Evolution, Epidemiology, and Eradication of Contemporary Staphylococcus aureus

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September 6, 2012

Case: Family D
- 2 week old infant with a buttock pustule
  - Resolved without medical intervention
- 1 week later: Mother developed mastitis, breast abscess, and sepsis
  - Hospitalized for 6 weeks
- 15 month old sister hospitalized with skin abscess and fever
- Father also developed fever and boils on his arms, back and buttocks
- Over the next 2 years, all family members had recurrent episodes of fever and boils
  - Caused by “antibiotic-resistant Staphylococcus aureus”

Outline
- Historical perspective of Staphylococcus aureus
- Emergence and epidemiology of community-associated methicillin-resistant S. aureus (CA-MRSA)
- Treatment of CA-MRSA infections
- Prevention of recurrent disease

Staphylococcus aureus
- Staphylococcus aureus is a commensal bacterium that commonly lives on the skin or in the nose of healthy people
- S. aureus is also a successful pathogen

Staphylococcus aureus Timeline

Newborn Nursery Epidemic: 1950s
- Infants discharged home from the hospital healthy
- Returned ~8 days of life with S. aureus infection
- Mothers presented ~14 days after delivery
- Phage Type 80/81
**Cloud Babies: Super-shedders**

- *S. aureus* 80/81 present in the air of the nursery
- Asymptomatic infants colonized with *S. aureus* 80/81
  - Some infants had viral infections of the upper respiratory tract
    - Hypothesis: Viral infection changed the ecology of the nose and throat

**Bacterial Interference**

- *S. aureus* 502A
  - Penicillin susceptible
  - Present in babies not colonized with 80/81 strain
  - Low pathogenicity
- Infants colonized with 502A did not develop colonization with 80/81 when exposed to other infants shedding 80/81
- Deliberate inoculation of newborns
  - Nares
  - Umbilical stump

**A Not So Innocuous Inoculum**

- Adverse outcomes due to 502A
  - Skin pustules in infants
  - Up to 34% of infants inoculated with 502A
  - Recurrent skin abscesses
  - Septicemia and death in a premature infant

**Methicillin-Resistant Staphylococcus aureus**

- Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to the β-lactam class of antibiotics
- Methicillin resistance is encoded by the *mecA* gene located on the SCCmec cassette
- The *mecA* gene encodes the Penicillin Binding Protein 2a, which has a decreased ability to bind to β-lactam antibiotics

**Staphylococcus aureus Timeline**

1946: Penicillin introduced
1947: Penicillin-resistant *S. aureus* detected
1959: Methicillin introduced
1961: MRSA detected in Europe
1967: MRSA detected in US

**Staphylococcus aureus Timeline**

1946: Penicillin introduced
1947: Penicillin-resistant *S. aureus* detected
1959: Methicillin introduced
1961: MRSA detected in Europe
1967: MRSA detected in US
1981: MRSA outbreak is noted among IVDA in Detroit
1993: MRSA is reported in previously healthy women without risk factors or IVDA

**Risk factors for MRSA**

- Advanced age
- Prolonged hospitalization
- Invasive procedures
- Prolonged antibiotic therapy
- Stay in an extended care facility
- Close proximity to persons with MRSA
**Staphylococcus aureus Timeline**

- 1959: Methicillin introduced
- 1998: Four deaths in previously healthy children due to MRSA
- 2012: MRSA is widespread in the community

**Outline**

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**Comparison of HA-MRSA vs. CA-MRSA**

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>CA-MRSA</th>
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<td>Population affected</td>
<td>Patients with history of hospitalization, surgery, dialysis, or residence in a long-term care facility</td>
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**S. aureus Infections in San Francisco, CA 1996-2004**

**CA-MRSA Virulence Determinants**

- **Arginine Catabolic Mobile Element (ACME)**
  - Acquired from *S. epidermidis*
  - Important for pH homeostasis on acidic human skin
  - Enhances growth, survival, and dissemination of CA-MRSA

- **α-type Phenol-Soluble Modulins (PSMs)**
  - Leukocidal, proinflammatory, chemotactic
  - Possible contributor to bacteremia and abscess formation

**Panton-Valentine Leukocidin (PVL)**

- Role of PVL in CA-MRSA pathogenesis is controversial
- Epidemiologic association with necrotizing pneumonia and skin infection

- **α-Hemolyzin**
  - Essential virulence factor in *S. aureus* pneumonia

**The Spectrum of CA-MRSA Entities**

- **COLDIZATION**
  - SKIN AND SOFT TISSUE INFECTIONS (SSTI)
  - 18,650 deaths

- **INVASIVE, LIFE-THREATENING INFECTIONS**
  - 14.2 million outpatient clinic visits
  - 800,000 hospitalizations

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**Miller LG et al., Clin Infect Dis 2008;46:752-60**

**San Francisco Community Health Network**

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**Diep et al., Trends in Microbiol 2008; 16:361-9**

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**Klevens RM et al., JAMA 2007; 298:1763-1771**

**Hersch AL et al., Arch Intern Med 2008; 168:1585-1591**

**Edelsberg J et al., Emerg Infect Dis 2009; 15:1516-1518**

**Klevens RM et al., JAMA 2007; 298:1763-1771**

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Increase in *S. aureus* Infections Diagnosed at St. Louis Children’s Hospital: 1999-2007

- >1200 children present with skin infections
- ~900 require painful drainage procedures
- ~50 children are treated for invasive *S. aureus* infections

Clinical Questions

- How prevalent is colonization?
- What is the significance of colonization?
- How can we intervene to reduce infections and improve outcomes?

Prevalence and Natural History of CA-MRSA Nasal Colonization in St. Louis Children

### Nasal Colonization Status

Participants were recruited from 11 pediatric practices from October 2005 to June 2006

- **1300 Participants**
  - **MRSA**: 32 (2.5%)
  - **MSSA**: 331 (25.5%)
  - **No S. aureus**: 937 (72%)

Fritz SA et al., *Pediatrics* 2008; 121:1090-1098

Geographic Distribution of Colonized Individuals

Pediatric Population Estimates in St. Louis City and St. Louis County:

- MRSA colonization: 8,455
- MSSA colonization: 84,552

Fritz SA et al., *J Infect* 2009; 59: 394-401

Children with MRSA Nasal Colonization Are More Likely to Develop Skin Infections

- **1300 Participants**
  - **MRSA**: 32 (2.5%)
  - **MSSA**: 331 (25.5%)
  - **No S. aureus**: 937 (72%)

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Risk Factors For SSTI Over 12 Months

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<th>Risk Factor</th>
<th>aOR</th>
<th>95% CI</th>
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<td>MRSA nasal colonization</td>
<td>3.0</td>
<td>0.9 – 9.4</td>
</tr>
<tr>
<td>Skin infection in year prior to enrollment</td>
<td>4.1</td>
<td>1.5 – 11.0</td>
</tr>
<tr>
<td>Interval skin infection in a household member during one-year follow-up</td>
<td>5.3</td>
<td>2.5 – 11.0</td>
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Fritz SA et al., J Infect 2009; 59: 394-401

Relationship between CA-MRSA Colonization and CA-MRSA Infection

Transmission of CA-MRSA

- CA-MRSA is transmitted by:
  - Direct skin-to-skin contact
  - Having contact with another person’s skin infection
  - Contact with a personal hygiene item or surface that has come into contact with someone else’s skin infection

Factors that Facilitate Transmission

- Crowding
- Skin-to-Skin Contact
- Compromised Skin
- Contaminated Surfaces and Shared Items
- Cleanliness

Locations Where the 5 C’s are Common

- Sports teams
- Households
- Military barracks
- Correctional facilities
- Daycare centers

Outline

- Historical perspective of *Staphylococcus aureus*
- Emergence and epidemiology of community-associated methicillin-resistant *S. aureus* (CA-MRSA)
- Treatment of CA-MRSA infections
- Prevention of recurrent disease
Management of SSTI in the Era of CA-MRSA

- Cutaneous abscess:
  - Incision and drainage (I&D) is the primary treatment
  - For simple abscesses and boils, I&D alone is likely to be adequate
  - Additional data are needed to further define the role of antibiotics, if any, in this setting

Liu C et al., Clin Infect Dis 2011; 52:285-292

Randomized, Controlled Trial of Antibiotics in the Management of Community-Acquired Skin Abscesses in the Pediatric Patient

- No significant difference in cure rates between TMP-SMX and placebo
- Antibiotic therapy may decrease new lesion development

Selmia G et al., Ann Emerg Med 2010; 56:283-287

Conditions in which Antibiotics are Recommended after I&D

- Severe or extensive disease
  - Involving multiple sites of infection
  - Rapid progression in presence of associated cellulitis
  - Signs and symptoms of systemic illness
  - Associated co-morbidities or immunosuppression
  - Diabetes mellitus, HIV/AIDS, neoplasm
  - Extremes of age
  - Abscess in an area difficult to drain
  - Face, hand, genitalia
  - Associated septic phlebitis
  - Lack of response to incision and drainage alone

Liu C et al., Clin Infect Dis 2011; 52:285-292

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Management of Recurrent SSTI

- Emphasize personal hygiene and appropriate wound care
  - Regular bathing
    - Shower after exercise and any activity that involves direct skin contact with others
  - Keep hands clean
    - Soap and water
    - Alcohol-based hand sanitizers
  - Avoid sharing personal hygiene items
- Environmental hygiene measures
  - Cleaning high-touch surfaces that may contact bare skin or uncovered infections

Liu C et al., Clin Infect Dis 2011; 52:285-292
Decolonization

- *S. aureus* colonization is a risk factor for SSTI\(^1\),\(^2\)
- Decolonization
  - The use of antimicrobial or antiseptic agents to suppress or eliminate *S. aureus* carriage\(^3\)
  - Traditionally used to prevent healthcare-associated MRSA (HA-MRSA) infections
  - Decolonization is frequently prescribed to patients in community settings to prevent recurrent SSTI

**Management of Recurrent SSTI**

- Decolonization may be considered in selected cases:
  - A patient develops a recurrent SSTI despite optimizing wound care and hygiene measures
  - Ongoing transmission is occurring among household members or other close contacts despite optimizing wound care and hygiene measures

Decolonization Regimens

- **Mupirocin**
  - Inhibits bacterial isoleucyl-tRNA synthetase
  - Protein synthesis inhibition
- **Chlorhexidine**
  - Biguanide cationic bactericidal agent
  - Disrupts integrity of cell wall and membranes
  - Causes coagulation of intracellular contents
- **Dilute Bleach (Sodium Hypochlorite)**
  - *S. aureus* antimicrobial activity both *in vivo* and *in vitro*

Uncertainty Surrounding Decolonization

- Do these measures actually eradicate the organism?
- Does decolonization prevent SSTI?
- Who should perform decolonization?

**StL StaRS**

St. Louis

*Staphylococcus aureus* Reduction Study

Randomized Controlled Trial Evaluating Decolonization Regimens in Patients with Community-Associated Skin Infections Colonized with *Staphylococcus aureus*

**Study Objectives**

- Investigate methods of decolonization to find an effective method for the eradication of CA-*S. aureus* carriage
- Compare rates of recurrent *S. aureus* infections between these groups

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(1) Fritz SA et al., *J Infect* 2009; 59:394-403
(2) Ellis MAV et al., *Clin Infect Dis* 2004; 39:971-9
Participant Enrollment

- Setting:
  - St. Louis Children’s Hospital
  - Barnes-Jewish Hospital

- 300 patients enrolled
  - Community-onset skin infection, plus
  - *S. aureus* colonization in the nose, axilla, and/or inguinal fold

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Health Tips

Throw out all lotions or creams that you dip your hands into, and replace with pumps or pour bottles. Alternatively, you may use tubs, but use a clean applicator to scoop out.

Use liquid (pour/pump) soaps instead of bar soaps.

Wash hands frequently or use hand sanitizer (with more than 60% alcohol) such as Germ-X® or Purell®.

Do not share personal care items such as razors and brushes.

Wash all sheets and towels in hot water. Wash sheets every week.

Use towels and wash cloths only once before washing and do not share.

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Randomization

<table>
<thead>
<tr>
<th>Randomization Arm</th>
<th>1 Month Post-Intervention % Decolonized (N)</th>
<th>P</th>
<th>4 Months Post-Intervention % Decolonized (N)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>38% (24/64)</td>
<td>--</td>
<td>48% (31/64)</td>
<td>--</td>
</tr>
<tr>
<td>Mupirocin alone</td>
<td>56% (35/62)</td>
<td>0.03</td>
<td>56% (32/57)</td>
<td>0.4</td>
</tr>
<tr>
<td>Mupirocin + Chlorhexidine</td>
<td>55% (35/64)</td>
<td>0.05</td>
<td>54% (31/57)</td>
<td>0.5</td>
</tr>
<tr>
<td>Mupirocin + Bleach Baths</td>
<td>63% (34/54)</td>
<td>0.006</td>
<td>71% (36/51)</td>
<td>0.02</td>
</tr>
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Fritz SA et al., Infect Control Hosp Epidemiol 2011;32:872-880

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Recurrent SSTI 1 and 4 Months After Performing Decolonization Measures

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<th>1 Month Post-Intervention % Reporting SSTI (N)</th>
<th>P</th>
<th>4 Months Post-Intervention % Reporting SSTI (N)</th>
<th>P</th>
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<tbody>
<tr>
<td>Control</td>
<td>26% (17/65)</td>
<td>--</td>
<td>41% (26/64)</td>
<td>--</td>
</tr>
<tr>
<td>Mupirocin alone</td>
<td>23% (14/62)</td>
<td>0.64</td>
<td>34% (20/59)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mupirocin + Chlorhexidine</td>
<td>11% (7/63)</td>
<td>0.03</td>
<td>33% (19/57)</td>
<td>0.41</td>
</tr>
<tr>
<td>Mupirocin + Bleach Baths</td>
<td>22% (12/55)</td>
<td>0.58</td>
<td>35% (18/52)</td>
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Twelve-Month Evaluation of a Household vs. Individual Approach to Decolonizing Children with Community-Associated *Staphylococcus aureus*

*Staphylococcus aureus* Decolonization Study (SuDS)
Study Objectives

• To measure *S. aureus* colonization in household contacts of children with *S. aureus* skin infections
• To identify sites of colonization in index patients
• To compare rates of skin infections over 12 months when decolonization measures are performed by the index patient alone vs. all household members

Participant Enrollment

• Setting:
  – 9 WU PAARC practices
  – St. Louis Children’s Hospital
    • Emergency Department and Wound Center
• 183 index patients enrolled
  – Community-onset *S. aureus* skin infection, plus
  – *S. aureus* colonization in the nose, axilla, and/or inguinal fold
• Cultures to evaluate colonization were collected from 609 household contacts of index patients

Household Contact Colonization

Colonization Swabs Obtained from 609 Household Contacts

128 colonized with MRSA (21%)
208 colonized with MSSA (34%)

Baseline Colonization Sites: Index Cases

MRSA Colonization Sites
- Nose Only
- Axilla Only
- Groin Only
- Nose + Axilla
- Axilla + Groin
- Groin Only
- Nose + Axilla + Groin

MSSA Colonization Sites
- Nose Only
- Axilla Only
- Groin Only
- Nose + Axilla
- Axilla + Groin
- Groin Only
- Nose + Axilla + Groin

* MRSA most frequently colonizes the groin (p=0.03)
* MSSA most frequently colonizes the anterior nares (p=0.05)

*S. aureus* Decolonization Protocol

• Hygiene curriculum
• Mupirocin ointment applied to the nose twice daily for 5 days
• Hibiclens® (chlorhexidine) solution used in the shower or bath daily for 5 days

Randomization

Index Decolonization 92 Households
Household Decolonization 91 Households
Eradication of *S. aureus* Carriage from Index Patients

- Eradication of *S. aureus* from index patients did not differ between index and household decolonization groups over 12 months.

Cumulative Incidence of Skin Infections in Index Patients

- Household decolonization significantly decreased incidence of skin infections in index patients over 12 months.

Cumulative Incidence of Skin Infections in Household Contacts

- Household decolonization significantly decreased incidence of skin infections in household contacts over 12 months.

Cumulative Rate of SSTI: Index Patients Stratified by Baseline *S. aureus* SSTI

- MRSA SSTI at baseline
- MSSA SSTI at baseline

Cumulative Rate of SSTI: Index Patients Stratified by SSTI Past Year

- SSTI in Past Year
- No SSTI in Past Year

Challenges to Decolonization
Mupirocin Resistance

- **Low-level resistance**
  - MIC 8-128 µg/mL
  - Alteration in the isoleucyl-tRNA synthetase gene ileS

- **High-level mupirocin resistance**
  - MIC ≥256 µg/mL
  - Confounded by the plasmid-encoded mupA gene
    - Encodes novel isoleucyl-tRNA synthetase
    - Plasmids carrying the mupA gene may carry resistance genes for other systemic antibiotics

Chlorhexidine Resistance

- Conferred by the plasmid-mediated qacA/B genes
  - Encode for proton-dependent multidrug efflux pumps
  - Plasmids may carry multiple determinants of antimicrobial resistance

- Implementation of chlorhexidine bathing associated with increased prevalence of MRSA strains possessing the qacA/B genes

CA-MRSA Transmission Dynamics

- **Study Objectives**
  - Define the transmission dynamics of CA-MRSA colonization and infection among pediatric index patients and their household contacts over one year
  - Identify hygiene and behavioral practices contributing to CA-MRSA transmission, colonization, and infection within households
  - Determine the role of environmental contamination in household CA-MRSA transmission

[References]

Participants and Study Design

- 135 index patients with active or recent confirmed CA-MRSA infections and their household contacts

Setting
- St. Louis Children’s Hospital
  - MRSA Clinic
  - PAWS
  - Inpatient Units
- Community pediatric practices affiliated with WU PAARC

Enrollment Visit

- Culture humans: nose, axilla, and inguinal folds
- Culture household environmental objects and surfaces
- Culture pet dogs and cats (nose)
- Detailed survey to evaluate individual health factors, hygiene practices, and activities

CA-MRSA Transmission Dynamics

- Molecular typing will be performed on all recovered CA-MRSA isolates
  - Determine whether infecting strains resemble:
    - Endogenous colonizing strains
    - Strains recovered from household contacts
    - Strains recovered from environmental surfaces
  - Identify the directionality of transmission

Summary

- CA-MRSA is a significant health burden
- Colonization is often associated with subsequent infections
- A household decolonization approach reduces the incidence of SSTI compared to an individual approach
- Decolonization should be applied to specific groups
- Widespread use of decolonization measures may lead to resistance

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