Community Methicillin-Resistant Staphylococcus aureus

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Sixth Plague of Egypt
(~ 1200 BCE)

“So they took soot from a kiln, and stood before Pharaoh; and Moses threw it toward the sky, and it became boils breaking out with sores on man and beast.”

Exodus 9:10

Epidemiology
Basic Features of Community MRSA

- First occurrences mid 1990s in US and Australia
- Novel methicillin-resistant gene cassette: SCCmec type IV or V
- Specific clones, not hospital clones
  - USA300 (ST8)
  - USA400 (ST1)
- Toxin production (Panton-Valentine leukocidin, PVL)

Populations with CA-MRSA

- Children, infants
- Jail and prison inmates
- Military recruits
- Native populations
- MSM
- HIV+ patients
- Homeless populations
- Football teams
- Wrestlers
- Gymnasts
- Fencing teams
- Injection drug users
- Tattoo recipients
- Individuals with no risk factors at all
Household Transmission of CA-MRSA

Clonal Distribution of MRSA in San Francisco Hospitals 2004-2005

Types of CA-MRSA Infections

Liu, CID 46:1637, 2008
Fridkin, NEJM 352:1436, 2005; Kaplan, CID 40:1785, 2005;
Liu, CID 46:1637, 2008; Purcell, Arch Ped Adolesc Med 159:980, 2005
Outcomes of CA-MRSA vs CA-MSSA

• ~ 4-fold higher rates of similar infections in household contacts of CA-MRSA patients (49% USA300)
• CA-MRSA infections more likely to be hospitalized
• Recurrence/relapse more common in CA-MRSA patients


Impact of MRSA

• Emergence as an important pathogen in out-patients
  – Empirical antibiotics used in the therapy of SSTIs must cover MRSA
• Predilection for more serious disease
• Enhanced transmissibility
• Tendency for recurrence

Treatment
Prevalence of MRSA among *S. aureus* isolates

Grundmann et al. Lancet 2006;368:874-85

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**Audience Interactive**

- A healthy 20-year-old college basketball player
- Abscess: area of erythema was 5 x 3 cm and a firm central area 2 cm in diameter.
- No direct trauma to the area.
- Subjective low-grade fevers the night before presentation, T= 37.7°C

Hammand and Baden, NEJM 359:e20 (Oct 9, 2008)

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**What is the most appropriate management option?**

1. I&D alone
2. I&D + MRSA agent
3. I&D + MSSA agent

Hammand and Baden, NEJM 359:e20 (Oct 9, 2008)
Rank of Management Options by Readers of NEJM

1. I&D + MRSA agent (41% of the 11,205 votes)
2. I&D alone: (31% of the votes cast)
3. I&D + MSSA agent (28% of the votes cast)

Hammand and Baden, NEJM 359:e20 (Oct 9, 2008)

MD Use of I&D + Antibiotics for Abscess as a Function MRSA Rate

P = 0.0015

Hammand and Baden, NEJM 359:e20 (Oct 9, 2008)

Effect of Initial Therapy on Outcome of SSTIs

Fridkin, NEJMJ. 2005; 352:1436
Treatment of MRSA SSTI

- 406 of 422 (96%) patients with complete information
- 85% had I&D performed + antibiotics
- 198/311 (64%) patients given antibiotics received a beta-lactam
- 57% of MRSA infections treated with “wrong” antibiotic
- MRSA infections no different in outcome and no adverse effect of “wrong” antibiotic on outcome.

Moran, NEJM. 2006; 355:666

Cefdinir vs. Cephalexin for uSSTIs

<table>
<thead>
<tr>
<th>Cure Rates</th>
<th>Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA (n=72)</td>
<td>MRSA (n=79)</td>
</tr>
<tr>
<td>66 (92%)</td>
<td>72 (91%)</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Giordano, Curr Med Res Opin. 2006; 22: 2419

Impact of Antibiotics on Outcome of Community-Onset MRSA SSTI

- Retrospective cohort study
- 531 episodes of abscess, furuncles, carbuncles, or cellulitis in 492 patients
  - All culture-positive for MRSA (71% CA-MRSA)
  - Clinical specimen obtained as OP or w/in 48h hospital admission
- Failure defined as any one of the following
  - I&D after 48h of therapy
  - Subsequent hospital admission
  - New lesion or microbiological failure

Impact of Antibiotics on Outcome of Community MRSA SSTI

- Types of infections
  - Abscess in 361 (68%)
  - Cellulitis, all with a focal lesion, in 116 (22%)
  - Furuncle or carbuncle in 54 (10%)
- Antimicrobial therapy
  - Active in 312 episodes (59%)
  - Inactive in 219 episodes (41%)
- Successful outcomes
  - 296 “active” (95%) vs. 190 “inactive” (87%): p =0.001
  - Only inactive therapy associated with failure (OR 2.82, 95% CI 1.49-5.34)
  - 24 (83%) of 29 “inactive” failures received a β-lactam


Randomized, double-blind, placebo controlled trial of cephalexin for SSTI


Cure Rates

Bar indicates upper 95% confidence interval
TMP/SMX (2 DS bid) v Placebo in OP Treatment of Drained Abscesses in Adults

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TMP/SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure @ EOT</td>
<td>27/102</td>
<td>15/88</td>
</tr>
<tr>
<td>(7 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence @ 30 day flu (phone)</td>
<td>14/50</td>
<td>4/46</td>
</tr>
</tbody>
</table>

Schmitz Ann Emerg Med 56:283, 2010

TMP/SMX v Placebo in OP Treatment of Drained Abscesses in Children

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TMP/SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure @ 10 days</td>
<td>4/76</td>
<td>3/73</td>
</tr>
<tr>
<td>Recurrence @ 10 days</td>
<td>14/50</td>
<td>4/46</td>
</tr>
<tr>
<td>Recurrence @ 3 mo</td>
<td>15/52</td>
<td>13/46</td>
</tr>
</tbody>
</table>

Duong, Ann Emerg Med 55:401 2010

TMP-SMX for Undrained/Not Cultured Abscesses in Children

- Nested case-control study of SSTIs in children treated with monotherapy
- Key results
  - Beta-lactams and clindamycin were similar in risk for treatment failure
  - TMP/SMX was associated with treatment failure

Elliot, Peds 123:e959, 2009
Role of Beta-Hemolytic Strep in Nonculturable Cellulitis

- Prospective case series
- Acute and convalescent serology for ASO Anti-Dnase B
- Cure rate in those treated with beta-lactams only was 96% (~100 patients)
- Cure rates based on serodiagnosis
  - BHS pos: 71/73
  - BHS neg: 21/23

Jeng, Med 89:217, 2010

Summary

- Incision and drainage is probably sufficient in most cases, especially in OP therapy
- Use of an antibiotic to which the isolate is susceptible may provide a marginal benefit in a minority of cases
- Beta-lactams may not only be ineffective, but could worsen outcome*

*Stevens, JID. 2007;195:202

"Spider Bite" Lesion.....Not!
Oral Antistaphylococcal Agents

- Trimethoprim-sulfamethoxazole
- Minocycline > doxycycline > tetracycline
- Clindamycin
- Fluoroquinolones (levofloxacin, moxifloxacin)
- Linezolid

IDSA Practice Guidelines: Stevens et al, CID 2005;41:1373

Trimethoprim-sulfamethoxazole

- Most MRSA are susceptible (~95%)
- Beta-hemolytic strep (GAS) coverage?
- Bactericidal, mostly
- Less efficacious than vancomycin in one comparative clinical trial (Markowitz)
- Dose? 1 DS (160/800) or 2 DS bid?
- Off-label use, not much published, most experience in minor to mod SSTI

Szumowski et al, Antimicrob Agents Chemother. 2007;51:423
Cenizal et al, Antimicrobial Agents Chemother. 2007;51:2628
Proctor, Clin Infect Dis. 2008; 46:584

Tetracyclines

- Minocycline > doxycycline > tetracycline
- Off-label use (except tigecycline)
- One observational study (*), and one clinical trial (**) indicate efficacy of ~90+% crossresistance occurs, but if tet resistance is due to efflux, doxy and mino, (not efflux substrates) are still active in vitro
- 90+% of MRSA are susceptible
- Activity against GAS unknown
- Contraindicated in children ≤ 8 years old

*Ruhe and Menon, Antimicrob Agents Chemother 2007;51:3298
**Cenizal et al, Antimicrob Agents Chemother 2007;51:2628
Clindamycin

- FDA approved for treatment of staphylococcal infections
- Oral dose at 300-450 mg tid
- Excellent coverage against GAS
- Major issue is cross-resistance with macrolides
  - ribosomal methylase producers are or can become resistant
  - macrolide efflux pump producers not cross-resistant
- My personal favorite

D-Test for Inducible Clindamycin Resistance

Is There a Role for Decolonization?
Case

- 42 y/o hospitalist
- First episode of abscess on face 3 months prior: drained
  - Three weeks later, abscess of arm, back: CA-MRSA, treated with T/S
  - Four weeks later, recurrence of facial abscess: treated with clinda and mupirocin
- Now comes in with new abscess L cheek

What would you recommend for this patient?

1. Retirement
2. Decolonization regimen of intranasal mupirocin for 5-7 days
3. Intranasal mupirocin + chlorhexidine baths for 5-7 days
4. Rifampin + TMP/SMX for 5-7 days
5. All of the above

Rationale for *S. aureus* Decolonization

- Nasal carriage is present in about of third of humans
  - 20% of persons are persistent carriers
  - 60% are intermittent carriers
  - 20% almost never carrier *S. aureus*
- Carriers can be a source of *S. aureus* transmission
- Colonization predisposes to infection
- Eradication of carriage could
  - Prevent transmission of *S. aureus* to others
  - Prevent occurrence of infection
  - Prevent recurrent infection
Strategies for Decolonization

• Targeted (i.e., known carrier) vs. untargeted
• Chlorhexidine or bleach (1/2 c in bathtub) baths: largely ineffective.
• Mupirocin-based topical application to anterior nares
• Systemic (i.e., rifampin-based) therapy
• Kitchen sink approach

Review of Mupirocin Decolonization for S. aureus Decolonization

• 9 prospective trials of eradication of nasal carriage
  – Mupirocin highly effective in the short term
  – Less effective in achieving long-term eradication
• 7 prospective trials to prevent infection
  “The body of literature currently does not support routine administration of prophylactic intranasal mupirocin to patients in an attempt to decrease the rate of clinical infection.”
  Clin Infect Dis. 2003;37:933

Targeted Intranasal Mupirocin To Prevent Colonization and Infection by Community-Associated Methicillin-Resistant Staphylococcus aureus Strains in Soldiers: a Cluster Randomized Controlled Trial

Michael W. Elko,1,2 Matthew E. Gifford,1 David P. Dooley,1,4 Joseph C. McLean,3 James H. Jorgensen2
Jan E. Peterson,3 Kajerly A. Dren,3 Joshua S. Herby,3 Jason A. Bregula,2 Robert G. Rowland2
Paula J. Gray,3 Julia M. Crampton,3 Mary A. Diliberti,3 and Diana R. Hospenthal2

Antimicrob Agents Chemother. 2007;51:3591
Study Design

- Randomized, double-blind placebo controlled
- US army personnel enrolled in a 16-week medic training course
- Screened for *S. aureus* by swab culture of anterior nares
- Mupirocin bid in each nostril for 5 days for those culture positive for CA-MRSA
- Primary outcome: infections occurring within 16 weeks

Results

- 3447 soldiers screened and randomized
  - 1669 to placebo group
  - 1778 to mupirocin group
- Colonization
  - 134 (3.9%) with CA-MRSA (54% USA300 and 40% ST5/USA800)
  - 1316 (38.2%) with MSSA
- 65 placebo-treated and 66 mupirocin-treated subjects completed follow-up
  - Placebo treated
    - Colonization decreased from 4.0% to 3.2%
    - 5 (7.7%) infections
  - Mupirocin treated
    - Colonization decreased from 3.8% to 1.9%
    - 7 (10.6%) infections

Detection of MRSA Carriage in ICU Patients

<table>
<thead>
<tr>
<th>Site sampled</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose only</td>
<td>69</td>
</tr>
<tr>
<td>Throat only</td>
<td>71</td>
</tr>
<tr>
<td>Groin only</td>
<td>67</td>
</tr>
<tr>
<td>Nose and throat</td>
<td>82</td>
</tr>
<tr>
<td>Throat and groin</td>
<td>91</td>
</tr>
<tr>
<td>Nose and groin</td>
<td>88</td>
</tr>
<tr>
<td>Nose, throat, groin</td>
<td>94</td>
</tr>
</tbody>
</table>

Marshall and Speelman, J Clin Microbiol. 2007;45:3855
Effect of Mupirocin on Nasal, Pharyngeal, Perineal Carriage of S. aureus

- Healthy adults
  - 16 persistent carriers
  - 26 intermittent carriers
  - 20 noncarriers

- Cultured 1 day before and 5 weeks after a 5d course of intranasal mupirocin

- Nasal carriage eliminated in 69% of persistent carriers, 58% of intermittent carriers; similar efficacy in throat carriers

- Perineal carriage did not change significantly


Value of Whole-Body Washing With Chlorhexidine for the Eradication of Methicillin-Resistant Staphylococcus aureus: A Randomized, Placebo-Controlled, Double-Blind Clinical Trial

C. Naukk, MD, M. S. Schlie, MD, M. W. Bierwagen, RN
K. Obreht, MD, C. Schindler, MD, R. von Boera, MD

Infect Control Hosp Epidemiol 28:1036, 2007

Study Design

- Randomized, double-blind trial in hospitalized patients colonized with MRSA
- Whole-body washing with 4% chlorhexidine for 5 days versus placebo
- All subjects also received mupirocin intranasally and chlorhexidine mouth wash
- Sites sampled: nares, throat, groin area, perineal region, skin defects, and any previously colonized site
- Sampled taken before treatment and on days 3, 4, 5, 9, and 30 after the end of treatment
- 58 placebo subjects, 56 chlorhexidine-treated
- Primary outcome: eradication of carriage @ 30 days
## Results

- Any benefit gone by 5 days
- Eradication @ 30 days
  - 7 (13%) placebo recipients
  - 4 (8%) chlorhexidine recipients
- Adverse events: all more common with chlorhexidine
  - Discontinuation of daily washing: 4 chlor vs 1 placebo
  - Skin Fissures (17.7% chlor vs. 1.8% placebo)
  - Itching (41.5% vs 10.9%) or burning of skin (50.0% vs 10.9%)
- Failure associated with
  - Colonization of groin
  - Colonization of perineum
  - Colonization > 1 site
- Success associated with single site of colonization

## Setting

- German village, 144 persons (30 children), 58 households
- Presence of a shooting club, local voluntary fire brigade, a local citizen’s group, and a soccer club
- One bar
- Case finding: retrospective, self-report
**Epidemiology**

- 98% participation rate
- Case rates: 8/30 children and 28/111 adults
- 23 cases (64%) had experienced at least 1 relapse.
- Overall attack rate of 26% (95% CI, 19%-34%).
  - In persons colonized with PVL-positive *S. aureus* attack rate of 78% (95% CI, 40%-97%)
  - In persons colonized with PVL-negative *S. aureus*, attack rate of 19% (95% CI, 8%-33%)
- Microbiological findings
  - 36% (51 of 140 tested) with nasal colonization
  - 9 PVL-positive (7 ST121, 2 ST-30)
  - Mo MRSA

**Multivariate Analysis of Risk Factors Associated with Furunculosis**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVL-positive strain</td>
<td>9.2 (1.2–73.1)</td>
</tr>
<tr>
<td>Contact with a case</td>
<td>4.7 (1.3–17.3)</td>
</tr>
<tr>
<td>Voluntary fireman</td>
<td>5.5 (1.6–19.0)</td>
</tr>
<tr>
<td>Sharing objects</td>
<td>3.6 (1.1–12.2)</td>
</tr>
<tr>
<td>Chronic skin disease</td>
<td>12.3 (1.5–100.2)</td>
</tr>
<tr>
<td>Owning live chickens</td>
<td>0.3 (0.1–0.7)</td>
</tr>
</tbody>
</table>

**Treatment Regimen**

- Mupirocin 3x daily for 5 days
- Alcohol-based hand sanitizer after mupirocin
- Octenidin-based wash of skin and hair daily
- 0.1% chlorhexidine solution gargle 3x daily
- Disinfection of personal items, bathtub/shower floor with an alcohol-based antimicrobial cleanser daily
- Towels, bedclothes, underwear, clothing changed and washed daily (water temperature > 60°C)
- Increased hand hygiene and minimized contact with other villagers during decolonization
- Cleaning and disinfection of fire-protective suits
Mupirocin for a Year

- 34 patients with recurrent MSSA infections treated with mupirocin for 5 days
- 17 randomized to placebo
- 17 randomized to mupirocin 5d treatment monthly for a year
- 8 mupirocin and 2 placebo patients remained free of nasal colonization (p < 0.01)
- 26 infections in mupirocin recipients vs 62 in placebo recipients (p < 0.002)

Raz, et al, Arch Intern Med. 1996;156:1109

Regimens for Eradication of S. aureus carriage

Falagas et al. Am J Infect Control 2007; 35:106

Decolonization

- Chlorhexidine:
  - Not effective alone,
  - Transient effect at best
- Mupirocin:
  - Effective short-term eradication of nasal and pharyngeal colonization
  - Little evidence that it prevents infection (with some exceptions?)
- Rifampin (with another active agent to prevent resistance)
  - Side-effects & drug interactions
  - Best agent for eradication of colonization
  - Little evidence at best that it prevents infection
- MRSA: no evidence supporting use of any regimen for prevention of infection
Cochrane Review of Mupirocin for Staph. aureus Nasal Colonization

- Hospitalized patients + positive nasal culture
  - Surgical patients
    - Cardiothoracic surgery
    - Orthopedic surgery
    - General surgery
  - Dialysis patients (CAPD)
  - General medicine patients???? (only one study, no benefit)
- General medicine patients???? (only one study, no benefit)

The Cochrane Library 2009, Issue 1