Update on the Management and Prevention of MRSA

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Disclosures
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Case Study Skin Infections

• 20-year-old wrestler presented to the ER with a “spider bite” on his arm. He developed a stinging feeling the previous day and now has pain in a golf ball-sized area

• Temperature, 38.7°C

• Fluctuant area on arm that is warm, red, tender, and 5 × 7 cm

• WBC, 12,800/µL

• Gram stain of aspirate showed gram-positive cocci
What is the most likely organism?

A. MRSA
B. MSSA
C. group A Streptococci
D. group B Streptococci
MRSA in U.S. EDs, August 2004

- 73% with MRSA had no risk factor for HCA infection

S. aureus
N=320

Total Isolates
N=422

What is the rate of penicillin resistance for group A streptococci at your hospital?

1. 0%
2. 25%
3. 65%
4. 100%
Epidemiology of *S aureus* Infections

- Organism usually spread by direct person-to-person contact
- Spread from inanimate objects can occur and has been seen in outbreaks among football players, fencers, river raft guides, etc.
- Common denominators: Crowding, Contact, Cleanliness, Compromise of skin

Epidemiology of *S. aureus* Infections

- Predominant reservoir of organisms = human beings
- Approximately 15% – 35% of normal people harbor *S. aureus* in nares or pharynx at a given point. Longitudinal view of carriage:
  - 30% prolonged, 50% intermittent, 20% never
  - Vaginal carriage in ~10% of premenopausal women
  - Rectal and perineal carriage also occur especially in CAMRSA
  - Oral pharyngeal colonization is higher for CAMRSA
- Patients with MRSA infections may have high prevalence (60%) of gastrointestinal colonization or carriage
Methicillin Resistant *S. aureus*

Healthcare and community associated

Invasive infections: 80,000  Deaths: 11,000
CA-MRSA Infections

Ocular, orbital infections

SSTI

Postpartum mastitis
Pneumonia

Hand infections

Endocarditis
Bacteremia
Clin Infect Dis 2006; 42:647-56

Surgical site infections

Necrotizing fasciitis

Pyomyositis

Prosthetic joint infections

Diabetic foot infections

Hematogenous osteoarticular infections
### S. aureus Susceptibility – Detroit and Akron

<table>
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<th></th>
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Definitions of VISA, hVISA and VRSA

Susceptible
MIC ≤ 2.0
ug/ml

hVISA
VISA MIC 4-8
ug/ml

VRSA MIC ≥ 16
ug/ml

??Treatment with vancomycin

CLSI M100-S16 16th suppl 2006;
Jones RN CID 2006;42:S13-24
Detection of Isolates with vanco MIC \( \leq 2 \); Broth Microdilution vs E test

<table>
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<tr>
<th>MIC</th>
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<th>E Test</th>
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<tr>
<td>1</td>
<td>97%</td>
<td>10%</td>
</tr>
<tr>
<td>1.5</td>
<td>0</td>
<td>58%</td>
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<tr>
<td>2</td>
<td>3%</td>
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</table>

Sader, AAC, 2009
Detection of VISA by different susceptibility testing methods

• Swenson, JCM 2008, compared to CLSI broth microdilution for detection of VISA
  – Phoenix, Microscan, E test overcalled some susceptible strains as VISA
  – Sensititre, Vitek 2 undercalled some VISA strains as susceptible
  – Vitek legacy, undercalled some VISA as susceptible, overcalled some VISA as resistant

• Acceptable variability for MIC methods is +/-1 doubling dilution
Vancomycin MIC’s and Outcome

• Probability of achieving AUC/MIC ≥ 400 is 0% if MIC = 2
• Elevated MIC (1.5-2mcg/ml) is associated with vancomycin treatment failures
• The presence or absence of “MIC creep” is controversial
  – Observation in some centers but not others
  – ?technical artifact related to test method used.
MRSA: Treatment Options

- FDA-approved
  - Vancomycin
  - Linezolid
  - Daptomycin
  - Tigecycline
  - Telavancin
  - Ceftaroline
  - Dalbavancin
  - Oritavancin
  - Tedizolid

- Not FDA-approved, but frequently used
  - TMP-SMX
  - Clindamycin
  - Tetracyclines

- Investigational agents
  - PBP-2a–targeted β-lactams (e.g., ceftobiprole)
  - Synthetic antimicrobial polypeptides (SAMPS)
  - FtsZ targets
Daptomycin

**Microbiology:** gram positive: MRSA, MSSA enterococci (VRE)

**Action:** cidal

**Indications:** Not pneumonia, bacteremia and right sided endocarditis, skin infections, prosthetic joint and septic arthritis

**Dose:**
- 4mg/kg IV q 24h soft tissue
- 6mg/kg q 24h for bacteremia (8-10mg/kg q24h off label)
- osteomyelitis 6mg/kg q 24h (off label)

**Adverse Events:** diarrhea (5-12%), vomiting (3-12%) anemia (2-13%), elevated CPK (3-9%), renal failure (2-3%), pneumonia (3%)

**Drug interactions:** avoid with BCG, typhoid vaccine, caution with statins
Daptomycin vs Standard Therapy for Bacteremia and Endocarditis Caused by S. aureus

N=124
Daptomycin 6mg/kg
Outcome: 53/120 D vs 48/115
44.2% vs 41.7% (Δ = 2.4, -10.2 to 15.1%)
Microbiologic failure = 19 D vs 11
Reduced D susceptibility in 11/19
Renal dysfunction = 11% D vs 26.3%

Fowler et al, NEJM 2006; 355: 653-665
Telavancin

Microbiology: gram positive, MRSA, VISA, MSSA, enterococci ampicillin sensitive

Action: cidal, dual mechanism

Indications: skin, skin structure, pneumonia (MRSA) HAP, VAP

Dose: 10mg/kg IV q 24h (reduce in renal disease)

Adverse Events: metallic taste (33%), nausea (5-27%), vomiting (14%), serum creatinine rise (8%), fetal risk in animals, interferes with reagents for coagulation assays

Pregnancy category: C
Ceftaroline

**Microbiology:** gram positives, MRSA, MSSA, not enterococci, gram negatives but less than 3rd generation cephalosporins

**Action:** cidal, cell wall PBP2A

**Indication:** skin, skin structure infections, pneumonia (not MRSA)

**Dose:** 600 mg q12h

**Adverse events:** (+) Coombs test without hemolysis (11%), pruritus (4%), rash (3%), diarrhea (5%), Increased transaminases (2%), *C. difficile* (<2%), cross reactivity with cephalosporins
Ceftaroline Heteroresistant *S. aureus*

**Definition:** subpopulations of lesser susceptibility within larger population of fully susceptible microorganisms

**Isolates:** N=57 MRSA(20), hVISA(4), VISA (20), DNSSA (7), LNSSA(6)

**Methods:** PAP (triplicate)

Resistance stability testing performed

**Results:** 21% isolates were heteroresistant

Occurred among strains with reduced susceptibility to vanco, dapto, and linezolid

did not occur in USA 300

resistance was unstable

S. Saravolatz, H. Martin, J. Pawlak, L. Johnson, L. Saravolatz  AAC 2014
TMP/SMX vs Vancomycin against S. aureus

N=101 IVDU’s Hospitalized
Bacteremia (65) Endovascular (49)
No difference in defervescence, WBC drop, hospital stay
Overall cure 37/43 (TS) vs 57/58 (v) P ≤ 0.02
Bacteremia duration
MSSA(N=54) 7.8d (TS) vs. 3.5d (V) P = 0.05
MRSA(N=47) 5.2d (TS) vs. 5.6d (V) P ≥ 0.2
Comparable rates for toxicities

Markowitz, Quinn, Saravolatz
Ann Intern Med 1992; 117; 390-398
**TMP/SMX vs Vancomycin for MRSA**

**Objectives:** Non inferiority of TMP/SX vs Vancomycin for severe MRSA infections

**Methods:** Open label, randomized controlled trial of TMP/SMX IV 320/1600 BID vs Vanco 1g q 12 h
Primary outcome= death, treatment failure at 7 days, persistence of bacteremia, and persisting organ failure

**Results:** N=252 (91 bacteremias- 36%)
Failure: 38% (TMP/SMX) v 27%, (V), RR= 1.38, 0.96, 1.99
Non inferiority difference 10.4%

**Conclusion:** High dose TMP/SMX did not achieve non inferiority compared to vancomycin

Paul et al, BMJ 2015; 350:2219
Clindamycin vs TMP-SMX for Uncomplicated Skin Infections

N= 524 patients with abscesses (30.5%), cellulitis (53.9%) and mixed infections (15.6%)

Clindamycin 300 mg T.I.D. vs SMX/TMP 2 SS B.I.D

Culture: N=296, *S. aureus* =41.4%, MRSA=77%

Clindamycin Resistant =12.4%,

SMX/TMP Resistant =0.5%

Cure rates = 89.5% (C) vs 88.2% (SMX/TMP)

Cure rates similar for abscesses and cellulitis

Miller et al, NEJM 2015:372
Figure 2. Comparison of the Efficacy of Clindamycin and TMP-SMX in Patients with Uncomplicated Skin Infection.

The graph shows the proportion of patients cured by the time of the test-of-cure visit in the intention-to-treat population and the population that could be evaluated. The actual confidence level was 95.60% after adjustment for interim analyses.
Dalbavancin – Therapy for SSTI

Dalbavancin – a lipoglycopeptide, half life=2 weeks, 53% protein bound,

Microbiology: MIC 90 =0.06 mcg/ml

Action: cidal

FDA approval: SSTI only

Clinical trial: Dalbavancin day 1(1500mg) vs 1 (1000mg)& 8(500mg)
Clinical outcomes on day 14 were 84% v 84.8% ( n=698)

Adverse events: SAE  D=2.6%, V-L= 4.0%  NS
Any events D 1 dose=20.1%, 2 dose=19.9%
Headache, nausea, vomiting, diarrhea <3%
Drug discontinuation 1.7% vs 1.4%

Dunne et al, CID: 2016
Boucher et al NEJM, 2014 Showed non inferiority to Vancomycin
Oritavancin - Lipoglycopeptide, prolonged half life 2 weeks

FDA approval: SSTI

Clinical Trial: Oritavancin 1200 mgx1(3h) vs Vanco 7-10d
Cure  0=79.6% vs. V= 80.0%
Adverse events: SAE 0=7.4% vs. V= 7.3%
Drug discontinuation 0=2.3% vs V=2.7%

Corey, NEJM, 2014
<table>
<thead>
<tr>
<th>Drug</th>
<th>DRTX Estimates</th>
<th>MD estimates</th>
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<tr>
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<td>Total Costs</td>
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<td>$13,022</td>
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Equity Research, Credit Suisse, January 2014
Prolonged Half Life Drugs

**PRO**
- Administration frequency
- Fewer compliance issues
- Adverse events
- No long term access
- May be helpful in chronic Infections (osteomyelitis)

**Con**
- Limited clinical experience/indications
- Allergy/adverse event exposure time
- Infusion time (0), 2 doses (D)
- Less closely monitored
- Most patients in trial were not MRSA
- Drug cost
- Resistance with overuse
Efficacy of Chlorhexidine on Hospital-Acquired Infections

**Background:** Chlorhexidine baths have been shown to reduce hospital-acquired infection and acquisition of multidrug resistant organisms.

**Methods:** A multicenter, cluster–randomized, non-blinded crossover trial (9ICUs, 6 BMT programs) chlorhexidine wash cloths versus non-antimicrobial washcloths for 6 months followed by a crossover for 6 months.

**Results:** N=7727 patients; MDRO= 5.10(C) vs. 6.6/1000 patient days, p=0.03, Hospital acquired bacteria= 4.78 (C) vs 6.6/1000 patient days, p=0.007.

**Conclusions:** Chlorhexidine washcloths reduced the rate of acquisition of MDR O’s and reduced the rate of hospital-acquired bacteremias.

Climo et al, NEJM, Feb, 2013
Retapamulin and Mupirocin Resistance

**Isolates:** 155 MRSA

**Results:**
- Retapamulin 2.6%,
- Mupirocin 10.3%
- Mupirocin High level, 10/155, 6.5%
- Low level 6/155, 3.9%

Saravolatz et al AAC 2013
Decreased Susceptibility – Retapamulin, Mupirocin and Chlorhexidine

Isolates: 200 (I-SSTI), 200 (≤ 3 SSTI) S. aureus

Results: Retapamulin resistance 38/400 (9.5%)
Mupirocin resistance 39/400 (9.8%)
Chlorhexidine resistance 14%

McNeil et al AAC 2014
LTX – 109 against *S. aureus*

LTX -109 SAMP – cidal via cell membrane disruption

**Isolates:** MRSA (96), VISA (33), VRSA (13), LNSSA (6), DNSSA (7)

**Results:**
- MIC range = 2-4 mcg/ml
- MBC range 2-8 mcg/ml
- Not influenced by resistance to other agents
- Formulation concentration = 20,000 mcg/ml
- Rapidly kills *S. aureus* in < 1 hour
- Post antibiotic effect may be up to 8 hours.

Saravolatz et al AAC, 2012, ICAAC, 2014
FtsZ Targets

- Bacterial cell division protein FtsZ- a new drug target.
- Critical role in cell division. If disrupted leads to cell death
- Active against \textit{S. aureus} resistant to various antimicrobial agents.

Kaul et al, AAC 2013
FtsZ Targeting Drugs inhibiting Bacterial Replicase

Images showing effects of Vehicle and TXA707 at different time points:
- **Vehicle - 1 hour**
- **TXA707 - 1 hour**
- **TXA707 - 4 hours**
- **TXA707 - 9 hours**
Recurrent MRSA SSTI: Decolonization Regimens

- Mupirocin twice daily x 5-10 days (CIII)
  - Raz – Arch Int Med 1996, RCT of pts with recurrent MSSA furunculosis: mup vs placebo: decrease nasal colonization (P<0.001), decrease recurrent SST (P<0.002)
  - Ellis AAC 2007, Cluster RCT decrease nasal colonization but not 1st time SSTI

- Mupirocin twice daily x 5-10 days AND topical skin antiseptic (e.g. chlorhexidine or dilute bleach baths) x 5-14 days (CIII)
  - Whitman ICAAC 2008, cluster RCT: CHG wipes no decrease in SSTI’s
  - Bode NEJM 2010 RCT combo decreased surgical site infection rates by 60%
  - Kaplan – bleach baths: (¼ cup, ¼ tub water or 1 tsp per gallon for 15 min, 2x/week x 3M
Recurrent MRSA SSTI: Decolonization Regimens

– Oral antimicrobials not routinely recommended (A III) Consider oral agent in combination with rifampin only if other measures fail (CIII)

  • Cochran Review 2003, No benefit in HA-MRSA eradication or reduction in infection rates

  • Falagas AJIC 2007, systematic review of rifampin – based combination regimens vs monotherapy with other antibiotics improved eradication of \textit{S.aureus}, no assessment of infection rates

  • Watch for rifampin resistance, drug interactions, side effects
Bleach Baths

**Study Design:** Randomized, single-blinded controlled trial of bleach baths BIWx3 months + routine hygienic measures (RHM) vs RHM alone. 5ml bleach/ 1 gallon H₂O

**Patients:** 3 m-18 years treated for suspected *S. aureus* STI

**Outcome:** nurse blinded to group contacted families at 2 W, 3, 6 and 12m
Results: RHM&B RHM alone
MA-STI (1y) 84/495(17%) 103/492 (20.9%) P=0.15

Conclusion: Most infections were MRSA (138/182)
60% colonized at ≥ 1 site.
Colonization sites groin (38%) > nares (22%) > throat (17%)
Colonization decreased with age (6y), 46% v 27% P<0.001
Bleach baths decreased recurrence MA-STI by 20% but
this was not statistically significant

Kaplan et al CID 2014
Percent Hand Washing Compliance among HCWs in 34 Observational Studies, 1981-2000

Percent Compliance

Median
Summary of Take Home Points

• MRSA is the major *S. aureus* pathogen in the hospital and the community

• Treatments in the hospital still favor vancomycin but other options include daptomycin, telavancin, and linezolid

• Oral therapies include SMX/TMP, doxycycline, clindamycin, and linezolid

• Prevention remains a challenge, but handwashing, chlorhexidine, and mupirocin currently should be used.
It’s no mystery you feel a song coming on... you have a staff infection.