1. What is MRSA?

• Methicillin-resistant *Staphylococcus aureus* (MRSA)
  
  – Background
    (Enright et al. Proc Natl Acad Sci USA 2002;99:7687.)
    
    • In 1959, methicillin introduced
    • In 1961, MRSA first reported; hospital-associated
    • In mid-1990s, infections in healthy individuals in community; no healthcare risk factors
    • Presently, world-wide
    – In 2005, 95,000 cases invasive MRSA in US
      (Kleven et al. JAMA 2007;298:1763.)

2. What is the difference between HA-MRSA and CA-MRSA?

3. What antibiotics are effective against MRSA?

4. How do we treat common MRSA infections?

5. Is vancomycin still a good drug for MRSA?

6. What are some of the clinical controversies in MRSA treatment?
1. What is MRSA?

- **Mechanism**
  (Oliveira et al. Microb Drug Resist 2001;7:349.)
  - Resistance mediated by PBP-2a
  - Encoded by mecA gene on mobile staphylococcal chromosome cassette (SCCmec)
  - 6 major clones SCCmec I-VI
  - Pulsed-field gel electrophoresis (PFGE) pattern

1. What is MRSA?

- **Colonization**
  (Sanford et al. CID 1994;19:1123.)
  - Anterior nares, skin (hands, axillae, perineum), and open wounds
    - Increases risk of infection
    - Durability from few days to several years

- **Transmission**
  (Davis et al. CID 2004;39:776.)
  - Contaminated hand or environmental surfaces
    - HA-MRSA hands of healthcare workers
    - CA-MRSA direct contact with colonized or infected individuals

1. What is MRSA?

- **Infections**
  - Skin and soft tissue infections (SSTI)
  - Bacteremia and infective endocarditis (IE)
  - Pneumonia
  - Bone and joint infections
  - Central nervous system (CNS) infections

2. What is the difference between HA-MRSA and CA-MRSA?

- **HA-MRSA vs. CA-MRSA**
  - Differences in clinical and molecular epidemiology
    (Klevens et al. JAMA 2007;298:1763.)
    | Onset          | HA-MRSA | CA-MRSA                |
    |----------------|---------|------------------------|
    | HA-MRSA       | >48 h hospitalization; ≤12 mo healthcare exposure | No healthcare exposure |

- **Risk Factors**
  - Prolonged hospitalization, antibiotic use, ICU, HD, colonization, IVDU, HIV, MSM
  - Severe, invasive: SSTI (35%), bacteremia, pneumonia

- **Outcomes**
  (Cosgrove et al. Infect Control Hosp Epidemiol 2005;26:166.)
  - Higher mortality
  - Higher co-morbidities
    (Blot et al. Arch Intern Med 2002;162:2229.)
    - Acute renal failure, hemodynamic instability
    - Longer hospital stay
    - Higher healthcare costs

2. What is the difference between HA-MRSA and CA-MRSA?

- **HA-MRSA vs. CA-MRSA**
  - Molecular epidemiology
    (Naimi et al. JAMA 2003;289:2976.)
    | HA-MRSA | CA-MRSA |
    |---------|---------|
    | Resistant gene (SCCmec) | Type II (II, III) | Type IV or V |
    | Strain type (PFGE) | USA100 or 200 | USA 300 or 400 |
    | Panton-Valentine Leukocidin (cytoxins) | 5% | Frequently present (almost 100%) |

- **Panton-Valentine Leukocidin**
  (John et al. J Infect Dis 2008;197:175.)
  - Cytotoxin leukocyte destruction and tissue necrosis; virulence
  - Encoded by lukSF-FV usually on SCCmec IV and V
  - Epidemiologic association with SSTI

- **Outcomes**
  - Higher mortality
  - Higher co-morbidities
  - Acute renal failure, hemodynamic instability
  - Longer hospital stay
  - Higher healthcare costs
2. What is the difference between HA-MRSA and CA-MRSA?

- **HA-MRSA vs. CA-MRSA**
  - Evolving epidemiology
    - HA-MRSA and CA-MRSA classifications
      (Miller et al. CID 2007;44:471.)
      - No longer clearly defined
    - CA-MRSA incidence surpass HA-MRSA
      (Liu et al. CID 2008;46:1637.)
    - CA-MRSA may replace hospital-acquired strains
      (Popovich et al. CID 2008;46:787.)

3. What antibiotics are effective against MRSA?

- **HA-MRSA**
  - Vancomycin
  - Co-trimoxazole
  - Rifampin*
  - Fusidic acid* (SAP)

- **CA-MRSA**
  - Vancomycin
  - Co-trimoxazole
  - Tetracyclines
  - Clindamycin?
  - Rifampin*
  - Fusidic acid* (SAP)

- **Newer agents**
  - Daptomycin
  - Linezolid
  - Tigecycline

- **Traditional agents**
  - Clindamycin
  - Co-trimoxazole (TMP-SMX)
  - Rifampin
  - Tetracycline
  - Vancomycin

- **Daptomycin** (Liu et al. CID 2011;52:1)
  - **Class:** Cyclic lipopeptide
  - **MOA:** Disrupts cell membrane via calcium-dependent
    binding; bactericidal
  - **Activity:** Staph (MRSA), Strep, Enterococcus (VRE)
  - **Ind:** Bacteremia + right-sided IE; complicated SSTI
  - **PK:** 90% albumin; soft tissue; t1/2 8 h
  - **Elim:** Renal; 80% unchanged
  - **Interact:** HMG-CoA reductase inhibitors may increase CK
  - **Dose:** SSTI - 4 mg/kg IV Daily; Bacteremia - 6 mg/kg IV Daily
    (CrCl <30 mL/min – Q48H)
  - **ADR:** GI, CK elevation, myopathy, eosinophilic pneumonia

- **Linezolid** (Liu et al. CID 2011;52:1)
  - **Class:** Oxazolidinone
  - **MOA:** Inhibits protein synthesis at 50S ribosomal subunit;
    bacteriostatic
  - **Activity:** Staph (MRSA), Strep, Enterococcus (VRE)
  - **Ind:** Nosocomial pneumonia, complicated SSTI
  - **PK:** F100%; 30% protein; CSF/lung/soft tissue/bone; t1/2 6 h
  - **Elim:** Hepatic oxidative metabolism
  - **Interact:** Weak MAOI; avoid SSRI
  - **Dose:** 600 mg PO/IV Q12H
  - **ADR:** GI, myelosuppression, optic/peripheral, neuropathies,
    lactic acidosis

- **Telavancin**
  - **Class:** Peptidoglycan
  - **MOA:** Inhibits bacterial peptidoglycan synthesis
    (Dutkowski et al. Antimicrob Agents Chemother 2008;52:6708.)
  - **Ind:** SSTI, MRSA bacteremia
  - **PK:** 50% albumin; soft tissue; t1/2 3 h
  - **Elim:** Renal, biliary, hepatic metabolism
  - **Interact:** Avoid MAOIs
  - **Dose:** 10 mg/kg IV Q24H
  - **ADR:** GI, rash, allergic reaction, anaphylaxis
3. What antibiotics are effective against MRSA?

- **Linezolid**
  - **Monitor:**
    - CBC weekly (if >7-10 d)
  - **Clinical Highlights:**
    - Always use PO unless not absorb or tolerate GI route
    - Drug interactions with SSRIs
    - Monitor CBC weekly with prolonged use
    - Pharmacare limited coverage drug
      - VRE
      - MRSA unresponsive or intolerant to vancomycin

- **Tigecycline** (Liu et al. CID 2011;52:1)
  - **Class:** Glycylcyline
  - **MOA:** Inhibits protein synthesis at 30S ribosomal subunit; bacteriostatic
  - **Activity:** Staph (MRSA), Strep, Enterococcus (VRE), Gram-negative (except Proteus, Pseudomonas), anaerobes
  - **Ind:** Intraabdominal, community-acquired pneumonia, complicated SSTI
  - **PK:** 70% protein; lung/biliary tract/soft tissue
  - **Elim:** Glucuronidation; biliary excretion; 30% renal
  - **Dose:** 100 mg IV load, 50 mg IV Q12H (Child-Pugh C - ½ dose)
  - **ADR:** N&V

- **Clindamycin** (Liu et al. CID 2011;52:1)
  - **Clinical Highlights:**
    - CA-MRSA 60-70% susceptible
    - Not approved for MRSA infections; bacteriostatic
    - Good bioavailability
    - Use in SSTI, bone and joint infections, and pneumonia
  - **Dose**
    - SSTI – 300-450 mg PO TID
    - Severe - 600 mg PO/IV Q8H
  - **Adverse effects**
    - GI upset, diarrhea

- **Co-trimoxazole (TMP-SMX)** (Liu et al. CID 2011;52:1)
  - **Clinical Highlights:**
    - CA-MRSA 95-100% susceptible
    - Not approved for staphylococcal infections
    - Few studies in MSSA bone and joint infections
    - Possible benefit in invasive staphylococcal infections
  - **Dose**
    - SSTI – 2DS PO BID; severe – 3.5-5 mg/kg/dose PO/IV Q8-12H
  - **Adverse effects**
    - Increased risk of hyperkalemia in renal insufficiency
    - Bone marrow suppression

- **Rifampin** (Liu et al. CID 2011;52:1)
  - **Clinical Highlights:**
    - Adjunct therapy for staphylococcal prosthetic infections
    - Penetrate biofilms
    - Lack of clinical studies in MRSA
    - Variable doses
      - 600 mg daily
      - 450 mg BID
      - 300 TID
    - Avoid monotherapy; rapid resistance
    - Drug interactions
      - Monitor baseline LFTs
3. What antibiotics are effective against MRSA?

- **Tetracyclines** *(Liu et al. CID 2011;52:1)*
  - **Clinical Highlights**:
    - CA-MRSA SSTI
    - Data lacking in invasive infections
    - **Dose**
      - Doxycycline 100 mg PO BID
      - Minocycline 200 mg PO x 1, then 100 mg PO BID
    - Avoid in <8 yrs; teeth staining and reduced bone growth
    - Teratogenic

- **Vancomycin** *(Liu et al. CID 2011;52:1)*
  - **Clinical Highlights**:
    - Main empiric parenteral regimen for invasive MRSA
    - Pre-level target 15-20 mg/L
    - Efficacy questioned
      - Slow bactericidal activity, resistance, and possible MIC creep
    - Kills slower than β-lactams *in vitro* with higher inocula
    - Inferior in MSSA bacteremia and IE
    - Limited penetration in bone, lung epithelial lining, and CSF
    - Consider alternative in adverse effects and reduced susceptibilities

4. How do we treat common MRSA infections?

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

- **IDSA Guidelines** *(Liu et al. CID 2011;52:1)*
  - Expert panel of adult and pediatric ID physicians and pharmacy
  - “Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances.”

<table>
<thead>
<tr>
<th>Category/grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>Good evidence to support a recommendation for or against use.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate evidence to support a recommendation for or against use.</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence to support a recommendation.</td>
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<tr>
<td>Quality of evidence</td>
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<tr>
<td>I</td>
<td>Evidence from &gt;1 properly randomized, controlled trial</td>
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<tr>
<td>II</td>
<td>Evidence from nonrandomized clinical trials, without randomization; from cohort or uncontrolled analytic studies with varying results from uncontrolled experiments</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
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4. How do we treat common MRSA infections?

- **IDSA Guidelines** *(Liu et al. CID 2011;52:1)*
  1. Skin and soft tissue infections (SSTI)
  2. Bacteremia and infective endocarditis (IE)
  3. Pneumonia
  4. Bone and joint infections
  5. Central nervous system (CNS) infections

- **Skin and Soft Tissue Infections (SSTI)**
  - CA-MRSA associated with increase SSTI
  - Cellulitis
  - Cutaneous abscesses
  - Complicated SSTI (cSSTI)
  - Recurrence
Skin and Soft Tissue Infections (SSTI)

- Cellulitis (Liu et al. CID 2011;52:1)
  - Epidemiology
    - Common in the elderly
    - Factors:
      - Poor hygiene
      - Diabetes
      - Obesity
      - Immunosuppression
  - Pathogens:
    - Staphylococci
    - Streptococci
    - Other bacteria
  - Clinical presentation:
    - Painful, red, swollen, tender area
  - Complications:
    - Necrosis
    - Gas gangrene
    - Septic shock
  - Diagnosis:
    - History
    - Physical examination
    - Laboratory tests
  - Treatment:
    - Antibiotics
    - Surgical intervention
    - Supportive care

Skin and Soft Tissue Infections (SSTI)

- Cutaneous abscesses (Liu et al. CID 2011;52:1)
  - Conditions:
    - Tissue necrosis
    - Purulent collection
  - Clinical presentation:
    - Painful, tender swelling
    - Erythema
    - Fever
    - Leukocytosis
  - Diagnosis:
    - Physical examination
    - Imaging studies
    - Laboratory tests
  - Treatment:
    - Incision and drainage
    - Antibiotics
    - Parenteral antibiotics

Clinical Controversy - I&D vs. I&D and antibiotics

- What is the evidence for I&D alone vs. I&D and antibiotics for treating MRSA cutaneous abscess?
  - Observational studies high cure rates 85-90% whether or not active antibiotic used
    - Moran et al. NEJM 2006;355:666.
    - Fridkin et al. NEJM 2005;352:1436.

Clinical Controversy - I&D vs. I&D and antibiotics

- Randomized controlled trial
  - Design: RDB PC cutaneous abscesses
  - Objective: Compare Cephalexin vs. Placebo (P) after I&D
  - Interventions: I&D, then Cephalexin 500 mg PO QD x 7 d vs. P
  - Endpoint: Clinical cure or failure at 7 d
  - Results: N=105; MRSA 89%
    - Cephalexin 94% (95%CI 0.7-0.9) in 62
    - P 97% (95%CI 0.82-0.95) in 44
    - Difference in log posterior odds, 0.0009; 95%CI -0.0481 to 0.0472; p<0.05
  - Conclusion: Antibiotics may be unnecessary after I&D uncomplicated CA-MRSA SSTI abscesses

Clinical Controversy - I&D vs. I&D and antibiotics

- Randomized controlled trial
  - Design: MC R DB PC N=188 uncomplicated abscesses
  - Objective: Compare TMP-SMX x 7 d vs. Placebo (P)
  - Interventions: I&D, then TMP-SMX x 7 d vs. Placebo (P)
  - Endpoint: Clinical failure at 7 d; reduction in lesions at 30 d
  - Results: Clinical failure
    - TMP-SMX (18.0% vs. P 27.19%; p=2)
    - Difference 9%, 95%CI -3% to 21%, p<0.12
    - New lesions (18.0% vs. P)
    - TMP-SMX (18.0% vs. P 14.5%; p=0.69)
    - Difference 3.5%, 95%CI -7% to 14%, p=0.12
  - Conclusion: After I&D, TMP-SMX not reduce treatment failure but may decrease subsequent lesions
Clinical Controversy - I&D vs. I&D and antibiotics

- What is the evidence for I&D alone vs. I&D and antibiotics for treating MRSA cutaneous abscess?

  - **Answer**
    - For uncomplicated CA-MRSA SSTI cutaneous abscesses
      - I&D alone may be sufficient
      - Antibiotics may not be necessary
    - Ongoing studies

Skin and Soft Tissue Infections (SSTI)

- Hospitalized patient with cSSTI (Liu et al. CID 2011;52:1)
  - Systemic and rapid progression
  - Deep, surgical/traumatic, major abscess, infected ulcer/burns
  - Treatment
    - I&D
    - Broad-spectrum antibiotics (consider MRSA) pending cultures
      - Vancomycin (A-I)
      - Linezolid 600 mg PO/IV Q12H (A-I)
      - Daptomycin 4 mg/kg IV daily (A-I)
      - Clindamycin 600 mg PO/IV Q8H (if susceptible) (A-III)
      - Duration: 7-14 d
    - β-lactam (e.g. cefazolin) for non-purulent (A-II)

Clinical Controversy - Addition of rifampin in SSTI

- What is the evidence for adding rifampin in MRSA SSTI?

  - Role of rifampin as adjunct therapy for SSTI
    - Not recommended (A-III) (Liu et al. CID 2011;52:1)
    - Not used as monotherapy

- No data support rifampin for SSTI (Perlroth et al. Arch Intern Med 2008;168:805.)
  - In animal models, decrease S. aureus CFU with adjunctive rifampin vs. antibiotic monotherapy, but others no activity
  - Methodology varied; unknown clinical relevance
  - No clinical trials for safety/efficacy of adjunctive rifampin for SSTI
    - Ceiling effect; cure rates >80-90% not achievable
    - Rifampin unlikely improve efficacy of other antibiotic
    - Drug interactions and adverse effects

Clinical Controversy - Addition of rifampin in SSTI

- What is the evidence for adding rifampin in MRSA SSTI?

  - **Answer**
    - No data to support adjunctive rifampin in MRSA SSTI
    - Additional data to define role

Skin and Soft Tissue Infections (SSTI)

- Recurrent MRSA SSTI (Liu et al. CID 2011;52:1)
  - >2 SSTI episodes different sites over 6 mo
  - Unclear pathogenesis
    - Pathogen, colonization, behaviour, environment
  - Few studies to guide management
  - Multi-faceted approach
    - Personal and environmental hygiene
    - Decolonization
Skin and Soft Tissue Infections (SSTI)

- Recurrent MRSA SSTI (Liu et al. CID 2011;52:1)
  - Personal hygiene and wound care
    - Cover draining wounds (A-III)
    - Maintain good personal hygiene (A-III)
    - Avoid reusing or sharing personal items (A-III)
    - Clean high-touch surfaces with commercial cleaners (C-III)

- Mupirocin Qmonthly reduces MSSA nasal colonization
- Mupirocin prevent recurrent MSSA colonization and SSTI

Nasal cultures Qmonthly; SSTI

- Mupirocin x 5 d, then 1) Mupirocin x 5 d/mo x 1 yr (N=17)
  2) Placebo (P) x 1 yr (N=17)

(Recurrence MRSA SSTI (Liu et al. CID 2011;52:1)

Clinical Controversy - Decolonization

- What is the evidence for decolonization in recurrent SSTI?

  - No data for recurrence of MRSA SSTI
    - Unknown regimen, frequency, duration
    - Unknown selection of resistance

Clinical Controversy - Decolonization

- Mupirocin
  - Controlled trial
  - Objective: Mupirocin prevent recurrent MSSA colonization and SSTI
  - Design: P C
  - Intervention: Mupirocin x 5 d, then 1) Mupirocin x 5 d/mo x 1 yr (N=17)
  2) Placebo (P) x 1 yr (N=17)
  - Endpoint: Nasal cultures Qmonthly; SSTI
  - Results: Nasal cultures (+): 22 Mupirocin vs. 83 P (p<0.001)
    SSTI: 26 Mupirocin vs. 62 P (p<0.002)
    Nasal culture (-) over 12 mo: 8/17 Mupirocin vs. 2/17 P
  - Conclusion: Mupirocin Qmonthly reduces MSSA nasal colonization and SSTI

Clinical Controversy - Decolonization

- Mupirocin
  - Randomized controlled trial
  - Objective: Mupirocin prevent SSTI in CA-MRSA colonized soldiers and new colonization/infection in training group
  - Design: P R DB PC (N=3477; 14 training groups); Jan to Dec '05
  - Intervention: Each training group randomized to Mupirocin vs. Placebo
  - Endpoint: Screen Q6-10 wk; SSTI monitor x 16 wk
  - Results: 134 (3.9%) CA-MRSA colonized
  - 789 (7.3%) MSSA colonized
  - 41 (1.4%) S. aureus infection
  - C/S (100%; 0/36/1.25; 33.3%) P developed SSTI
  - SSTI in non-colonized
    - SNAP (6.9%; SNAP 8, 2.3-52.9%) mupirocin vs. SNAP (4.1%; SNAP 2.7-65.6%) P developed SSTI
### Clinical Controversy - Decolonization

**Mupirocin**
- **Randomized controlled trial**
- **Results**
  - 3,080 (26%) second sampling and follow-up
  - New CA-MRSA colonization:
    - 254, 607 (1.4%); 695, 05% to 4.9%
  - Mupirocin vs. bleach
    - 264, 659 (1.4%); 95% CI, 0.75% to 2.3%
  - **Conclusion**
    - CA-MRSA eradication in colonized participants not decreased SSTI in mupirocin-treated individuals or those within training groups
    - CA-MRSA eradication not prevent new colonization within study group

### Clinical Controversy - Decolonization

**Topical antiseptics**
- **Chlorhexidine and hexachlorophene extrapolated from community outbreak** (Liu et al. *CID* 2011;52:1)
  - Used with other interventions
  - May prevent transmission and infection
- **Chlorhexidine wipes** (Whitman TJ et al. *Infect Control Hosp Epidemiol* 2010;12:1207.)
  - No effect on SSTI

### Clinical Controversy - Decolonization

**Oral antimicrobials**
- No clinical trials oral antimicrobials prevention of recurrence of CA-MRSA SSTI
- **Systematic review of controlled trials** (Falgas et al. *Am J Infect Control* 2007;35:106.)
  - Rifampin + antibiotic vs. antibiotic monotherapy
  - Eradicate *S. aureus* carriage
  - No studies evaluated infection rates
  - Resistance and adverse effects

### Clinical Controversy - Decolonization

**MRSA resistance in community settings**
- Colonization of other sites (axilla, groin, rectum) may involved in recurrence

### Clinical Controversy - Decolonization

**What is the evidence for decolonization in recurrent SSTI?**

- **Answer**
  - **Mupirocin**
    - Inconclusive
    - Resistance?
    - Decolonization of other sites?
  - **Chlorhexidine and bleach**
    - Combine with other agents?
  - **Rifampin**
    - No evidence
    - No definitive regimen
4. How do we treat common MRSA infections?

- MRSA bacteremia and infective endocarditis (IE)
  - Serious infections with high morbidity and mortality
    (Miro et al. CID 2005;41:507.)
  - 30% mortality
  - Identify source and extent
    - TTE/TEE
    - Removal of intravascular and prosthetic devices
  
- Bacteremia and IE
- Persistent bacteremia

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**Bacteremia and Infective Endocarditis (IE)**

**MRSA bacteremia and IE** (Liu et al. CID 2011;52:1)

- Uncomplicated vs. complicated

<table>
<thead>
<tr>
<th>Positive blood culture:</th>
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<tbody>
<tr>
<td>No endocarditis</td>
</tr>
<tr>
<td>No implanted prosthesis</td>
</tr>
<tr>
<td>Negative cultures obtained 2-4 d after</td>
</tr>
<tr>
<td>Defervescence ≤72 h</td>
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<tr>
<td>No metastases</td>
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**Treatment**

- For bacteremia or native valve IE
  - Addition of gentamicin not recommended (A-II)
  - Addition of rifampin to vancomycin not recommended (A-I)

- For prosthetic valve IE
  - Vancomycin + rifampin 300 mg PO Q8H x 6 wks
    + gentamicin 1 mg/kg/dose IV Q8H x 2 wks (B-III)

- Valve replacement
  - >10 mm vegetation; ≥1 embolic event 1st 2 wks; valvular damage; heart failure; abscess; heart block; persistent fevers; bacteremia (A-II)

---

**Monitor**

- Blood cultures 2-4 d after and as needed (A-II)
- Document clearance

---

**Clinical Controversy—Combination therapy in IE**

- What is the evidence for combination therapy in MRSA endocarditis?
  - Addition of gentamicin and/or rifampin synergy
    - Shorten bacteremia?
    - Improve outcome?
**Clinical Controversy - Combination therapy in IE**

- **Addition of gentamicin**
  - Vancomycin with low-dose gentamicin for MRSA bacteremia and native IE
    - Increase in nephrotoxicity
      (Fowler et al. NEJM 2006;355:653)
      - Vancomycin + gentamicin 20.4% (N=46) vs. daptomycin 6.7% (N=113)

- **Addition of rifampin**

**Clinical Controversy - Combination therapy in IE**

- **Addition of rifampin**
  - Similar bacteremia duration to monotherapy
    - Vancomycin + rifampin median 9 d (N=22) vs. Vancomycin median 7 d (N=20)

- **Outcome in S. aureus native IE not improved**

**Clinical Controversy - Combination therapy in IE**

- **Retrospective study**

- **Objective:**
  - Care for MRSE prosthetic valve IE

- **Intervention:**
  - Rifampin 900-1200 mg d with Vancomycin or β-lactam x 6 wks; Aminoglycoside 8 pts x 14 d.

- **Endpoint:**
  - Cure

- **Results:**
  - 13/15 (87%) Rifampin and Vancomycin
  - 3/6 (50%) Rifampin plus β-lactam (p= 0.026)

- **Conclusion:**
  - Rifampin + Vancomycin bactericidal activity
  - Rifampin-resistance in 2 pts persistent infection

**Clinical Controversy - Combination therapy in IE**

- **What is the evidence for combination therapy in MRSA endocarditis?**

- **Answer**
  - Evidence for combination therapy lacking

**Bacteremia and Infective Endocarditis (IE)**

- **Persistent MRSA bacteremia**
  (Liu et al. CID 2011;52:1)
  - Removal of source (A-III)
  - Daptomycin 10 mg/kg/d in combination with another agent (B-III)
  - Check MIC if persistent for 7 d
  - If reduced susceptibility (C-III)
    - TMP-SMX 5 mg/kg IV Q12H
    - Linezolid 600 mg PO/IV Q12H
Pneumonia

• MRSA pneumonia (Liu et al. CID 2011;52:1)
  – Community-acquired pneumonia (CAP) not common; severe
  – May be preceded by influenza-like illness
  – MRSA pneumonia be considered (A-III)
    ○ Severe CAP requiring hospitalization
    ○ Require ICU admission
    ○ Necrotizing or cavitary infiltrates
    ○ Empyema
  ➢ Pneumonia
  ➢ Empyema

Clinical Controversy - Linezolid vs. vancomycin

• Is linezolid better than vancomycin for MRSA pneumonia?
  – Vancomycin limited penetration to pulmonary tissue and epithelial lining fluid
  – Retrospective studies suggest linezolid may be superior to vancomycin (Wunderink et al. Chest 2003;124:1789.)
  – No difference in microbiological response rates (Wunderink et al. Chest 2008;134:1200.)

Clinical Controversy - Linezolid vs. vancomycin

• Results: 8 trials; 4 DB; 4 OL; N=1041

  - Clinical success for MRSA
    | Study or Subgroup | Success / Total | Risk Ratio (95% CI) | Random Effect, Risk ratio (95% CI) |
    |-------------------|----------------|---------------------|-----------------------------------|
    | Linezolid         | Glycopeptide   |                     |                                   |
    | Stevens et al. 2002 | 12 / 23       | 14 / 35             | 0.97 (0.57, 1.64)                |
    | Wunderink et al. 2003* | 22 / 62     | 22 / 62             | 1.06 (0.92, 1.23)                |
    | Goycochea et al. 2004 | 5 / 17      | 9 / 16              | 0.83 (0.20, 3.73)                |
    | Kohne et al., 2007 | 17 / 34       | 6 / 19              | 1.20 (0.43, 3.74)                |
    | Wunderink et al., 2008 | 10 / 23     | 9 / 19              | 1.19 (0.84, 1.69)                |
    | Total Clinical Success, MRSA | 81 / 159 | 80 / 142            | 1.23 (0.79, 1.85)                |
    | I2 (heterogeneity): 71% p=0.00 |             |                     |                                   |

  - RCT clinical success MRSA vs. non-MRSA pneumonia
    ➢ Linezolid 1.23; 95%CI 0.97-1.67 vs.
      Glycopeptide 0.83; 95% CI, 0.20-3.73; p=0.07

Clinical Controversy - Linezolid vs. vancomycin

• Conclusions:
  – RCTs do not support superiority of linezolid over glycopeptide nosocomial pneumonia
  – Empiric therapy based on local availability, resistance patterns, preferred routes, and cost
  – Clinical and microbiological outcomes, and adverse effects not significantly different

  - Limitations:
    – Small sample sizes amongst studies
    – Vancomycin dosing

Clinical Controversy - Linezolid vs. vancomycin

• Meta-analysis of randomized controlled trials
  • Design: Systematic review and meta-analysis of P RCT
  • Objective: Efficacy and safety of linezolid vs. glycopeptide for nosocomial pneumonia
  • Data Source: PubMed, MEDLINE, Cochrane, Trials; aged 12 yr
  • Intervention: Linezolid 600 mg PO/IV Q12H vs. Vancomycin 1 g IV Q12H (N=6) or Teicoplanin (N=2)
  • Endpoints: Mortality, clinical cure, microbiological cure, and ADR
Clinical Controversy - Linezolid vs. vancomycin

- Randomized controlled trial (abstract)
- ZEPHyR
  - Linezolid in the treatment of subjects with nosocomial pneumonia proven to be due to methicillin-resistant Staphylococcus aureus
- Design: Phase 4, R DB MC (non-inferiority, nested superiority)
- Objective: Efficacy and safety of linezolid vs. vancomycin for MRSA nosocomial pneumonia
- Intervention: Linezolid 600 mg IV Q12H vs. Vancomycin 15 mg/kg IV Q12H (adjusted by pharmacist) x 7-14 d
- Endpoints: Clinical cure in per protocol group at 7-30 d

Clinical Controversy - Linezolid vs. vancomycin

- Results: N=1286 randomized
  > 448 proven MRSA pneumonia (mITT)
  > 348 evaluable at end of study (PP)

- Baseline

<table>
<thead>
<tr>
<th></th>
<th>Linezolid (N=172)</th>
<th>Vancomycin (N=176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>61 yr</td>
<td>62 yr</td>
</tr>
<tr>
<td>Gender – Male</td>
<td>110 (67%)</td>
<td>112 (64%)</td>
</tr>
<tr>
<td>APACHE II</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Ventilated at Baseline</td>
<td>52% (95%)</td>
<td>40% (41%)</td>
</tr>
<tr>
<td>Bacteremia at Baseline</td>
<td>10% (6%)</td>
<td>9% (11%)</td>
</tr>
</tbody>
</table>

- Vancomycin trough (Day 3)
  - Median 12.3 mg/L, mean 14.1 mg/L
  - Range 2.8-520 mg/L
- Vancomycin MIC 1 mg/L in 83% isolates

Clinical Controversy - Linezolid vs. vancomycin

- Results:
- Safety
  - Similar between groups
    > Linezolid ≥1%: diarrhea, rash constipation, nausea
    > Vancomycin ≥1%: diarrhea, rash, nausea, anemia, acute renal failure
- Mortality at 60 d (N=194)
  > Linezolid 94 (16%) vs. Vancomycin 100 (17%)
- Other analyses in VAP
  - Clinical cure at end of study
    > Linezolid (N=139) 52% (95%CI 2-23.3%)
    > Vancomycin (N=147) 43% (95%CI -3.5-21.1%)

Clinical Controversy - Linezolid vs. vancomycin

- Conclusions:
  - Linezolid and vancomycin success rates (58% vs. 47%); 95%CI 0.5-21.6%, p=0.042
  - Linezolid was non-inferior and statistically superior based on sponsor-assessed clinical outcomes
  - Adverse events and mortality comparable

- Limitations:
  - Abstract data
  - More ventilated and bactermic in vancomycin group
  - Primary outcome wide 95%C1
  - Different outcome in sponsor vs. investigator assessment
  - Low vancomycin levels
  - Adverse events analyzed with mITT data

Clinical Controversy - Linezolid vs. vancomycin

- Is linezolid better than vancomycin for MRSA pneumonia?

- Answer
  - Linezolid and vancomycin similar efficacy for nosocomial pneumonia
  - ZEPHyR trial may provide additional information
Osteomyelitis (OM)

- MRSA osteomyelitis (OM) and joint infections
  - Hematogenous, contiguous, or direct inoculation
  - Definitive treatment
    - Debridement (A-II)
    - Abscess drainage
    - Antimicrobial therapy
  - Case series, case reports, and animal models for MSSA
  - Optimal antibiotic and route not established (A-III)
  - Monitor ESR/CRP (B-III)
- OM, septic arthritis, and prosthetic joint infection

- Treatment
  - Debridement (A-II)
  - Abscess drainage
  - Antimicrobial therapy

CNS Infection

- MRSA CNS infections
  - Secondary to neurosurgery
  - Hematogenous origin
  - Blood-brain barrier limits penetration
  - Drain abscesses and remove foreign body (A-II)
  - No prospective randomized trials
  - Meningitis
  - Brain abscess, subdural empyema, spinal epidural abscess

- Treatment
  - Vancomycin (B-II)
    - Addition of rifampin 600 mg Daily or 300-450 mg BID (B-III)
      "expert opinion"
    - Alternatives
      - Linezolid 600 mg PO/IV Q12H (B-II)
      - TMP-SMX 5 mg/kg/dose TMP IV Q8-12H (C-III)
  - Duration
    - 2 wks for meningitis (B-II)
    - 4-6 wks for brain abscess, subdural empyema, spinal abscess (B-II)

Clinical Controversy - Vancomycin vs. MRSA

- Is vancomycin still a good drug for MRSA?
  - Clinical and Laboratory Standards Institute (CLSI) (Mohr et al. CID 2007:44)
    - Changed vancomycin breakpoint for S. aureus
    - Higher clinical failures with MIC of 4 µg/mL

<table>
<thead>
<tr>
<th>Period</th>
<th>Susceptible (µg/mL)</th>
<th>Intermediate (µg/mL)</th>
<th>Resistant (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre 2006</td>
<td>≤4</td>
<td>8-16</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Present</td>
<td>≤2</td>
<td>4-8</td>
<td>≥16</td>
</tr>
</tbody>
</table>
Clinical Controversy: Vancomycin vs. MRSA

  - Difficult to calculate AUC/MIC clinically
    - Trough surrogate marker
      » Trough levels of 9.4 mg/L and 20.5 mg/L correlates to Mean AUC 318±111 µg·h/mL and 418±152 µg·h/mL
    - Trough of 15-20 mg/L for invasive infections
      - MIC ≤1 mg/L, probability of AUC/MIC >400 is ~100%

- Probability of achieving AUC/MIC of >400 (Mohr. CID 2007;44:1536; adapted from Jeffres et al.)
  - Low-dose (trough concentration ≤15 µg/mL)
  - High-dose (trough concentration >15 µg/mL)

Clinical Controversy: Vancomycin vs. MRSA

- In recent years, report of MIC creep MRSA
  - Gradual shift in vancomycin MICs
  - Loss of vancomycin activity; clinical failures MIC of 2 mg/L
  - Conflicting data
- Risk factors for vancomycin MIC of 2 mg/L (Lubin et al. CID 2011;52:997.)
  - Age >50 years
  - Vancomycin >48 h week prior to bacteremia
  - Chronic liver disease
  - History of MRSA bacteremia
  - Central line

Clinical Controversy: Vancomycin vs. MRSA

- MRSA in Canada, 1995-2008 (Canadian Nosocomial Infection Surveillance Program)

Clinical Controversy: Vancomycin vs. MRSA

  - Vancomycin (Liu et al. CID 2011;52:1)
    - Higher targets improve PK/PD, penetration, minimize resistance
    - Dose 15-20 mg/kg/d IV Q8-12H adjust renal function (B-III)
    - Loading dose of 25 mg/kg for serious infections (C-III)
    - Clinical data lacking
      - Trough levels at 4th to 5th dose; no peak levels (B-II)
      - Target trough levels 15-20 mg/L for serious infections 1 g Q12H with no trough levels (B-II)
      - Trough levels in morbidly obese, renal dysfunction, or fluctuating volume of distribution (A-II)
      - Continuous infusion not recommended (A-II)
      - For isolate vancomycin MIC ≤2 mg/L, clinical response (A-III)
      - For isolates vancomycin MIC >2, use alternate agent (A-III)
Clinical Controversy - Vancomycin vs. MRSA

- Vancomycin (Thalakada, Luey, Legal, Lau, Batterink, Ensom)

What is Next for the Treatment of MRSA?

- Ceftobiprole
- Ceftaroline
- Telavancin
- Dalbavancin
- Oritavancin

Summary

- HA-MRSA associated with severe, invasive disease
- CA-MRSA causes SSTI in young, health individuals no healthcare exposure
- Distinction between HA-MRSA and CA-MRSA blurring
- Vancomycin remains mainstay of therapy
- Ongoing studies with newer agents determine future role of vancomycin
- Numerous controversies yet to be answered