Methicillin-Resistant Staphylococcus aureus (MRSA): Today’s Plague

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Staphylococcus aureus: Lovely isn’t it?
3-D Rendering of Genetic Components: Staphylococcus aureus
Pre-Test Question No. 1

1. Which one of the following would be an appropriate oral antibiotic for treatment of most community-associated MRSA infections?

a. Oral vancomycin
b. Oral cefadroxil
c. Oral minocycline
d. Oral nitrofurantoin
e. Oral dicloxacillin
2. Which one of the following antimicrobial agents is an appropriate parenteral antibiotic for treatment of severe MRSA?

a. Daptomycin  
b. Nafcillin  
c. Cefazolin  
d. Clindamycin  
e. Levofloxacin
Goals and Objectives

- Review the most frequently asked questions about MRSA
- Help each attendee develop a common-sense approach to and understanding of MRSA infection with specific emphasis on community-associated MRSA disease
- Understand the evolving nature of staphylooccal disease especially CA-MRSA disease
<table>
<thead>
<tr>
<th>Age</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 y.o.</td>
<td>Mother purchased plastic cups, dishes, cutlery (separate cabinet) and watched pt clean the family bathroom after each and every use. Pt hesitated to engage in any age-appropriate sexual behavior, even hand-holding or kissing. Mother asked patient to move out of house – she moved in with her father.</td>
</tr>
<tr>
<td>29 y.o.</td>
<td>Cutaneous scarring on arms and legs and owns pet care company (grooming, sitting, walking). Clients asked about skin lesions/scars and at least 5 clients withdrew their business for fear of their pets getting MRSA from patient.</td>
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<tr>
<td>62 y.o.</td>
<td>Works as bus driver. Supervisor found out about MRSA and asked pt to use alcohol or bleach on the seat cushion and steering wheel after completing a shift. Eventually pt asked to get his own seat cushion and take it with him after his shift. He has been stigmatized and discriminated against by other drivers. Fears for losing his job because of this.</td>
</tr>
<tr>
<td>12 m.o.</td>
<td>One of two twins with recurrent MRSA skin infections @ 7 mos. Nanny immediately packed her bags and left. Since then they have had a “revolving door” of nannies or potential nannies – most declined employment offers when tendered. Agency or family or friends had told the nannies not to work with “MRSA kids.”</td>
</tr>
<tr>
<td>37 y.o.</td>
<td>One year of recurrent MRSA. Wife was “extremely concerned” and then youngest child (toddler) got MRSA. Wife uses bleach on every surface and makes patient (husband) wash with chlorhexidine exclusively. She made him move out of bedroom and assigned him his own bathroom in the house which children are not allowed to use. He now lives in car garage and is not allowed to touch, pick up or hug the children.</td>
</tr>
</tbody>
</table>
Quotable Quotes – “What we don’t know About *Staphylococcus aureus*”

- “*Staphylococcus aureus* is one of the most successful and adaptable human pathogens.” Mayo Clin Proc 2007; 82: 1463-1467.
- “No clinical features distinguish with certainty skin and soft-tissue infections caused by MRSA from those caused by MSSA.” N Engl J Med; 357: 380-390.
- “Decolonization strategies are frequently recommended in such cases, although neither the indications for their use nor their effectiveness in reducing the risk of recurrences is clear.” N Engl J Med; 357: 380-390.
Remote History: MRSA in the Community

- **Detroit Metro-Area:**
  - Late 1970’s: Outbreak of HA-MRSA infections in IVDUs
  - First proof of effectiveness of TMP-SMX

- **West Coast (San Francisco, Los Angeles):**
  - Also with outbreaks in IVDUs in late 1970’s

- **These were HA-MRSA strains that were passed from one person to another with shared “personal equipment” – i.e., drug paraphernalia**
  - Sometimes this happened even in hospital
More Recent History: Community-Acquired MRSA

- 1990’s – Australian aborigines and Native Americans in Canada – little or no contact with health care systems

- Outbreaks reported:
  - Prisons
  - Sport teams: football, rugby, fencing, wrestling and multiple others

- Risk factors: minor skin trauma, sharing of personal care and sporting equipment

- Most current cases: no defined contact with someone with documented CA-MRSA and often no defined skin trauma
Secret of *Staphylococcus aureus’* Success

- One of the most adaptable human pathogens
- Acquisition of antibiotic-resistance mechanisms
- Acquisition of advantageous pathogenic determinants
- Modifiable genetic materials that make it “smarter faster”:
  - New toxins
  - New antimicrobial resistant mechanisms
## Genetic Basis of Resistance

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mechanism</th>
<th>Gene Basis</th>
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</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Beta-lactamase</td>
<td><em>blaZ</em> gene</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Altered PBP with decreased affinity</td>
<td><em>mecA</em> carried on staphylococcal cassette</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chromosome SCCmecc</td>
</tr>
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</table>
SCCmec Element

- Mobile genetic element

- Contains:
  - $mecA$ gene itself
  - Regulatory genes
  - Insertion sequence element
  - Recombinase genes ($ccr$) responsible for the integration and excision of SCCmec
Five Types of \textit{mec} Elements

- Type I SCC\textit{mec}: \textit{mecA} is sole resistance determinant (small gene sequence)
- Types II & III SCC\textit{mec}: multiple resistance determinants for non-beta-lactam antibiotics (responsible for multiple drug-resistant nosocomial MRSA strains)
- Type IV SCC\textit{mec}: single resistance determinant (small gene sequence)
- Type V SCC\textit{mec}: single resistance determinant with additional stabilization element on chromosome (small gene sequence)
Three Groups of Patients

- People with community-onset MRSA infections without health-care-associated risk factors
- People with community-onset MRSA and health-care-associated risk factors
- People with nosocomial MRSA infections which now can be “old” MRSA strain or “new” MRSA strain (CA-MRSA)
Staphylococcus aureus
Virulence Factors

- Resistance determinants
- Adherence factors
- Colonization factors (bacteriocins)
- Superantigens (enterotoxins)
- Exotoxins
- Pore-forming toxins (necrosis factors)
- Exfoliative toxins
PVL = Panton-Valentine Leukocidin (1)

- Carried on SCC\textit{mec} IV gene
- One of the pore-forming toxins
- Elicits tissue necrosis
- Clinical correlation: tissue necrosis and abscess formation
- Although usually found in only 2% of all \textit{Staph aureus} clinical isolates, the PVL genes have been found in virtually all isolates of CA-MRSA causing epidemic furunculosis.
PVL = Panton-Valentine Leukocidin (2)

- May also be found in MSSA strains
- May be horizontally transmitted via phages
- Encode a bicomponent leukotoxin
- PVL contact with human neutrophils, monocytes, macrophages, and erythrocytes results in pore formation and cell lysis through osmotic rupture
- Also associated with necrotizing pneumonia with rapid progression to septic shock and ARDS and high mortality
# CA-MRSA Syndromes

<table>
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<tr>
<th>Clinical Syndrome</th>
<th>Virulence Factors</th>
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<tbody>
<tr>
<td>Epidemic furunculosis and necrotizing fasciitis</td>
<td>- Collagen adhesion protein</td>
</tr>
<tr>
<td></td>
<td>- Salt tolerance</td>
</tr>
<tr>
<td></td>
<td>- Bacteriocin of SA (bsa)</td>
</tr>
<tr>
<td></td>
<td>- Pore-forming toxins (PVL)</td>
</tr>
<tr>
<td>Necrotizing pneumonia</td>
<td>- Collagen adhesion protein</td>
</tr>
<tr>
<td></td>
<td>- Superantigens</td>
</tr>
<tr>
<td></td>
<td>- Pore-forming toxins (PVL)</td>
</tr>
<tr>
<td>Toxic shock syndrome</td>
<td>- Superantigens</td>
</tr>
<tr>
<td></td>
<td>- Pore-forming toxins (PVL)</td>
</tr>
</tbody>
</table>
Some Issues With Some Of Our “Old” Anti-MRSA Antimicrobials

- Vancomycin
- Clindamycin
Vancomycin Failures: Reasons

- Inadequate vancomycin levels at the site of infection
- Antagonistic combinations
- Failure to drain large collection of pus
- Failure to remove foreign body
- Severe illness
Achieving Effective Vancomycin Concentrations at the Site of Infection

- Are the present recommendations for acceptable serum levels adequate?
  - Peak of 20-25 µg/ml; Trough of 5-10 µg/ml
  - Half-life varies greatly from 3-12 h
  - Time dependent killing, hence, the level above MIC should exceed at least 40% between dosing

- 50% protein bound (50% free drug for diffusion to extravascular sites)
Issues with Vancomycin Serum Levels

- > 40% of patients receiving the standard dose of vancomycin (1g q12h IV) had inadequate levels for treatment of even fully susceptible Staphylococcus aureus strains.
- Among published failures, only one patient had adequate serum levels
- The others had excessively low trough and/or low peak serum levels
- Underdosing is as dangerous as overdosing and leads to many clinical failures of therapy

Inducible Clindamycin Resistance: The “D-test”
Figure Legend. **Top Panel:** Shows a stylized cartoon of a negative D-test observed for an erythromycin-resistant culture of *S. aureus*. The small discs labeled E & C represent disks containing either 15 µg erythromycin (E) or 2 µg clindamycin (C) placed 15 to 20 mm apart on an agar plate that has been inoculated with the clinical isolate (indicated by the green background). The lack of a zone of inhibition around the erythromycin disc indicates bacterial resistance to macrolides (e.g. perhaps due to expression of a P-glycoprotein efflux pump that affects macrolides). The large clear zone of inhibition around the clindamycin disc indicates sensitivity to clindamycin. **Bottom Panel:** Depicts a positive D-test. Diffusion of erythromycin from the disc towards the clindamycin disc does not kill bacteria due to *S. aureus* resistance to macrolides. However, in this case the bacterial isolate contains a strain of *S. aureus* with an erythromycin-inducible methylase (iMLS-B) that is encoded by a plasmid-borne gene (*erm*). When this methylase is induced it alters the binding site on the 23S subunit of the 50S ribosome that both erythromycin and clindamycin bind to, making both antibiotics ineffective (inducing resistance). As a result, as erythromycin diffuses outward into Zone 1 bacterial resistance to clindamycin is induced prior to its diffusion from the neighboring disk. In contrast, growth inhibiting concentrations of clindamycin reach zone 2 before erythromycin can arrive to induce resistance (due to the shorter distance for diffusion), resulting in inhibited growth. The inhibition of bacterial growth in zone 2 but not zone 1 produces a “D” shape surrounding the clindamycin disk, which is considered a “positive” D-test. (Adapted from Woods 2009).
Frequently Asked Questions About MRSA Infection

Let’s review these one-by-one.
FAQ # 1: Is CA-MRSA really a problem?

- **Answer:** It is THE current staphylococcal problem
- *S. aureus* isolated from 320 of 422 pts with skin & soft tissue infections (76%) in 11-center study.
- Prevalence of MRSA was 59% (11-74%).
- USA300 isolates accounted for 97% of isolates.
- **Conclusion:** “MRSA is the most common identifiable cause of skin & soft tissue infections among patients presenting to emergency departments in 11 US cities.”
FAQ # 2: What is the scientific explanation for CA-MRSA?

1. High-prevalence of genes encoding the two-component Panton-Valentine leukocidin – this exotoxin is associated with necrosis of the skin, severe necrotizing pneumonia, and abscess formation. (Greater invasiveness)

2. Small DNA cassettes mediating methicillin resistance have been detected in CA-MRSA isolates suggesting easy transfer. These cassettes differ from those in hospital-associated MRSA strains which are larger and presumably less mobile. (Easier resistance transfer)
FAQ # 3: Patients at greatest risk for CA-MRSA infection?

- Household contacts of patients with proven CA-MRSA infection.
- Children.
- Day-care center contacts of hospitalized patients with CA-MRSA infection.
- Military personnel.
- Incarcerated persons.
- Athletes, contact sports.
- Native Americans.
- Pacific Islanders.
- Intravenous drug users.
- Persons with a previous CA-MRSA infection.
- Tattoo recipients.
FAQ # 4: Can we stem the transmission of CA-MRSA?

- We must counter the “5 C’s”:
  1. **Crowded** living conditions
  2. Frequent skin-to-skin **Contact**
  3. **Compromised** skin: scratches, abrasions, chronic skin diseases, etc.
  4. Sharing **Contaminated** personal items such as towels and razors
  5. Lack of **Cleanliness**: personal hygiene may be single most essential component to stress
FAQ # 4: (continued)
Can we stem the transmission of CA-MRSA?

- Physicians can help control spread of CA-MRSA in communities by:
  1. Encouraging hand hygiene.
  2. Maintaining high degree of suspicion for MRSA as etiologic agent for skin and soft tissue infections.
  3. Knowing local rates of CA-MRSA.
  4. Emphasizing importance of overall hygiene to patients with MRSA.
  5. Discouraging sharing of personal items such as towels and razors.
  6. Draining lesions should be kept covered.
  7. Return to team sports only when skin lesions healed or able to be adequately covered.
FAQ # 5: Is nasal carriage an issue in CA-MRSA?

- A 2001-2002 population-based study in the US shows that the prevalence of nasal colonization with S. aureus and with MRSA was 31.6% & 0.84%. [MRSA carriage probably higher now].
- May be axillary and perineal colonization independent from or coexistent with nasal colonization.
- Colonization rates are greater in healthcare workers.
- Nasal colonization with S. aureus is a risk factor for subsequent infection.
- Same people are not always the ones colonized (moving target).
- We do not understand the factors that turn “colonization” into “disease.”
**S. Aureus Nasal Carriage Rate by Age**

![Graph showing the S. Aureus nasal carriage rate by age. The graph indicates a decrease in carriage rate with increasing age.](image-url)
FAQ # 5: (continued)
Is nasal carriage an issue in CA-MRSA?

- Both higher rates of *S. aureus* nasal carriage and subsequent higher rates of *S. aureus* infection have been associated with many underlying diseases, the common factor being repeated violation of the skin or mucosa as anatomical barriers:
  1. Insulin-dependent diabetes mellitus.
  2. Long-term hemodialysis.
  3. Intravenous drug abuse.
  4. Repeated injections for allergies.
  5. Liver cirrhosis.
  7. HIV infection.
  8. Hospitalization.
  9. Contact sports.
FAQ # 6: Should nasal decolonization be used as a strategy to limit spread of CA-MRSA?

- In selected patients, decolonization could help reduce infection.
- However, widespread use of decolonization is NOT recommended because:
  1. It is expensive.
  2. Its benefit is usually short-lived – most patients become re-colonized during the next few months.
  3. It carries the risk of promoting resistance to agents such as mupirocin, that are used in decolonizing regimens.
  4. The exact science of decolonization is not well-delineated at the present time.
FAQ # 6: (continued)
Should nasal decolonization be used as a strategy to limit spread of CA-MRSA?

- I tend to use decolonization therapy:
  1. In patients with documented recurrent invasive staphylococcal infection, especially recurrent bacteremia.
  2. Preventively in high-risk patients previously documented to have invasive staphylococcal disease prior to:
     a. Prosthetic cardiac valve surgery
     b. Prosthetic joint surgery
     c. Vascular graft surgery
     d. Occasional other implant surgical procedure
FAQ # 7: What are the clinical syndromes due to CA-MRSA?

1. Skin and soft tissue infections. Necrotic skin lesions are common and often incorrectly attributed to “spider bites.” [Majority of cases]
2. Necrotizing pneumonia.
3. Pleural empyema.
5. Septic thrombophlebitis with pulmonary embolization.
6. Severe sepsis with purpura fulminans.
Funuculosis due to CA-MRSA
CA-MRSA Necrotizing Pneumonia: CT of Thorax in Fatal Case
Cellulitis & Septic Thrombophlebitis due to CA-MRSA in IVDU
Necrotizing fasciitis (knee) due to CA-MRSA after debridement
Sepsis syndrome with purpura fulminans
FAQ # 8: What should be the appropriate treatment protocol?

FAQ # 9: Antibiotic Treatment?
What are the oral treatment options for CA-MRSA?

FAQ # 9: Antibiotic Treatment?
What are the IV treatment options for CA-MRSA?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>15-20 mg/kg every 8-12 hours</td>
<td>Weight-dependent; Check levels; Bactericidal</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>4-6 mg/kg every 24 hours</td>
<td>Myositis (check CPK); Bactericidal; Expensive</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg every 12 hours</td>
<td>Marrow toxicity; Serotonin syndrome; Bacteriostatic; Expensive</td>
</tr>
<tr>
<td>Telavancin</td>
<td>10 mg/kg every 24 hours</td>
<td>Bactericidal; Expensive; currently not available</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>600 mg every 12 hours</td>
<td>Newest addition to armamentarium; Bactericidal</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>600 mg every 8-12 hours</td>
<td>Diarrhea; Bacteriostatic; Make certain the MRSA strain is documented sensitive to Clinda</td>
</tr>
<tr>
<td>Others: TMP-SMX; Tetracyclines; Rifampin</td>
<td>Doses vary by agent</td>
<td>Variably “static” vs. “cidal”; may be used when allergies or failures with other agents</td>
</tr>
</tbody>
</table>
Another Reminder About Clindamycin:

Inducible Clindamycin Resistance:
The “D-test”
## Anti-MRSA Antimicrobial Pricing

<table>
<thead>
<tr>
<th>2011 Pricing of MRSA Agents</th>
<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin 500 mg vial</td>
<td>$242.90</td>
</tr>
<tr>
<td>Telavancin 750 mg vial</td>
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<td>Telavancin 250 mg vial</td>
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<td>Ceftaroline 600 mg vial</td>
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<td>Linezolid 600 mg IV</td>
<td>$96.53</td>
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<tr>
<td>Linezolid 600 mg PO</td>
<td>$73.92</td>
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<table>
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<tr>
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<tr>
<td>Daptomycin 6 mg/kg (450 mg)</td>
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</tr>
<tr>
<td>Daptomycin 8 mg/kg (600 mg)</td>
<td>$485.80</td>
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<tr>
<td>Daptomycin 10 mg/kg (750 mg)</td>
<td>$485.80</td>
</tr>
<tr>
<td>Telavancin 10 mg/kg (750 mg)</td>
<td>$149.00</td>
</tr>
<tr>
<td>Ceftaroline 600 mg IV q12h</td>
<td>$79.08</td>
</tr>
<tr>
<td>Linezolid 600 mg IV q12h</td>
<td>$193.06</td>
</tr>
<tr>
<td>Linezolid 600 mg PO q12h</td>
<td>$147.84</td>
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### For a 75 kg Patient

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<td>$485.80</td>
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<tr>
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<tr>
<td>$147.84</td>
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### For a 100 kg Patient

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### For a 165 kg Patient

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### For a 200 kg Patient

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<tr>
<td>$398</td>
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<td>$79.08</td>
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<tr>
<td>$193.06</td>
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<tr>
<td>$147.84</td>
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</tbody>
</table>
FAQ # 10: What can we do for recurrent skin and soft tissue infections with CA-MRSA?

- If necessary, verify that *S. aureus* is the problem once again.
- Investigate potential familial or sporting contacts.
- Re-treat the person with longer-term options:
  1. Use ALL other infection control measures to make sure patient isn’t contributing to the problem (towels, laundry).
  2. Use long-term doxycycline or minocycline or TMP-SMX.
  3. Use concomitant oral agents: oral drug + rifampin + intra-nasal mupirocin (decolonization technique).
  4. Give patient access to oral therapy immediately upon relapse of illness: give Rx to pt, have him/her fill it, and have it on-hand at home so that it can be started immediately upon relapse of illness: patients know sxss.
  5. Use OTC chlorhexidine in home hygiene approach to recurrent disease or intra-familial disease spread.
Post-Test Question No. 1

1. Which one of the following would be an appropriate oral antibiotic for treatment of most community-associated MRSA infections?
   a. Oral vancomycin
   b. Oral cefadroxil
   c. Oral minocycline
   d. Oral nitrofurantoin
   e. Oral dicloxacillin
2. Which one of the following antimicrobial agents is an appropriate parenteral antibiotic for treatment of severe MRSA?
   a. Daptomycin
   b. Nafcillin
   c. Cefazolin
   d. Clindamycin
   e. Levafloxacin


