Getting Smart about Skin Infections and MRSA

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Topics

- Clinical infections
- Epidemiology
- Treatment
- Prevention

Disclosures

- Pfizer: consultant, grant recipient
- Cubist Pharmaceuticals: grant recipient
- GSK: grant recipient
- NIH, CDC, AHRQ: grant recipient

Skin & Soft Tissue Infections associated with *S. aureus*

- Impetigo
- Folliculitis
- Cellulitis
- Erysipelas
- Furuncles (boils)
- Staphylococcal Scalded Skin Syndrome
- Toxic Shock Syndrome

Other Syndromes associated with *S. aureus*

- Bacteremia and sepsis
  - Arthritis, osteomyelitis, endocarditis, meningitis, lung abscess, empyema, pyomyositis, etc.
- Surgical site infections
- Pneumonia
  - Nosocomial
    - Community-acquired
- Catheter-associated infections
- Infections of prosthetic devices
- “Food poisoning”

Methicillin-resistant *S. aureus*

- First described in 1961
- Infections in hospitalized patients
  - Strains typically R to commonly used antibiotics except vancomycin & gentamicin, rifampin
- Community infections first in IDU in Detroit, ‘80-81
- Australia, New Zealand in early 1990’s
  - Community MRSA that was not MDR

Swartz MN. In Mandell GL et al. Principals and Practice of Infect. Dis. 2000; 1037-1057
Waldvogel FA. In Mandell GL et al. Principals and Practice of Infect. Dis. 2000; 2069-2092
JH Jorgenson. Centers for Disease Control and Prevention
CA-MRSA Outbreaks

Miller LG & Diep BA. Clin Infect Dis 2008; 46: 752-60

Endemic CA-MRSA

Table 5. Bacterial isolates from wound and soft tissue infections in 11 U.S. emergency departments.

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients Enrolled (N=412)</th>
<th>MSSA (N=411)</th>
<th>Other Bacteria (N=411)</th>
<th>No Bacterial Growth (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuquerque</td>
<td>42</td>
<td>32 (76)</td>
<td>19 (46)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Atlanta</td>
<td>52</td>
<td>31 (60)</td>
<td>9 (18)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Charlotte, N.C.</td>
<td>25</td>
<td>17 (68)</td>
<td>0</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Kansas City, Mo.</td>
<td>58</td>
<td>43 (74)</td>
<td>6 (10)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>47</td>
<td>24 (51)</td>
<td>6 (13)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Minneapolis</td>
<td>28</td>
<td>11 (39)</td>
<td>4 (14)</td>
<td>9 (32)</td>
</tr>
<tr>
<td>New Orleans</td>
<td>49</td>
<td>41 (84)</td>
<td>11 (22)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>New York</td>
<td>20</td>
<td>7 (35)</td>
<td>8 (40)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Philadelphia</td>
<td>56</td>
<td>32 (57)</td>
<td>12 (22)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Phoenix, Ariz.</td>
<td>30</td>
<td>18 (60)</td>
<td>8 (27)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Portland, Ore.</td>
<td>13</td>
<td>7 (54)</td>
<td>2 (15)</td>
<td>3 (23)</td>
</tr>
</tbody>
</table>


CA-MRSA Transmission

• The 5 C’s of CA-MRSA
  – Contact
  – Crowding
  – Contaminated items and environmental surfaces
  – Compromised skin integrity
  – Cleanliness

J Hageman. Centers for Disease Control and Prevention

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J Hageman. Centers for Disease Control and Prevention
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J Hageman, Centers for Disease Control and Prevention

Risk Factors for CA-MRSA Among Persons w/ CA S. aureus Infections

<table>
<thead>
<tr>
<th></th>
<th>MRSA (n=120)</th>
<th>MSSA (N=82)</th>
<th>OR [95% CI]</th>
<th>P value</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, in years)</td>
<td>41.4</td>
<td>49.1</td>
<td>0.96 (per year)</td>
<td>0.96 - 0.98</td>
<td>&lt;0.001</td>
<td>---</td>
</tr>
<tr>
<td>Charlson Co-Morbidity (mean)</td>
<td>0.88</td>
<td>1.3</td>
<td>0.76</td>
<td>0.61 - 0.94</td>
<td>0.01</td>
<td>---</td>
</tr>
<tr>
<td>Snorted/smoked drugs</td>
<td>28%</td>
<td>12%</td>
<td>2.9</td>
<td>[1.2 - 6.8]</td>
<td>0.01</td>
<td>78%</td>
</tr>
<tr>
<td>Jailed in past 12 mo</td>
<td>20%</td>
<td>8%</td>
<td>2.6</td>
<td>[1.1 - 7.3]</td>
<td>0.03</td>
<td>79%</td>
</tr>
<tr>
<td>Recent close contact w/ person w/ skin infection</td>
<td>16%</td>
<td>7%</td>
<td>2.5</td>
<td>[0.9 - 7.2]</td>
<td>0.08</td>
<td>76%</td>
</tr>
</tbody>
</table>


MRSA Skin Infection

“Spider bites” and MRSA

Range of recluse (genus Loxosceles) spiders in the United States

Differences between HA- and CA-MRSA

HA-MRSA
- Multi-drug R (clinda, gent, FQ)
- Contain SCCmec I, II, III
- Usually PVL-

CA-MRSA
- Usu only R to eryth, β FOs
- Contain SCCmec IV
- Usually PVL +
- Appears:
  - highly virulent (esp skin)
  - highly transmissible
  - to recur commonly

Modified from JH Jorgenson. Centers for Disease Control and Prevention

SCCMec types in MRSA

<table>
<thead>
<tr>
<th>Type</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>IVa</td>
<td>B</td>
</tr>
<tr>
<td>IVb</td>
<td>C</td>
</tr>
<tr>
<td>III</td>
<td>D</td>
</tr>
<tr>
<td>II</td>
<td>E</td>
</tr>
</tbody>
</table>


Severe CA-MRSA Syndromes

- Necrotizing fasciitis
- Necrotizing pneumonia

Pseudomembranous

Bozkurt SB. Clin Infect Dis 2005; 40:941-7

Severe CA-MRSA Sepsis in Adolescents

- 93% had bone/joint infections
- 57% had pyomyositis in neighboring muscles


Figure courtesy of Sheldon Kaplan MD

S. aureus treatment

- β-lactams: oxacillin, nafcillin, dicloxacillin
- cephalaxin, cefazolin, cefadroxil
- Vancomycin
- Telavancin
- Erythromycin
- Clindamycin
- Tetracyclines (including doxy, mino)
- Tigecycline
- Trimethoprim-sulfamethoxazole
- Fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin
- Quinupristin/dalfopristin
- Linezolid
- Daptomycin

Figure courtesy of Sheldon Kaplan MD

LYCOMING COLLEGE

Football
LYCOMING COLLEGE MOURNS LOSS OF FOOTBALL PLAYER

Cause of death is bloodstream infection caused by Staphylococcus aureus (MRSA).

WILLIAMSPORT, PA – Rocky Larocca of Philadelphia, a senior at Lycoming College and a wide receiver on the Warrior football team died of an sudden, unexpected illness Saturday evening, November 3, in Williamsport. Pa. He was 21 years old.

According to the Coroner, Charles Keselrige, he was admitted to the hospital at 7 p.m. Saturday evening and died at 7:35 p.m. The cause of death is unconfirmed.

The autopsy report on Monday December 8 gave the cause of death as a bloodstream infection caused by Staphylococcus aureus (MRSA).
### CA-MRSA & CA-MSSA Susceptibility at Harbor-UCLA

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MRSA (n=120)</th>
<th>MSSA (n=82)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thee G</td>
<td>0%</td>
<td>13%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0%</td>
<td>100%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ceftazolin</td>
<td>0%</td>
<td>100%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>7%</td>
<td>84%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>15%</td>
<td>88%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>88%</td>
<td>100%</td>
<td>0.01</td>
</tr>
<tr>
<td>Imipenem</td>
<td>81%</td>
<td>94%</td>
<td>0.11</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>95%</td>
<td>100%</td>
<td>0.94</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100%</td>
<td>99%</td>
<td>0.99</td>
</tr>
<tr>
<td>Linezolid &amp; daptomycin</td>
<td>100%</td>
<td>100%</td>
<td>0.99</td>
</tr>
</tbody>
</table>


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

Department of Medicine, Division of Infectious Diseases, University of California San Francisco, California; Division of Infectious Diseases, San Francisco General Hospital, San Francisco, CA; Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, PA; and Division of Infectious Diseases, Harbor-UCLA Medical Center, Torrance, CA. 

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

IDSA MRSA Guidelines
- Skin infections
- Recurrent MRSA skin infections
- Bloodstream infection
- Bacteremia and Endocarditis
- Pneumonia
- Bone and Joint Infections
- CNS infections
- Adjunctive Therapy
- Vancomycin dosing
- Persistent MRSA Bacteremia
- Vancomycin susceptibility testing
- Neonates


### Treatment of Skin Infections

OLDBIES BUT GOODIES

OLDIES BUT GOODIES

VOL. 4

OLDIES BUT GOODIES

VOL. 4

Original recordings from the greatest rock 'n' roll hits

VOL. 4

TREATMENT OF SKIN INFECTIONS

VOL. 4

TREATMENT OF SKIN INFECTIONS
IDSA MRSA Guidelines: Skin Abscesses

- For cutaneous abscess, incision and drainage (I&D) is the primary treatment (A-II)
- For simple abscesses or boils, I&D alone is likely adequate
  - additional data needed to further define role of antibiotics, if any


Purulent Cellulitis

- For outpatients w/ purulent cellulitis, empiric Rx for CA-MRSA rec’d pending Cx results
- Empirical therapy for β-hemolytic streptococci likely unnecessary (A-II)
- Rx for 5-10 days of therapy


Outpatient Skin Infection Treatment

<table>
<thead>
<tr>
<th>Outpatient MRSA</th>
<th>Outpatient beta-hemolytic Strep</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>A II</td>
<td>A II</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>A II</td>
<td>Not rec’td Must add B-lactam</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>A II</td>
<td>Not rec’td Must add B-lactam Includes doxy, mino</td>
</tr>
<tr>
<td>Linezolid</td>
<td>A II</td>
<td>A II</td>
</tr>
</tbody>
</table>

Non-Purulent Cellulitis

- Empirical therapy for infection due to β-hemolytic streptococci rec’d (A-II)
- Role of CA-MRSA is unknown
- Empirical coverage for CA-MRSA rec’d for patients who don’t respond to β-lactam Rx
- Considered MRSA Rx if systemic toxicity
- Rx 5-10 days


Hospitalized Patients with Skin Infection

- Surgical debridement, if needed
- Vancomycin (AI)
- Linezolid (po or IV) (AI)
- Daptomycin 4 mg/kg/day (AI)
- Telavancin 10 mg/kg/day (AI)
- Clindamycin 600 mg po or IV (AI-III)


The D-test

- Tests for inducible clinda resistance
- D test +:
  - Clinda may not be useful
- D test -:
  - Clinda prob. useful

Figure 1. Double-disk diffusion test (D test) demonstrating erythromycin disk induction of clindamycin resistance; a blunting of the zone of inhibition around the clindamycin disk is produced that forms a D shape (arrow).


Hospitalized Patients with Skin Infection

- β-lactam antibiotic (e.g., cefazolin) (A-II)
  - may be considered in patients w/ non-purulent cellulitis
  - Use MRSA-active Rx if no clinical response
- Rx 7-14 days


Vancomycin

- Traditional Rx of choice for MRSA
- Bacteriocidal
- Inferior to β-lactams in difficult to treat infections
  - Endocarditis
  - Bacteremia
  - Osteomyelitis

Tice AD et al. J Antimicrob Chemother 2003; 51, 1261-1269
Vancomycin MIC & Treatment Failures in MRSA Infections


MRSA Bacteremia

- Uncomplicated:
  - exclusion of endocarditis
  - no implanted prostheses
  - follow-up blood Cx’s 2–4 days after initial set negative for MRSA
  - defervescence w/in 72 h of initiating effective Rx
  - no evidence of metastatic sites of infection
- Otherwise complicated


MRSA Bacteremia

- Uncomplicated Bacteremia:
  - Vancomycin    (A-II)
  - Daptomycin 6 mg/kg/day    (AI)
  - At least 2 weeks
- Complicated Bacteremia
  - At least 4-6 weeks
  - Consider daptomycin 8-10 mg/kg/day    (BIII)


Linezolid for MRSA Pneumonia

- Secondary analysis of ventilator-assd MRSA pneumonia, linezolid superior to vancomycin in terms of:
  - Clinical cure
    (59% vs. 26%, OR 3.3 [1.3-8.3], p=0.01)
  - Survival
    (80% vs. 64%, OR 2.2 [1.0-4.8], p=0.05)

Bauer T. Chest 2000; 124: 1632-34

MRSA Pneumonia

- Vancomycin (A-II)
- Linezolid po/IV 600 mg bid (A-II) or
- Clindamycin 600 mg PO/IV 3x day (B-III), if MRSA susceptible

Vancomycin Dosing

- 15–20 mg/kg/dose (actual body weight) q8–12 h for pts w/ normal renal function
  - not to exceed 2 g per dose
- In seriously ill patients with suspected MRSA infection, consider 25–30 mg/kg loading dose


Vancomycin Monitoring

- Monitor troughs only in:
  - Severe infections
  - Morbid obesity
  - Renal dysfunction
  - Fluctuating volumes of distribution


Vancomycin Guidelines

- Weight based dosing (All)
  - Consider loading dose 25–30 mg/kg (BIII)
- Trough concentrations
  - should be >10 mg/L (BIII)
  - 15–20 mg/L for complicated infections (BIII)
    - E.g., bacteremia, endocarditis, osteomyelitis, pneumonia
- MIC > 2 mg/L with normal renal function
  - Target AUC/MIC of >400 not achievable


Vancomycin Monitoring

- Aim for trough of 15–20 μg/ml for severe MRSA infections:
  - bacteremia
  - endocarditis
  - osteomyelitis
  - meningitis
  - pneumonia
  - severe SSTI (e.g., necrotizing fasciitis)


S. aureus Treatment

New Drugs/Pipeline

- Glycopeptides
  - Telavancin (qd)
  - Oritavancin (qd)
  - Dalbavancin (q week)
- Ceftaroline, ceftobiprole,
  - Cephalosporins with anti-MRSA activity
- Iclaprim
  - selective dihydrofolate inhibitor


Telavancin

- Glycopeptide
  - Same class as vancomycin
- Approved for SSSI
- Non-inferior to vancomycin for VAP
- Dosing data
  - poorly understood in pediatrics
  - None in CF patients
- Avoid treatment in pregnancy


Ceftaroline

- β-lactam antibiotic with activity vs. MRSA
  - 1,3-thiazole ring attached via a sulfur linker on the cephalosporin ring
  - high affinity for PBP2a on MRSA
- Active vs. gram negative pathogens
  - Not Pseudomonas or ESBL+ GNB
- Safety profile similar to other cephalosporins

Lim L et al. Am J Health Syst Pharm 2011; 68:491-8

Tigecycline

- A "glycycycline"
  - IV only minocycline derivative
- Broad spectrum, including S. aureus, MRSA
- Approved for Rx of SSSI
- Adverse effects:
  - Gastrointestinal (N/V)
  - Tooth discoloration
  - Other
- Most MRSA appear S to tigecycline


Rifampin

- Potent activity vs. S. aureus
- When used alone, R almost invariably develops
- Limitations:
  - Drug interactions
  - Hepatotoxicity
  - Color tears, urine, sweat
  - No compelling data synergistic Rx except where biofilm present (devices, osteomyelitis)
- Data for treatment in pneumonia, decolonization suggestive of benefit

Jung YJ et al. Crit Care Med 2010; 38: 175-180

Potential Mechanisms to Control CA-MRSA

- "Search and Destroy"
- Topical nasal antibiotics
  - mupirocin
  - others
- Body decolonization
  - chlorhexidine
  - hexachloraphene
  - diluted bleach
  - others
- Systemic antibiotics
  - rifampin
  - clindamycin
  - others
- Environmental decolonization
  - sprayable ethyl alcohol
  - bleach solutions
  - others

MRSA summary

- MRSA infections common
  - community
  - healthcare settings
- Skin infections typically MRSA
- Many older abx appropriate for MRSA Rx
  - IDSA MRSA Guidelines can provide guidance
  - Abx may not be needed after I&D for skin infxn
