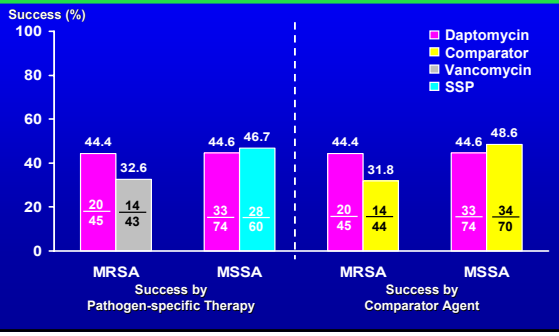
## Vancomycin/Beta-Lactam is Better Than Vancomycin for Empiric Therapy for MSSA Endocarditis in Drug Users

| Group | Infection Related Mortality (%) | | |
|---|---|---|---|
| | Beta-Lactam (N=44) | Vancomycin (N=28) | P Value |
| All | 5 (11.4) | 11 (39.2) | 0.005 |
| Left-sided/bilateral | 3 (27.3) | 6 (66.7) | 0.08 |
| Right-sided | 2 (6.1) | 5 (26.3) | 0.04 |
| Definite IE (Duke Criteria) | 5 (13.9) | 11 (40.7) | 0.02 |

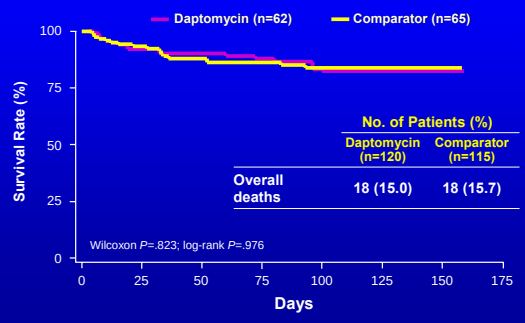
Revision of antibiotic therapy after susceptibility known (22/28: Vanco to beta-lactam); Mortality Vanco (33%) vs. switch (40.9%) (p=0.7)

Lodise, AAC 2007; 51:3731-3733.

## *S. aureus* Bacteremia - Daptomycin vs Comparator Success at Test of Cure (ITT)




## Daptomycin vs. Comparator Treatment *S. aureus* Bacteremia



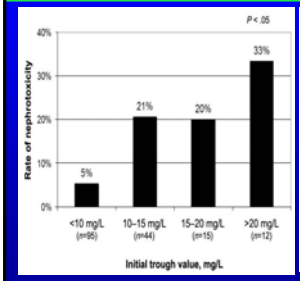

## Treatment of MRSA Bacteremia or Native Valve IE in Patients with Normal Renal Function

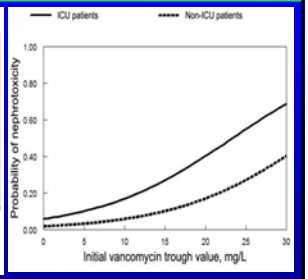
- **Vancomycin 15-20 mg/kg (actual body wt) IV q 8-12 h (not > 2 g/dose)**
  - If septic, consider loading dose - 25-30 mg/kg
  - Trough conc 15-20 µg/ml (AUC:MIC > 400 if MIC < 1.0)
  - If dose ≥ 1.5 g, infuse over 1.5-2 hrs
  - Monitor trough weekly
  - MIC- E test, MicroScan, BD Phoenix overestimate; 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.

## Vancomycin Nephrotoxicity Correlates with Initial Trough Concentration




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

## 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.

## 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 ; **patients treated 1/2005- 5/2007

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

## 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 at 1 month | 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.

## Development of Reduced Vancomycin Susceptibility in Methicillin-Susceptible *Staphylococcus aureus*

Satish K. Pillai,[1,2] Christine Wennersten,[1] Lata Venkataraman,[1] George M. Eliopoulos,[1,2] Robert C. Moellering, Jr.,[1,2] and Adolf W. Karchmer[1,2]

[1]Division of Infectious Diseases, Beth Israel Deaconess Medical Center, and [2]Harvard Medical School, Boston, Massachusetts

***Background.*** Most cases of reduced vancomycin susceptibility in *Staphylococcus aureus* reported in the literature have been in methicillin-resistant strains. We report the development of reduced vancomycin susceptibility in a series of clonally related, methicillin-susceptible *S. aureus* (MSSA) clinical isolates. This isogenic series permitted us to determine whether the evolution of reduced vancomycin susceptibility in MSSA is similar to that seen in MRSA.

***Methods.*** Differences in vancomycin population analysis profiles; chemical autolysis; vancomycin, oxacillin, and daptomycin minimum inhibitory concentrations; and bactericidal activities were examined.

***Results.*** Progressive vancomycin resistance correlated with increasing daptomycin nonsusceptibility. Chemical autolysis and the bactericidal activity of vancomycin, oxacillin, and daptomycin were reduced in the final, vancomycin-intermediate *S. aureus* isolate, compared with the vancomycin-susceptible MSSA progenitor.

***Conclusions.*** Clinicians should recognize that reduced vancomycin susceptibility can occur in *S. aureus* irrespective of background methicillin susceptibility and that development of intermediate vancomycin susceptibility in MSSA may result in increased tolerance to several classes of anti-staphylococcal antibiotics.

Clinical Infectious Diseases 2009; 49:1169–74

## 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.

## 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

## Treatment of Endocarditis Due to Methicillin-Resistant Staphylococci in the Presence of a Prosthetic Valve or Other Prosthetic Material

| Antibiotic | Dosage and Route | Duration (wk) |
|---|---|---|
| Vancomycin | 15 mg/kg per 8-12 h IV (target trough 15-20ug/ml) | ≥ 6 |
| plus | | |
| Rifampin | 300 mg po every 8h | ≥ 6 |
| and | | |
| Gentamicin* | 1.0 mg/kg IM or IV every 8h | 2 |

*Use during initial 2 weeks of treatment; alternative fluoroquinolone to which isolate is susceptible (animal model data)

## *Emergence of Rifampin Resistance Among Coagulase Negative Staphylococci During Therapy*

| Initial Treatment | Patients with PVE* | | |
|---|---|---|---|
| | No. with Resistant Strains | Total Treated | Percent |
| Vancomycin-Rifampin | 7 | 19 | 37 |
| Vancomycin-Rifampin-Gentamicin | 0 | 13 | 0 |

*Treated with antibiotics ≥ 2 days before surgery or treated medically

## Valve Culture Status After Single vs. Combination Agent Therapy for Staphylococcal IE

| | No. Rx'd | Median (d) to Surgery | No. Sterile Valve (%) |
|---|---|---|---|
| NVE (S. aureus) | | | |
| Single | 32 | 10.5 | 13 (41)* |
| Combination | 36 | 9/11 | 14 (39)* |
| PVE (S. aureus and CoNS) | | | |
| Single | 14 | 17 | 6 (43)** |
| Combination (all) | 47 | 5/10 | 33 (70)** |
| Rifampin 3 drug | 4 | 8.5 | 4(100) |

*OR culture negative, adjusted for duration of Rx 0.45 (0.12-1.66)
**p 0.062; OR culture negative, adjusted for duration of Rx 5.9 (1.3-27.5)

Drinkovic, J Antimicrob Chemother 2003; 52:820-825.

## Standard Therapy of Endocarditis Due to Enterococci*

| Antibiotic | Dosage and Route | Duration(wks) |
|---|---|---|
| ➢ Aqueous penicillin G | 18-30 million U/24 h IV either continuously or every 4 h in 6 equally divided doses | 4-6 |
| plus | | |
| Gentamicin | 1 mg/kg IM or IV every 8 h | 4-6 |
| ➢ Ampicillin | 12 g/24 HIV given continuously or every | 4-6 |
| plus | 4 h in 6 equally divided doses | |
| Gentamicin | 1 mg/kg IM or IV every 8 h | |
| ➢ Vancomycin*# | 30 mg/kg per 24 h IV in 2 equally divided | 4-6 |
| plus | doses, not to exceed 2g/24 h unless serum levels are monitored | |
| Gentamicin | 1mg/kg IM or IV every 8 h | 4-6 |

· Test for antimicrobial susceptibility in order to select optimal therapy.
# Cephalosporins are not alternatives to penicillin/ampicillin in pen-allergic pts.

## Screening for Resistance in Enterococci

| *SCREENING TEST* | *IMPLICATION* |
|---|---|
| Growth in Streptomycin at ≥ 2000 mcg/ml | No synergy, strep |
| Growth in Gentamicin at ≥ 500-1000 mcg/ml | No synergy with any aminoglycosides except possibly streptomycin |
| Nitrocefin chromogenic cephalosporin (Beta lactamase production) | Lose penicillin/ampicillin synergy effect |
| MIC penicillin/ampicillin > 32 mcg/ml (PBP change) | Lose penicillin/ampicillin synergy |
| MIC vancomycin ≥ 32 mcg/ml | Lose vancomycin synergy |

## Therapy of Endocarditis Due to Resistant Enterococcus

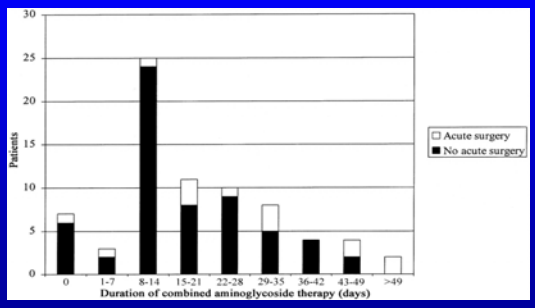
- No simple formula
- Synergistic therapy is ideal
  - Cell wall active agent -- achievable concentration
  - Aminoglycoside -- no high level resistance
- Options for therapy when synergy not achievable
  - Penicillin/ampicillin
  - Vancomycin
  - Ampicillin-sulbactam
  - Linezolid ?
  - Synercid ( *E. faecium* only)?
  - Daptomycin??
  - Double beta-lactam: imipenem-ampicillin, ceftriaxone -ampicillin
- Surgery

## Treatment of Enterococcal Endocarditis: Shorter Courses of Aminoglycosides

| | Cases | Cure | Died | Relapse | Antibiotic Days* Cell Wall/Ag |
|---|---|---|---|---|---|
| All | 93 | 75 (81%) | 15 (16%) | 3 (3%) | 42/15 |
| NVE | 66 | 54 (82%) | 10 (15%) | 2 (3%) | 42/16 |
| PVE | 27 | 21 (78%) | 5 (19%) | 1 (4%) | 42/15 |

*Median
FU 41 patients > 1 month (mean 90D)
Olaison, et al., CID 2002; 34:159-166.

## Duration of Combined Aminoglycoside Therapy in 75 Cured Enterococcal IE




Oliason, L., et al: CID 2002; 34:159-166.

## Ampicillin-Ceftriaxone Treatment of E. faecalis IE*

| | Number Cases (%) | | |
|---|---|---|---|
| | HLAR N=40 | Non-HLAR N=78 | All N=118 |
| Failed | 13 (33) | 14 (18) | 27 (23) |
| Died on Rx | 11 | 9 | 20 (17) |
| Died after Rx | 1 | 3** | 4 (3) |
| Relapse | 0 | 2** | 2 (2) |
| AE | 1 | 10 | 12 (10) |
| Cured @ 3 mos | 27 (67) | 64 (82) | 91 (77) |

*PVE = 47, NVE = 71, Pacers = 3
**1 pt relapsed and died
HLAR = High Level Aminoglycoside Resistant

Gavalda, et al., Ann Int Med 2007; 146:574.
Gavalda, et al., ICAAC 2008

## Cardiac Surgical Intervention in Endocarditis

*PATIENTS FOR CONSIDERATION*

- Congestive heart failure due to valve dysfunction
- Myocardial invasion -- abscess
- Resistant pathogens
  - Fungi
  - Gram-negative bacilli
  - Multi-resistant enterococci
- Relapse of PVE
- *S. aureus* endocarditis -- left-sided
- *S. aureus* PVE
- High risk for embolic complications
- Culture-negative endocarditis unresponsive to antimicrobial therapy

## Timing Surgery for Endocarditis

- Hemodynamic status is primary consideration
- Mortality is proportional to hemodynamic disability
- Mortality is increased by continuing antibiotics in the face of worsening hemodynamics
  - Delaying surgery in the face of deteriorating hemodynamics increases mortality from 6-11% to 17-33%
- Delayed surgery is acceptable when the operation is "elective"

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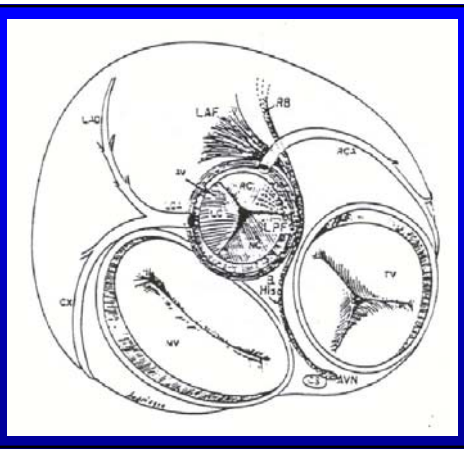


## Detection of Myocardial Abscesses Associated With Infective Endocarditis

| Abscess | At surgery or Autopsy | Detection On TTE | On TEE |
|---|---|---|---|
| Aortic-root NVE | 14 | 5 | 11 |
| Ring of PV | | | |
| Aortic | 12 | 4 | 11 |
| Mitral | 4 | 1 | 3 |
| IV septum | 9 | 2 | 9 |
| Mitral-NVE | 6 | 1 | 6 |
| Papillary muscle | 1 | 0 | 0 |
| Total (%) | 46 (100) | 13 (28) | 40 (87) |

Daniel et al. NEJM. 1991;324:795-800.

## Potential Role of Surgical Treatment in *S. aureus* Endocarditis in Non-addicts (Mitral/Aortic Valve)

**ACTIVE IE:*** Multivariate analysis
Only *S. aureus* infection correlates with mortality

**ACTIVE IE: #** Multivariate analysis
*S. aureus* correlates with increased operative mortality

*D'Agostino et al. Ann Thorac. Surg. 1985; 40:429.
#Mullaney et al. World J. Surg. 1989; 13:132.

## Outcome for 49 Patients With IE Due to *S. aureus*

| Outcome | Visualized by TTE (n = 19) | Vegetations Visualized only by TEE (n = 30) | P Value |
|---|---|---|---|
| Death due to *S. aureus* infection | 6 (31.6%) | 2 (6.7%) | .04 |
| Any major embolic event | 11 (57.9%) | 3 (10.0%) | < .01 |
| Cerebrovascular | 5 (26.3%) | 1 (3.3%) | .03 |
| Pulmonary | 5 (26.3%) | 2 (6.7%) | NS |
| Other | 4 (21.1%) | 2 (6.7%) | NS |
| Major embolic event or death due to *S.aureus* infection | 13 (68.4%) | 5 (16.7%) | < .01 |

Fowler et. al. CID. 1999; 28:106.

## Impact of Cardiac Surgery on Outcome of *S. aureus* IE

116 definite cases (17 PVE, 30 right sided); 55 early surgery (47%), Hospital deaths: surgery 9/55 (16%) vs. medical 21/61 (34%) [p0.03]

| | In Hospital | | Overall 36 Mos | |
|---|---|---|---|---|
| Risk Factor for Death | OR (CI) | P | OR (CI) | P |
| Comorbidity | 4.5 (1.2-18.5) | 0.03 | 2 (1-3.9) | 0.04 |
| Severe sepsis | 23 (6-93) | 0.0001 | 3.7 (2-7.1) | 0.0001 |
| CHF | 3.7 (1-13.8) | 0.049 | | |
| CNS event | 9.2 (1.7-48) | 0.008 | | |
| PVE | 9.1 (2-40) | 0.003 | 2 (1-4.3) | 0.055 |
| Surgery | 0.3 (0.1-1.2) | 0.1 | 0.5 (0.2-1) | 0.047* |

*Exclude right IE: OR 0.41 (0.37-0.8) p 0.02

Remadi, et al., Ann Thorac Surg 2007; 83:1295-1302.

## Outcome of *S. aureus* PVE

| Treatment | Died/Treated (%) |
|---|---|
| Medical | 59/81 (73) |
| Medical-surgical | 12/48 (25) |

Wolf et al., John et al., Kuyvenhoven et al., Tormos et al., Yu et al., Roder et al., Sett et al.

## Survival After *S. aureus* PVE (14/33 {42%} Dead at 3 Months)

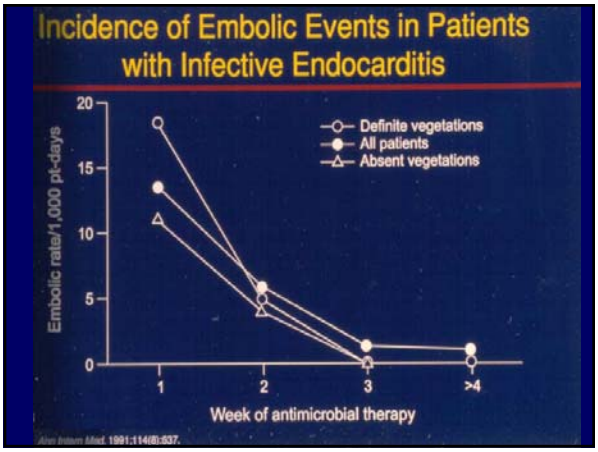
| Risk Factor | Univariate Odds Ratio (95% CI) | Multivariate Odds (95% CI) | *P* value |
|---|---|---|---|
| Cardiac complications | 5.4 (0.9 - 31) | 13.7 (1.4 - 131) | .02 |
| CNS complications | 3.8 (0.8 - 17.2) | | |
| Any systemic complication | 1.0 (0.2 - 5.5) | | |
| Valve surgery during antibiotic Rx | 0.1 (0.02 - 0.6) | 0.05 (0.005 - 0.42) | .004 |

John et al. CID. 1998; 26:1302.

## Vegetation Size and Complications of Endocarditis

| Status | # Cases | Death | CHF | % with Event Emboli | Surgery |
|---|---|---|---|---|---|
| Vegetations present | 343 | 20 | 62 | 36 | 50 |
| No vegetations | 363 | 9 | 24 | 12 | 12 |
| Vegetations | | | | | |
| > 10 | 92 | | | 33 | |
| 0-10 | 128 | | | 19 | |

Aragam & Weyman. Principles and Practice of Echocardiography, 1994.




## Risk of Stroke in Patients with Left Sided Infective Endocarditis

- Stroke in 219/1437 (15.2%) patients, 50% before diagnosis; similar with NVE (13.3%) and PVE (13.8%)
- Risk of Stroke: OR - Mitral valve (1.93),*S aureus* (1.55),Intracard abscess(1.56) viridans strep (0.59)
- Risk falls with antibiotic therapy: rate/1000 pt days: 4.82 wk 1, 1.71 wk 2; of strokes after rx 68/91( 74.7%) in first 2 wks. Declining rate similar for *S aureus* and mitral IE.
- Surgery in 40% cases (549/1437) – only 3.5% (51/1437) had surgical rx solely because of embolic risk

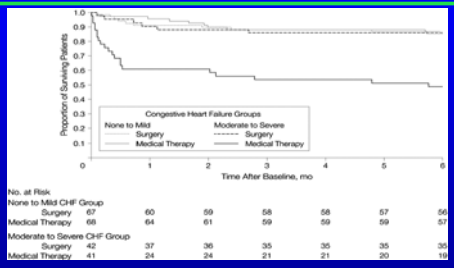
Dickerman,SA et al Am Heart J 2007;154:1086-94

## Cardiac Surgical Intervention in Endocarditis

**PATIENTS FOR CONSIDERATION**

- Congestive heart failure due to valve dysfunction
- Myocardial invasion -- abscess
- Resistant pathogens
  - Fungi
  - Gram-negative bacilli
  - Multi-resistant enterococci
- Relapse of PVE
- *S. aureus* endocarditis -- left-sided
- *S. aureus* PVE
- High risk for embolic complications
- Culture-negative endocarditis unresponsive to antimicrobial therapy

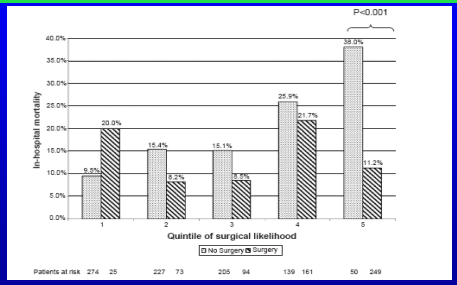
## Impact of Valve Surgery on 6 month Mortality - Propensity Analysis 109 Matched Surgically and Medically Treated Patients




Surgical therapy is associated with reduced mortality when adjusted for baseline mortality risk and confounders (surgical propensity) HR 0.40 (0.18-0.91) [p=.03] with impact related to mod/severe CHF

Vikram,et al, JAMA 2003;290:3207

## In-Hospital Mortality of Native Valve IE Treated with Medical vs. Medical-Surgical Therapy by Propensity Groups




Cabell et al Am Heart J 2005:150:1092-8

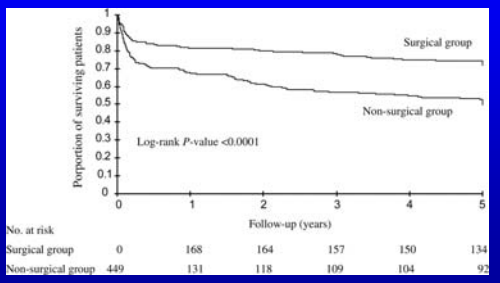
## Clinical Characteristics of Patients in Propensity Groups

| | Propensity group | | | | |
|---|---|---|---|---|---|
| | 1 (n = 299) | 2 (n = 300) | 3 (n = 299) | 4 (n = 300) | 5 (n = 299) |
| Female | 47.5 | 33.7 | 35.5 | 25.0 | 20.1 |
| S aureus | 31.4 | 20.0 | 27.1 | 24.3 | 16.1 |
| Coagulase-negative staphylococci | 2.7 | 5.0 | 5.0 | 9.0 | 12.4 |
| Viridans group streptococci | 39.1 | 34.3 | 23.1 | 21.0 | 23.4 |
| AV vegetation | 10.0 | 20.0 | 26.8 | 31.7 | 52.2 |
| MV vegetation | 32.4 | 33.0 | 38.5 | 37.0 | 26.8 |
| TV vegetation | 10.4 | 5.0 | 5.7 | 4.3 | 1.7 |
| CHF | 0.7 | 12.0 | 36.5 | 68.0 | 73.6 |
| Abscess | 0.0 | 0.0 | 0.0 | 6.0 | 43.1 |
| Embolization, systemic | 31.8 | 31.3 | 37.5 | 36.3 | 30.1 |

Values are presented as percentages. AV, Aortic valve; MV, mitral valve; TV, tricuspid valve; CNS, central nervous system.

Cabell et al Am Heart J 2005:150:1092-8

## Impact of Valve Surgery in Endocarditis on Survival




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| Surgical group | 0 | 168 | 164 | 157 | 150 | 134 |
| Non-surgical group | 449 | 131 | 118 | 109 | 104 | 92 |

Bannay, A. et al. Eur Heart J 2009

## Deaths After Cardiac Surgery for Endocarditis

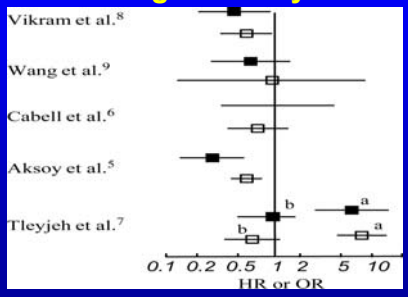
| | Hazard Ratio (95% CI) | |
|---|---|---|
| | ≤ 14 days | 15 days – 5 yrs |
| Unadjusted | 2.76 (1.7-4.6) | 0.48 (0.32-0.71) |
| P-value | <0.0001 | 0.0003 |
| Adjusted for prognostic factors[c] | 3.90 (2.34-6.51) | 0.58 (0.38-0.88) |
| P-value | <0.0001 | 0.011 |
| Adjusted for prognostic factors and surgery predictors[d] | 3.69 (2.17-6.25) | 0.55 (0.35-0.87) |
| P-value | <0.0001 | 0.010 |

[c]Prognostic factors: Age, co-morbid diseases, valvular disease, vascular events, septic shock, and C-reactive protein >120 mg/L

[d]Surgery predictors: Age, tobacco use, peripheral vascular emboli, incident heart failure, largest vegetation, intracardiac abscess, and time between first symptom and admission

Bannay A, Europ Heart J 2009 (Feb)

## Comparison of Relationship between Surgical Therapy and Death – Methodological Analysis



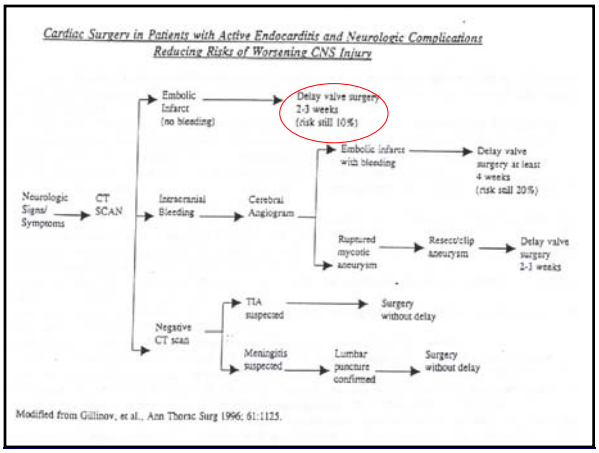

Solid box = original study; open box = French data

Bannay, A. et al. Eur Heart J 2009

## Influence of Interval Between Cerebral Event and Cardiac Surgery on Postoperative Exacerbation of CNS Injury (Including Related Death)

| Interval Event to Surgery (Days) | Patients Worsened Preoperative Event/Number Operated (%) Infarction N = 111 | Hemorrhage N = 34 |
|---|---|---|
| ≤ 1 | 5/11 (45) | 1/1 (100) |
| 2-7 | 7/16 (44) | 0/1 (0) |
| 8-14 | 2/12 (17) | |
| 15-21 | 1/10 (10) | 1/5 (20) |
| 22-28 | 2/19 (10) | 0/6 (0) |
| 29+ | 1/43 (2) | 4/21 (19) |

Eishi et al. J Thorac Cardiovasc Surg. 1995; 110: 1745.



## Outcome of 214 IE Patients treated Surgically with/without Preop Embolic Stroke

- 65 patients CNS emboli (55 prior to admission)
  - Event to surgery – median 4 days (0-38 d)
  - 6 preop intracerebral bleed (4 died postop- 1 rebleed)
- 30 day mortality
  - CNS event 11/65 (17%) (complicated stroke 39% mort)
  - No CNS event 19/149 (13%)
- Survival similar 1 yr (81% with CNS vs. 86% with out CNS event)
- Recovery stroke – full in 70% of patients (middle cerebral artery stroke – 50%)
- Early surgery after CNS event acceptable

Ruttmann, et al., Stroke 2006; 37:2094.

## *Microbiology of Surgically Excised Infected Valves*

| Percent Standard Therapy at Surgery (N) | Number Positive/Number Examined (%) | | | |
|---|---|---|---|---|
| | Gram Stain Micro | Culture | Gram Stain Pathology | Inflammatory Cells |
| ≤ 25 (106) | 88/100 (88) | 76/106 (72) | 51/63 (81) | 4/63 (14) |
| 25-50 (113) | 85/101 (84) | 40/108 (37) | 50/70 (71) | 17/70 (24) |
| 51-75 (57) | 37/50 (74) | 7/54 (13) | 21/39 (54) | 12/39 (31) |
| 76->100 (102) | 49/77 (64) | 7/91 (8) | 47/89 (53) | 22/89 (25) |
| ≤ 1 mo off (22) | 7/15 (47) | 0/19 (0) | 9/20 (45) | 4/20 (20) |
| > 1 mo off (33) | 4/18 (22) | 1/22 (5) | 6/25 (24) | 9/25 (36) |

Morris, et al., CID 2003; 36:697-704.

## Recurrent IE After Surgery in 358 IE Cases*
(1 in 221 NVE, 2 in 65 Mechanical PVE)

| Variable (N) | Relapse/Total Cases | |
|---|---|---|
| | Yes | No |
| Antibiotic > 3 wks (358) | 2/236 | 1/122 |
| Perivalve invasion (358) | 1/131 | 2/227 |
| Positive valve culture (341) | 1/116 | 1/225** |
| Positive gram stain (322) | 1/244 | 1/78 |
| Bacteria in histopath (225) | 0/157 | 1/98 |

*49% had < 50% Rx course; 38% staph, 34% strep, 28% other
**Relapses 0/54 Rx ≤ 14 d, 1/170 Rx 14 - >43 d

Morris, et al., CID 2005; 41:187.

## Antibiotic Duration After Surgery for IE

| Valve Culture, Perivalve Extension | No. Cases | 1963-93 Days Rx* | No. Cases | 1994-99 Days Rx* |
|---|---|---|---|---|
| **Positive** | | | | |
| Extension | 31 | 36 (28-42) | 22 | 28 (21-28) |
| No extension | 39 | 29 (28-41) | 25# | 28 (21-30) |
| **Negative** | | | | |
| Extension | 63 | 28 (25-42) | 13 | 14 (14-28) |
| No extension | 112** | 27 (17-28) | 36 | 14 (9-20) |

* Median (interquartile range)
**Relapse NVE viridans strep
# Relapse PVE *S. epidermidis*

Morris, et al., CID 2005; 41:187.

## New Major References

- Infective Endocarditis
  Diagnosis, Antimicrobial Therapy, and Management of Complications.
  Statement of the AHA
  Baddour, LM et al. Circ 2005;111: e394-e433

- Prevention of Infective Endocarditis. A Guideline from the AHA. Wilson, W et al. Circulation online 4/19/2007. http://circ.ahajournals.org

## Rationale for Changes in AHA IE Prophylaxis Guidelines

- Bacteremia: Tooth brushing 154,000 times greater/yr than single extraction, daily activity possibly 5.6 x $10^6$ greater/yr
- Antibiotics do not eliminate bacteremia, not clear reduces IE
- No prospective studies of prophylaxis efficacy
- Case controlled study dental event not increased in IE
- If 100% effective, antibiotics prevent rare cases of IE

Wilson, et al., AHA Committee. Circulation Online 4/19/07

## Rationale for Changes in AHA IE Prophylaxis Guidelines

- Estimates of IE risk with dental procedure
  - MVP 1:1.1 million
  - CHD 1:475 x $10^3$
  - RHD 1:142 x $10^3$
  - PV 1:114 x $10^3$
  - Prior IE 1:95 x $10^3$
- Adverse reactions, cost, malpractice
- Lifetime IE risk wrong target
- Data less convincing for GU/GI procedures, thus no prophylaxis advised

Wilson, et al., AHA Committee. Circulation Online 4/19/07

## Cardiac Conditions Associated with High Risk for Adverse Outcome Prophylaxis Advised with Dental Work

- Prosthetic cardiac valve
- Prior IE
- Congenital heart disease (CHD)
  - Unrepaired cyanotic CHD includes shunts/conduit
  - Repaired CHD with prosthetic material (within 6 mos)
  - Repaired CHD with residual defect
- Cardiac transplant with valvulopathy

Wilson, et al., AHA Committee. Circulation Online 4/19/07

## Risk of Endocarditis After Correction of Congenital Heart Disease

| Lesion (Cases) | Pt Years Follow-Up | Cases | Cumulative % (yrs) | Cases/1000 % (yrs) |
|---|---|---|---|---|
| Aortic valve stenosis (178) | 1814 | 13* | 20.6 | 7.2 |
| Prosthetic valve | | 3 | 26.0 (10) | |
| No prosthesis | | 10 | 15.0 (25) | |
| Pulmonary atresia/VSD (50) | 262 | 3# | 6.4 (10) | 11.5 |
| Pulmonary atresia (32) | 157 | 1* | 5.3 (10) | 6.4 |
| Coarctation (563) | 6675 | 3* | 3.5 (30) | 1.2 |
| Tetrology of Fallot (430) | | 5* | 1.3 (30) | 0.7 |
| VSD (557) | 6310 | 4* | 4.1 (30) | 0.6 |
| Dextrotransposition great arteries (208) | 1390 | 1 | 4.0 (20) | 0.7 |
| Primum ASD/cleft mitral (114) | 1117 | 2 | 2.8 (20) | 1.8 |
| Complete A-VSD (165) | 996 | 1 | 1.1 (15) | 1.0 |

*Residual surgical or congenital abnormalities
#Conduit placed

Morris et al. JAMA. 1998; 279:599-603.

## Prophylaxis with Dental Procedures Involving Giingival or Periapical Manipulation

| Agent | Single Dose* |
|---|---|
| Amoxicillin | 2 gm PO |
| Ampicillin | 2 gm IM/IV |
| Cefazolin/Ceftriaxone* | 1 gm IM/IV |
| Cephalexin* | 2 gm PO |
| Clindamycin | 600 mg PO/IM/IV |
| Azithro/Clarithro | 500 mg PO |

*Not used if pen/ampi causes anaphylaxis, urticaria, angioedema

Wilson, et al., AHA Committee. Circulation Online 4/19/07

## Prevention of Endocarditis in High Risk Patients

- Treat GU infection before manipulation, cover enterococci
- Prophylaxis for respiratory tract (mucosal) surgery (tonsillectomy, bronchoscopic surgery)
- Treat infected (*S. aureus*, streptococci) skin or skin structures before or with procedure

Wilson, et al., AHA Committee. Circulation Online 4/19/07