Methicillin-Resistant Staphylococcus Aureus (MRSA)-The drug-resistant `Superbug’ that won’t die

Michael A. Miller, MD
Assistant Professor of Pediatrics
Jacksonville

OBJECTIVES

1. Understand the basic microbiology of Staphylococcus aureus including mechanism of resistance (MRSA)
2. Understand what makes community-associated and hospital-associated MRSA different
3. Understand the changing epidemiology of MRSA
4. Describe the different clinical manifestations of MRSA infections in children
5. Identify which antibiotics are preferred for management of various MRSA infections especially skin and soft-tissue infections
6. Identify methods of MRSA transmission interruption in the community and the healthcare setting
**Gram Positive**

- *Streptococcus* spp.
  - *S. agalactiae* (GBS)
  - *S. pneumoniae*
  - *S. pyogenes* (GAS)
- **Staphylococcus spp.**
  - *S. aureus*
    - Coagulase negative
- *Enterococcus* spp.
- *Listeria monocytogenes*

**Gram Negative**

- *Escherichia coli*
- *Klebsiella* spp.
- *Pseudomonas* spp.
- *Serratia* spp.
- *Enterobacter* spp.
- *Acinetobacter* spp.
- *Citrobacter* spp.

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**History**

- “Micrococcus, which, when limited in its extent and activity, causes acute suppurative inflammation (phlegmon), produces, when more extensive and intense in its action on the human system, the most virulent forms of septicaemia and pyaemia”
  
  — Alexander Ogston, on the organism now known as *S. aureus*

Ogston A. J Anat 1882; 17:24-58
Introduction-Basic Facts

- S. aureus is a member of the Micrococcaceae family
- On microscopic examination, organism appears as gram-positive cocci in clusters
- S. aureus is distinguished from other staphylococcal species on the basis of gold pigmentation of colonies and positive results of certain biochemical tests
- S. aureus is a commensal bacterium that colonizes the nares (its primary reservoir), axillae, vagina, pharynx, and/or damaged skin surfaces
- S. aureus is unique in its ability to invade and cause disease in previously normal tissue at virtually all sites

What makes S. aureus an MRSA?
The 2 organisms “most out of control” are:

- Methicillin-resistant *S. aureus* (MRSA)
- Vancomycin-resistant Enterococci (VRE)

Source: www.Medscape.com
Rising MRSA tide in Jacksonville

Herigon JC et al. Pediatrics 2010; 125; e1294-1300.


Baptist Hospital Data. Courtesy of Dr. Halstead (Jacksonville Pathology Associates, P.A.)
Table II. Overview of general characteristics of community- and healthcare-associated meticillin-resistant Staphylococcus aureus (CA-MRSA and HA-MRSA)[9,10,12,14-16,27]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common manifestations</td>
<td>SSTI, necrotizing pneumonia</td>
<td>Nosocomial bacteraemia, pneumonia, wound infections</td>
</tr>
<tr>
<td>Antibacterial susceptibility</td>
<td>Frequently susceptible to non-β-lactam antibacterials, low prevalence of MLSA resistance</td>
<td>Broad resistance to non-β-lactam antibacterials, MLSA resistance common</td>
</tr>
<tr>
<td>SCCmec type</td>
<td>IV, V</td>
<td>I, II, III</td>
</tr>
<tr>
<td>Accessory gene regulator type</td>
<td>agr II</td>
<td>agr I, II</td>
</tr>
<tr>
<td>Genotype (PFGE)</td>
<td>USA300, USA400, USA1000 USA1100</td>
<td>USA100, USA200, USA500, USA600, USA800</td>
</tr>
<tr>
<td>Sequence type (MLST)</td>
<td>ST1, ST8, ST30, ST59, ST80</td>
<td>ST5, ST36, ST46</td>
</tr>
<tr>
<td>Virulence genes/factors</td>
<td>pvl, sea, seb, sec, seh and type I ACME common; higher expression of PSM; more rapid in vitro growth</td>
<td>pvl uncommon, type I ACME absent</td>
</tr>
</tbody>
</table>

ACME = arginine catabolic mobile element; MLSA = inducible macrolide-lincosamide-streptogramin B; MLST = multi-locus sequence typing; PFGE = pulsed-field gel electrophoresis; PSM = α-type phenol-soluble modulins; SCC = staphylococcal cassette chromosome; SSTI = skin and soft tissue infection.


A Single Pulsed-Field Type (USA300) has Accounted for Most Community-Associated MRSA Infections in the U.S.
CA-MRSA: CDC Population-Based Surveillance Definition

- MRSA culture in outpatient setting or within 1st 48 hours of hospitalization and patient doesn’t have any risk factors for healthcare-associated MRSA:
  - Indwelling devices
  - Dialysis
  - Surgery
  - History of MRSA
  - Long-term care
  - Hospitalization

Definitions

- Colonization
  - Normal area of skin or mucus membrane in which organisms are multiplying but without any host response (i.e. disease or symptoms)

- Infection
  - Deposition or multiplication of bacteria in tissues or surfaces of the body with an associated host response
Outbreaks of MRSA in the Community-Who’s at risk?

• Often first detected as clusters of abscesses or “spider bites”
• Various settings
  – Sports participants
  – Inmates in correctional facilities
  – Military recruits
  – Daycare attendees
  – Native Americans / Alaskan Natives
  – Men who have sex with men
  – Tattoo recipients
  – Hurricane evacuees in shelters

Risk Factors for MRSA acquisition & transmission-the 5”C”s

• Contact
• Crowding
• Contaminated Surfaces and Shared Items
• Compromised Skin integrity
• Cleanliness
Additional Risk factors for MRSA acquisition

- Prolonged hospitalization
- Prolonged previous antibiotic exposure
  - Use of β-lactams, fluoroquinolones,
- Exposure to other patients with MRSA
- Susceptible host
  - Intensive care unit or burn unit

"Neonate" as compromised host... CDC

Relative Risk of the usage of specific classes of antibiotics and MRSA infection or colonization

CA-MRSA-Clinical Manifestations

- Skin and Soft-tissue infections (SSTIs)
- Bacteremia/sepsis
- Endocarditis
- Osteomyelitis
- Toxic Shock syndrome
- Pyomyositis/myositis
- Pneumonia
- Meningitis
- UTI
- Omphalitis
- Septic thrombophlebitis
CA-MRSA Infections are mainly SSTIs

<table>
<thead>
<tr>
<th>Disease Syndrome</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin/soft tissue</td>
<td>1,266 (77%)</td>
</tr>
<tr>
<td>Wound (Traumatic)</td>
<td>157 (10%)</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>64 (4%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>61 (4%)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>43 (3%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>31 (2%)</td>
</tr>
</tbody>
</table>

CA-MRSA SSTIs

- Abscess
- Carbuncle
- Furuncle
- Impetigo

Fridkin et al NEJM 2005;352:1436-44
Osteomyelitis

Fig. 1. Etiology of acute osteoarticular infections 2000-2004 at Le Bonheur Children’s Medical Center, Memphis, TN

Management

Strategies for Clinical Management of MRSA in the Community: Summary of an Experts’ Meeting Convened by the Centers for Disease Control and Prevention

March 2006

Rachel J. Gorwitz¹, Daniel B. Jernigan¹, John H. Powers¹, John A. Jernigan¹, and Participants in the Centers for Disease Control and Prevention- Convened Experts’ Meeting on Management of MRSA in the Community

¹Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention
²Center for Drug Evaluation and Research, U.S. Food and Drug Administration
³Appendix A
Management of Skin Infections in the Era of CA-MRSA

- I&D should be routine for purulent skin lesions
- Obtain material for culture
- No data to suggest molecular typing or toxin-testing should guide management
- Empiric antimicrobial therapy may be needed
- Use local antibiogram to guide treatment
- Patient education is extremely important
- Follow-up patients in outpatient setting

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**Table 1. Oral Agents for the Outpatient Treatment of Pusitive Community-Associated MRSA Infections.**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adults</th>
<th>Children</th>
<th>Formulations</th>
<th>Main Side Effects and Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin (Cleocin)</td>
<td>300 mg</td>
<td>16 mg/kg</td>
<td>Tablet, suspension</td>
<td>Diarrhea caused by C. difficile</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (Bactrim, Septra)</td>
<td>1 to 2 double strength tablets twice daily and tablet containing trimethoprim, 160 mg, and sulfamethoxazole, 800 mg</td>
<td>4 to 8 mg/kg, in one dose or two divided doses</td>
<td>Diarrhea caused by C. difficile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
<td>Tablet, suspension</td>
<td>Nausea, vomiting, rash, photosensitivity, hemorrhagic eruption especially thrombocytopenia, Stevens-Johnson syndrome</td>
<td></td>
</tr>
<tr>
<td>Doxycycline (Vibramycin, Vibotek)</td>
<td>200 mg</td>
<td>4 mg/kg</td>
<td>Capsule, tablet, suspension</td>
<td>Nausea, photosensitivity, dependence in teeth and bones</td>
<td></td>
</tr>
<tr>
<td>Minocycline (Minocin)</td>
<td>200 mg</td>
<td>4 mg/kg</td>
<td>Capsule, tablet, suspension</td>
<td>Nausea, photosensitivity, dependence in teeth and bones</td>
<td></td>
</tr>
<tr>
<td>Lincomycin (Zyvox)</td>
<td>600 mg</td>
<td>16 mg/kg</td>
<td>Capsule, tablet, suspension</td>
<td>Nausea, photosensitivity, dependence in teeth and bones</td>
<td></td>
</tr>
<tr>
<td>Rifampin (Rifin, Rimactane)</td>
<td>20 mg/kg</td>
<td>20 mg/kg</td>
<td>Capsule, tablet, suspension</td>
<td>Nausea, photosensitivity, dependence in teeth and bones</td>
<td></td>
</tr>
</tbody>
</table>

*Optimal doses have not been established for all drugs listed.

### Table 3. Parenteral Agents for the Treatment of Pusative Community-Associated MRSA Infections.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dose*</th>
<th>Main Side Effects and Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin (Vancocin)</td>
<td>2-4 g/day, in two to four divided doses</td>
<td>The red-man syndrome (a histamine-release syndrome usually manifested as flushing)</td>
<td>Slowing the rate of administration is usually sufficient management for the red-man syndrome, but accompanying hypotension may require discontinuation of the drug or additional intervention in rare cases. Extensive monitoring of serum creatinine and serum sodium should be monitored in such patients to avoid drug accumulation, whether such monitoring is routinely necessary in patients with normal renal function is not clear, but it should be performed when multiple nephrotoxic drugs are administered simultaneously.</td>
</tr>
<tr>
<td>Ceftriaxone (Clenox)</td>
<td>100 mg thrice daily</td>
<td>Unknown</td>
<td>Diarrhea caused by C. difficile</td>
</tr>
<tr>
<td>Panotericin (Cubacin)</td>
<td>4.4 mg/kg once daily</td>
<td>Unknown</td>
<td>Potential renal toxicity</td>
</tr>
<tr>
<td>Tigecycline (Tigact)</td>
<td>100 mg loading dose, then 50 mg every 12 hr</td>
<td>Unknown</td>
<td>Nausea, vomiting, phototoxicity, eruption in skin and mucous membranes, anemia, neutropenia, neutrophilia, hemolysis, pseudotumor cerebri</td>
</tr>
</tbody>
</table>
| Linezolid (Zyvox) | 600 mg, every 12 hr | 10 mg/kg/day, in two to three divided doses | Hypersensitivity (usually neutrophilia, but also anemia or thrombocytopenia), mostly with previous use of 
| Quinupristin and Dalfopristin (Synercid) | 7.5 mg/kg, every 8-12 hr | 7.5 mg/kg, every 8-12 hr | Diarrhea adjustment may be necessary in patients with hepatic impairment |

* Optimal doses have not been established for all drugs listed. \( I \) Data are from Fowler et al. \( ^{15} \)

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### Figure 1 Treatment Algorithm for Children with Community-Acquired Methicillin-Resistant Staphylococcus aureus Infections

D-zone test for Inducible Clindamycin Resistance

- Clinical implications unclear, but treatment failures have occurred
- Perform on erythromycin-resistant, clindamycin-susceptible S. aureus isolates
- Does not require pre-treatment or co-treatment with erythromycin in vivo
What is a minimal inhibitory concentration (MIC)?

Figure 1. A fixed culture of bacteria is added to each of the 6 test tubes. The first tube serves as the growth control, and no antibiotic is added to this tube. Tubes 2–6 contain antibiotic in serially diluted proportions ranging from 0.5 to 8 μg/mL. After 18–24 h of incubation, the first serial-plated agar dish demonstrating no growth (or a 99.9% decrease) represents the MIC. In the case above, the MIC is 2 μg/mL, and the MBC is 4 μg/mL.


Vancomycin & clinical outcomes

TABLE 1. Comparison of outcomes between high ($>1.5$ mg/liter) and low ($<1.5$ mg/liter) vancomycin MICs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High MIC ($n = 66$)</th>
<th>Low MIC ($n = 26$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall failure*</td>
<td>24 (36.4)</td>
<td>4 (15.4)</td>
<td>0.049</td>
</tr>
<tr>
<td>30-day mortality*</td>
<td>12 (18.2)</td>
<td>3 (11.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Microbiologic failure*</td>
<td>6 (9.1)</td>
<td>0 (0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Recurrence within 60 days*</td>
<td>11 (16.7)</td>
<td>1 (3.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospital length of stay after blood culture collection, median (IQR)</td>
<td>21 (9.0–43.0)</td>
<td>10.5 (9.0–16.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Switched to alternative antibiotic*</td>
<td>12 (19.7)</td>
<td>2 (7.7)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* All data presented are no. (percent) of patients.

Vancomycin MIC distribution for MRSA in Jacksonville

Baptist Hospital Data. Courtesy of Dr. Halstead (Jacksonville Pathology Associates, P.A.)

Vancomycin vs. Linezolid

FIGURE 1. Clinical cure rates at follow-up for linezolid and vancomycin among intent-to-treat, clinically evaluable, and microbiologically evaluable patients.

Vancomycin vs. Daptomycin

Figure 3. Analysis of success rates among patients with methicillin-resistant Staphylococcus aureus (MRSA) bacteremia or endocarditis who received treatment with daptomycin (6 mg/kg/day) or standard therapy (low-dose gentamicin plus vancomycin or penicillin). Reprinted with permission from [24]. © 2007 Thiene Medical Publishers. Cosgrove SE, Fowler VG Jr. Optimizing therapy for methicillin-resistant Staphylococcus aureus bacteremia. Semin Respir Crit Care Med 2007; 28(6):624-631.


Vancomycin vs. Tigecycline

Table 3. Clinical response (rate of cure) at TOC assessment in patients with MRSA infection

| APACHE II Score | Site of infection | Tigecycline | | Vancomycin | |
|-----------------|-------------------|------------|-------------------|---------------|
|                 | n/N               | % (95% CI) | n/N               | % (95% CI)    |
| ME population   |                   |            |                   |               |
| ≤15             | cSSSI             | 50/58      | 86.2 (74.6–95.9)  | 19/22         | 86.4 (65.1–97.1) |
|                 | other             | 17/21      | 81.0 (58.1–94.6)  | 6/6           | 100.0 (54.1–100.0) |
| >15             | cSSSI             | 1/1        | 100.0 (2.5–100.0) | 1/1           | 100.0 (2.5–100.0) |
|                 | other             | 2/6        | 33.3 (3.3–72.7)   | 0/2           | 6.0 (0.0–84.2)    |
| overall         |                   | 52/86      | 81.4 (71.6–90.0)  | 26/31         | 83.0 (66.1–94.5)  |
| m-mITT population |                   |            |                   |               |
| ≤15             | cSSSI             | 54/69      | 78.3 (66.7–87.3)  | 19/22         | 86.4 (65.1–97.1)  |
|                 | other             | 17/22      | 77.3 (54.6–92.2)  | 7/7           | 100.0 (59.0–100.0) |
| >15             | cSSSI             | 1/1        | 100.0 (2.5–100.0) | 1/1           | 100.0 (2.5–100.0) |
|                 | other             | 3/8        | 37.5 (8.6–75.5)   | 0/1           | 60.0 (0.0–70.0)   |
| overall         |                   | 75/100     | 75.0 (65.3–83.1)  | 27/33         | 81.8 (64.5–93.0)  |

APACHE, Acute Physiologic and Chronic Health Evaluation; cSSSI, complicated skin and/or skin structure infection; ME, microbiologically evaluable; m-mITT, microbiological modified intent-to-treat.
Prevention of Transmission in the hospital setting

Isolation Gowns Prevent HCWs From Contaminating Clothes/Hands

- 40% (14/35) HCWs’ gowns were culture (+) for MRSA or VRE on exiting rooms of colonized or infected patients
- Clothing underneath was culture (-)
- 11 (69%) of 16 HCWs wearing freshly laundered white coats had detectable contamination

Barrier Precautions Work to Prevent Transmissions

• 16-fold decrease in transmission of MRSA when contact/droplet precautions were used during an outbreak ($p < 0.0001$).\(^1\)

• 38-fold increased risk of transmission from unisolated compared with isolated patients
  - 38 transmissions vs. 1,
  - $RR = 38.0$ (95% CI=6.4-1539.9, $p<10^{-6}$)\(^1\)

\(^1\)Jernigan. Am J Epidemiol 1996;143:496-504

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APIC®
ASSOCIATION FOR PROFESSIONALS IN INFECTION CONTROL & EPIDEMIOLOGY, INC.

Summary of MRSA Prevention Guidelines from the Association for Professionals in Infection Control and Epidemiology (APIC)

• Targeted active surveillance cultures (ASC)
  - Depending on the hospital, this approach may involve testing of patients at high-risk for MRSA colonization or infection, or all patients being admitted to a hospital (ie, universal ASC). “High-risk” groups include:
    - Long-term care residents
    - Patients with recent or frequent hospitalizations
    - Dialysis patients
    - Athletes
    - Veterinarians
    - Those with a history of incarceration
    - History of IV drug use
  - Prompt identification of MRSA colonized patients and initiation of proper interventions preventing MRSA-associated infections, including:
    - Isolation
    - Contact precautions
    - Decolonization, and treatment to minimize further MRSA transmission
  - Timing is a critical factor in successful infection control because rapid detection allows sooner implementation of proper precautions and treatment, minimizing risks of complications and transmission.
Role of Pets

- Greatest risk of *Staph aureus / MRSA* exposure in most humans is other humans
- When household pet animals carry MRSA, likely acquired from a human
- Transmission of MRSA from an infected or colonized pet to a human is possible, but likely accounts for a very small proportion of human infections
- Reasonable to consider pet as a source if transmission continues in a household despite optimizing other control strategies
- Little evidence that antimicrobial-based eradication therapy is effective in pets; however, colonization tends to be short-term*

Barton et al 2006; Can J Infect Dis Med Microbiol

Screening and Decolonization

- In general, colonization cultures of infected or exposed persons in community settings are not recommended. (May have a role in public health investigations).
- Decolonization regimens:
  - May have a role in preventing recurrent infections (more data needed to establish efficacy and optimal regimens for use in community settings).
  - *After treating active infections and reinforcing hygiene and appropriate wound care*, consider consultation with an infectious disease specialist regarding use of decolonization when there are recurrent infections in an individual patient or members of a household.
What’s next for MRSA research?

Table 1

<table>
<thead>
<tr>
<th>Product</th>
<th>Corporate Sponsor</th>
<th>Composition</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>StaphVAX</td>
<td>Nabi</td>
<td>CP5 and CP8</td>
<td>Phase 3 failed</td>
</tr>
<tr>
<td>V710 (0657 nl)</td>
<td>Merck</td>
<td>IsdB</td>
<td>Phase 2 in progress</td>
</tr>
<tr>
<td>Passive immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH-A21 (Veronate)</td>
<td>Inhibitex</td>
<td>Clumping factor A (CfA, selected IVIG)</td>
<td>Phase 3 failed</td>
</tr>
<tr>
<td>Tefibazumab (Aurexis)</td>
<td>Inhibitex</td>
<td>CfA (mAb)</td>
<td>Phase 2 completed</td>
</tr>
<tr>
<td>Altastaph</td>
<td>Nabi</td>
<td>Antibodies to CP5 and CP8</td>
<td>Phase 2 completed</td>
</tr>
<tr>
<td>Aurograb</td>
<td>NeuTec</td>
<td>Antibodies to ATP-binding cassette transporter</td>
<td>Phase 3 completed</td>
</tr>
<tr>
<td>Pagibaximab (BSYX-A110)</td>
<td>Biosynex</td>
<td>Lipoteichoic acid (mAb)</td>
<td>Phase 2 completed</td>
</tr>
</tbody>
</table>

Conclusions

• New strains of MRSA have emerged in the community, with implications for the management staphylococcal infections.
• The incidence of MRSA at Baptist Medical Center was 66%.
• SSTIs are the most common clinical presentation of MRSA but osteomyelitis, bacteremia, pneumonia and other invasive infections are also possible.
• Incision and drainage remains a primary therapy for purulent skin infections.
• Oral treatment options are available for patients with skin infections that require ancillary antibiotic therapy.
• Strategies focusing on increased awareness, early detection and appropriate management, enhanced hygiene, and maintenance of a clean environment have been successful in controlling clusters / outbreaks of infection.

Questions?

Thanks for Your Attention!