Best Antimicrobials for *Staphylococcus aureus* Bacteremia

I. Methicillin Susceptible *Staph aureus* (MSSA)

A. *In vitro* - Anti-Staphylococcal β-lactams (Oxacillin, Nafcillin, Cefazolin) are more active

B. Clinical Trials

   - Prospective, multicenter, observational study from 1994-1996
   - Pts identified by +BCx w/ staph → enrolled → observed (primary MD chose abx)
   - FU BCx drawn at the discretion of primary MD
   - Follow-up – 6 months for bacteremia, 3 years for endocarditis
   - Results
   - Bacteriologic Failure (persistent bacteremia >7 days &/or relapse)
     - Nafcillin – 0% failure (0/18)
     - Vancomycin – 19% failure (13/70)
     - Vancomycin predisposed to relapse on multivariate analysis (p < 0.048)

   - Cefazolin vs Vancomycin for MSSA in Dialysis Dependent Patients
   - treatment failures – Vancomycin (31%), Cefazolin (13%) – p .02

   - Matched Case Control Study
   - 27 vancomycin patients, 54 β-lactam patients (2:1 ratio)
   - Controls (β-lactam group) were matched using a complex matching system
     - A little more endocarditis in vanc arm (p 0.04)
   - All of the following were worse in patients who received vancomycin compared to β-lactams:
     - Overall deaths (41% vs 15% -- p 0.03)
     - *Staph aureus* related deaths (37% vs 11% -- p 0.006)
     - Cure rate (59% w/ vanc, 82% w/ β-lactams – p 0.05)
   - Conclusion - **Vancomycin is inferior to β-lactams for treatment of MSSA Bacteremia**

C. Oxacillin 12 gram continuous infusion is likely similar to 2 grams every 4 hours

II. Methicillin Resistant *Staph aureus* (MRSA)

B. Vancomycin

- Class - Glycopeptide
- Mainstay for the past 40 years
- Slowly bactericidal - Not as potent as Beta-lactams (*in vitro or in vivo*)

1. Dose
   - 15mg/kg IV BID
   - For a 70kg patient, this is 1 gram BID
   - Consider higher doses in younger patients (<40 yrs old) as vancomycin is cleared rapidly in these patients
   - **Loading dose of 25-30 mg/kg** can be given
   - Continuous Infusion (30 mg/kg q day)
     - May reach goal levels faster
     - Similar efficacy and safety……probably

2. Goal troughs
   - **IDSA guidelines**
     - Serious infections (bacteremia, endocarditis, osteomyelitis, HAP, meningitis) - 15-20
     - Other infections - Keep trough over 10 to avoid development of resistance
- Endocarditis Guidelines – 10-15
- Continuous infusion – 20-30

3. Minimum Inhibitory Concentrations (MIC)
- ≥16 — resistant (VRSA) — altered binding site due to VanA gene (usually donated from VRE)
  - 11 cases reported in USA
- 4-8 — intermediate (VISA) — thicker cell wall
- ≤ 2 — Susceptible
  - MIC 0.5 — 22% failure rate
  - MIC 1 — 27% failure rate
  - MIC 2 — 51% failure rate

- Prospective, cohort study, Evaluation was based on 86 patients (bacteremia, pneumonia).
- Final response based on target trough achievement (trough 15-20).
  - MIC ≤ 1 — 85% response (when target trough is reached)
  - MIC = 2 — 62% response (when target trough is reached) – p=.02

5. Nephrotoxicity?
- Primarily noted when vancomycin is used with concomitant nephrotoxins
- If trough levels go too high, then may have some nephrotoxicity
- Large daptomycin trial (see below) – vanc troughs of 15-20, but still had similar rates of
  nephrotoxicity compared to β-lactams

C. Daptomycin
1. Background
- Spectrum – gram positives only
- Initially approved in 2003 for SSTI - Dose for SSTI – 4mg/kg qday
- Later, approved for bacteremia and right sided endocarditis - Dose – 6 mg/kg
- Also active against VRE - Dose – 8-10 mg/kg
- Failed pneumonia trial vs ceftriaxone - Surfactant likely binds daptomycin - do not use
- As Vanc MIC rises, so will Dapto’s MIC frequently (due to thick cell wall)
- Side effects - elevated CK - Consider stopping statins
- Time-Kill curves suggest that Daptomycin is one of the most active agents against MRSA in vitro

- Open-label, Randomized Trial from 2002-2005.
- 235 patients
  - Inclusion criteria – Age >18, at least one positive blood culture for Staph aureus
  - Exclusion criteria – CrCl<30, osteomyelitis, polymicrobial bacteremia, pneumonia.
- Two arms – 14-42 days
  - Daptomycin 6mg/kg
  - Usual therapy
    - MSSA – oxacillin plus gentamicin (4 days)
    - MRSA – vancomycin plus gentamicin (4 days)
      - Vancomycin was adjusted based on levels
- All patients underwent TEE within five days of starting antibiotics
- Cardiologist was blinded to study meds
- Patients were followed until 42 days after the end of therapy
- Failure
  - Clinical (ongoing symptoms) or Death
  - Microbiological (persistent bacteremia or relapse)
Receipt of effective nonstudy antibiotics
- Failure to obtain final blood culture
- Discontinuation of study medication
- Outcomes after 42 days of therapy
  - Overall success rate
    - Daptomycin 44.2%, STD 41.7% (Oxacillin 45%, Vanc 38%)
    - Vs MSSA – Dapto 44%, STD 48% (p=0.74)
    - Vs MRSA – Dapto 44%, STD 32% (p=0.28)
- Success was similar according to diagnosis (bacteremia, endocarditis, etc)
- Reasons for Failure
  - Daptomycin – microbiologic failure (15.8% vs 9.6% (p=0.17))
    - 7 of 23 Daptomycin failures resulted in rising S aureus MICs
  - Standard Therapy - adverse events (14.8% vs 6.7% (p=0.06))
    - Likely due to 4 days of Gentamicin
- Safety
  - Daptomycin - Elevated CK
    - 25% had elevated CK levels
    - 6.7% were “clinically significant”
    - 2.5% withdrew due to elevated CK
  - Standard therapy
    - Significant renal impairment – 18% vs 6.7%
      - (Ox – 18%, Vanc 20%)
    - Worsening creatinine clearance 47% vs 20%
      - Likely due to short course of gentamicin
- Conclusions
  - Daptomycin is noninferior to standard care (Oxacillin + Gent OR Vanc + Gent) for *Staph aureus* bacteremia and right sided endocarditis.
  - When Daptomycin fails, it is frequently due to microbiologic failure and some resistance. Need drainage!

D. Telavancin

1. Background
   - Semisynthetic derivative of Vancomycin
   - FDA approved on 9/11/2010 for cSSTI
   - Rapidly bactericidal in vitro – Theoretically, should be similar (or better) than vanc
   - Two mechanisms of action
     - Inhibits cell wall synthesis (similar to vanc)
     - Disrupts cell membrane & alters permeability
   - Complicated Skin & Soft Tissue Infections - Non inferior to vancomcyin
   - Nosocomial Pneumonia
     - Higher cure rates w/ monomicrobial S aureus infections w/ vancomycin MIC >= 1 (87% vs 74% -- p=0.03)
     - Overall cure and MRSA cure rates were similar
     - FDA needs more studies for nosocomial pneumonia
     - Unpublished – data on file w/ company
   - No bacteremia trials, No FDA indication for bacteremia
   - Safety
     - May be teratogenic
     - More nephrotoxicity than Vanc
- Red Man Syndrome
- QTc prolongation
  - Interference w/ coagulation tests (Does not interfere w/ coagulation
  - Draw INR, PTT prior to next dose

E. Ceftaroline
1. Fifth Generation Cephalosporin - +MRSA activity
   - Antimicrobial spectrum is similar to cefotaxime + MRSA (misses pseudomonas)
   - FDA approved for cSSTI and Pneumonia (including MRSA infections)
   - First β-lactam with activity vs MRSA
     - May be superior to vanc, if you extrapolate oxacillin/cefazolin data
     - However, ceftaroline has not he demonstrated to be superior to vanc yet
2. Bacteremia studies - minimal
     - Retrospective, salvage therapy in six patients with MRSA bacteremia
     - All six patients rapidly cleared bacteremia on ceftaroline
3. Not enough data to support routine use for MRSA bacteremia --- could be considered for salvage therapy
   - Ceftaroline was not FDA approved when the ISDA MRSA guidelines came out - thus, not listed.

F. Linezolid
1. Background
   - Class – oxazolidinone
   - Bacteriostatic vs S aureus
   - Near 100% bioavailability (IV=PO)
   - FDA approved in 2000, not approved for bacteremia
   - Spectrum – gram positives only (Staph aureus, enterococcus, strep pneumoniae, streptococci)
   - Side effects
     - Bone Marrow suppression
       - Especially thrombocytopenia
       - Usually starts after 14 days
       - Usually reversible
     - Neuropathy (usually after 28 days) – Irreversible - Peripheral, Optic
     - Serotonin Syndrome - Usually when combined w/ SSRIs
   - Retrospective study of persistent Staph aureus bacteremia (≥ 7 days) using salvage therapy
   - Showed a great advantage for Linezolid (microbiologic response, mortality), but many flaws
   - Vancomycin arm – more endocarditis, brain complications, and low vanc troughs

G. Quinupristin-Dalfopristin (Synercid)
1. Background
   - Two streptogramins that bind bacterial ribosome, Approved in 1990’s
   - If clindamycin is susceptible, then this drug is bactericidal. In vitro – not too shabby
   - Very expensive ($427 per day at UH)
   - Many adverse effects – especially myalgias and thrombophlebitis ; need central line
   - Never shown to be superior to vanc

H. Tigecycline
1. Background
   - Class – Glycylcycline (tetracycline derivative)
   - Broad spectrum antibiotic -- Gm+, Gm-, anaerobes, No pseudomonas
   - Theoretical concerns - Low serum levels, bacteriostatic
   - Not easily tolerated – approx 30% of patients will have nausea and vomiting
- FDA Drug Safety Communication 2010 - Increased risk of death w/ tigecycline compared to other antibiotics used to treat similar infections.

   - Retrospective, subgroup analysis of 8 studies – Bacteremia patients
     - Higher rates of **persistent bacteremia** (>24 hrs) vs comparator antibiotic (9.8% vs 1.3%).

I. Trimethoprim/Sulfamethoxazole
   1. Background
      - Very low rate of resistance - <2%
      - **Need high dose for Staph aureus – 2 tabs BID**
      - Excellent oral bioavailability, Bactericidal *in vitro*, best activity vs MRSA out of all oral abx
      - Adverse reactions in 6-8% of pts

   - Prospective, randomized, double-blind in IVDU
   - 1982-1985, Detroit, 101 pts
   - Doses
     - T/S - 320mg (TMP component) BID (equivalent to 2 DS PO BID)
     - Vanc – 1g IV BID - Vanc levels were adjusted by unblinded pharmacist
     - 47% w/ MRSA, 65% w/ bacteremia, 25% w/ R sided endocarditis
     - Cure rate – Vanc 98%, T/S 86% (p 0.014)
       - ALL treatment failures were in MSSA group
       - R endocarditis – Vanc 92% (7 of 11 pts), T/S 64% (9/12) – p 0.095
       - Non-endocarditis – Vanc 100%, T/S 94% - p 0.06
     - T/S group had +BCx for 2 more days than vanc group (P 0.10)
     - No organisms developed resistance on therapy
   - Conclusion
     – it’s never good when you lose to vancomycin.
     - However, T/S is the most active oral agent for MRSA and has a role in lesser infections

III. Adjuncts (used with β-lactam or vancomycin)
   1. Gentamicin
      A. Background
         - Survey of ID physicians in 2006 showed that many favor the addition of gentamicin to achieve earlier clearance of blood cultures.
         - In vitro, the addition of gentamicin to either antistaphylococcal penicillins or vancomycin resulted in a more rapid bactericidal activity.
      B. Sande MA, Courtney KB. J Lab Clin Med 1976; 88:118-24
         - Patients with predominantly left-sided, MSSA endocarditis.
         - Patients were given 6 wks of nafcillin with or without low dose gentamicin for the first two wks.
           - Significant renal impairment in gent arm
           - Bacteremia was cleared one day sooner with gent
           - Morbidity and mortality were not affected
         - Conclusion – Give gentamicin for the first 3-5 days only --- this has now fallen out of favor
      C. Cosgrove, Sara et al. Clin Infec Dis. 2009;48; 713-721. - Review of large Daptomycin trial (see above)
         - Median Gentamicin exposure - 4 days, 2-3mg/kg per day
         - Adverse renal event
           - Daptomycin6. 7%
           - Standard therapy – 18%
- Vancomycin 19%
- Nafcillin 17%
- Higher in diabetics and age > 65
- Clinically sig decrease in CrCl – 22% vs 8% (p .005)
- Sustained 50% decrease in CrCl – 6% vs 0% (p .02)
- Sustained 25% decrease in CrCl – 21% vs 9% (p .02)
- No patients required long-term hemodialysis

Conclusion
- Low-dose gentamicin appears to cause significant renal dysfunction.
- Gentamicin synergy should not be used on a routine basis

2. Rifampin
   A. Background
   - Highly active against most Staph aureus strains (97%)
   - Excellent tissue penetration, active in biofilms
   - Resistance can develop rapidly – never use as monotherapy
     - One step mutation in target site
     - Resistance can even develop w/ combination therapy (21% in one study)
   - Many drug interactions, elevated LFTs
      - Cohort study, 42 patients with endocarditis
      - (Vancomycin) VS (Vancomycin + Rifampin – 600mg once a day)
      - Clinical outcome was identical
      - Duration of bacteremia was two days longer in the rifampin arm (9 days vs 7 days)

3. Levofoxacin
   - Never use quinolones as monotherapy for serious Staph aureus infections – resistance can develop
      - Prospective, randomized trial from 2000-2002 in Finland, 381 patients
      - No change in mortality, time to defervescence, # of complications, or decrease in CRP.

   A. Workup
      - All patients with bacteremia need echocardiogram (TEE preferred over TTE)
      - Serial blood cultures until negative
      - Assess for source of infection and possible metastatic infection sites
   B. MRSA Bacteremia &/or Endocarditis
      - Recommended - vancomycin or daptomycin
      - Not recommended for routine bacteremia - addition of gentamicin or rifampin
      - Persistent bacteremia on therapy
        - Daptomycin (10 mg/kg) in combination with either gentamicin, rifampin, linezolid, or a β-lactam.
        - Search for source of infection and debride as needed
        - Ceftaroline was approved after these guidelines came out - utility in salvage therapy?
   C. Duration
      - Uncomplicated bacteremia - 2 weeks
        - Definition - no endocarditis, no implanted prosthesis, negative blood cultures at 2-4 days, no metastatic infections, defervescence within 72 hours of starting therapy
      - Complicated bacteremia - 4-6 weeks
        - Definition - NOT uncomplicated as above