In purulent ABSSTI, 76% staph aureus and 59% of those were MRSA

Antibiotic therapy not concordant with cultures in 57%

Let’s meet Eli...

- 25 year old male seeing you for a painful skin lesion...
- Third visit this year for skin lesions
- Picks at this skin
- Works in a gym
- No pets
- Labs normal, HIV negative
- Wants treated and does not want this to come back...

Epidemiology of MRSA ABSSTI

- First described in 1961 after introduction of methicillin
- Initially healthcare associated, now CA-MRSA most common cause of ABSSTI in ED patients
  - In purulent ABSSTI, 76% staph aureus and 59% of those were MRSA
  - Antibiotic therapy not concordant with cultures in 57%

Characteristics of CA-MRSA

CA-MRSA
- SCC mec type IV
- β-lactam resistance
- PVL toxin positive
- ABSSTI, necrotizing pneumonia
- Crowding and close contacts

HA-MRSA
- SCC mec type I, II, III
- Multidrug resistance
- PVL toxin rare
- Nosocomial pneumonia, catheter-related / bloodstream infections
- Long-term care residents, ICU, prolonged hospitalizations, catheters
CA-MRSA and USA 300

- Virulence factors allow it to colonize surfaces and spread between close contacts
- **5 (or 6)** C's of CA-MRSA transmission
  - Contact (skin-to-skin)
  - Cleanness
  - Compromised skin integrity
  - Contaminated objects, surfaces
  - Crowded living conditions
  - Capsules (antibiotics exposure)

Who gets CA-MRSA?

- Athletes, soldiers, correctional facilities, daycare children, households
- Men who have sex with men (MSM) and persons with HIV
  - MSM had a RR 13.2 in acquisition of USA300 CA-MRSA
  - Sexual transmission?
  - Increased incidence in lower CD4 counts
- Human host factors + poor skin integrity = CA-MRSA

OBJECTIVES

- Epidemiology of acute bacterial skin and soft tissue infections (ABSSTI)
- Characteristics of Methicillin-Resistant Staphylococcus Aureus (MRSA), including community acquired (CA-MRSA)
- Clinical disease and diagnosis
- Treatment with incision and drainage (I&D) and/or antimicrobials
- Chronic carriage and decolonization for recurrent infections

Back to Eli...

- Elevated risk for CA-MRSA
  - Picks at his skin
  - Gym exposure
  - Screened negative for HIV

Clinical Presentation

- **ABSSTIs** such as simple abscesses / cellulitis to deeper infections
- Often necrotic attributed to a “spider bite”
- Positive nasal swab?
  - Colonization leads to infection in up to 38% of cases
  - HR 6.52 for future MRSA-positive disease over the next year

Diagnosis

- Culture of purulent lesions directs antibiotics, especially with severe disease or prior non-response
- Ultrasound can be helpful
  - Changed management in 56%
  - Ensures adequacy of drainage
  - Helpful in treatment failure or deeper abscess

Diep Ba, Annals.2008

Gupta AK, Int J of Derm. 2015
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Management of “Simple” Disease

• Minor infections may resolve with heat or topical mupirocin
• “Simple” abscesses, I/D adequate?
• TMP-SMX (T) vs placebo (P) post I/D
  • Failure in 57% (T) vs 26% (P)
  • New lesion development in 13% (T) vs 26% (P)

Would Use Antimicrobials...

• Severe disease of multiple sites or progression with cellulitis
• Systemic illness
• Comorbidities or immunosuppression (diabetes, AIDS, neoplasm)
• Extremes of age
• Areas difficult to drain or large abscesses (> 5 cm)
• Associated septic phlebitis
• Lack of response to previous I/D

Empiric Antibiotics

• If purulent, I/D and empirically treat with MRSA-active antibiotic
• Additional coverage for β-hemolytic streptococci?

Uncomplicated MRSA ABSSTI

• Clindamycin 300-450 mg po TID or 600 mg po IV TID
  • Excellent tissue and bone penetration
  • Bacteriostatic so not for endovascular or CNS infections
  • Diarrhea in 20% with increased risk of Clostridium difficile

<table>
<thead>
<tr>
<th></th>
<th>TMP/SMX + cephalaxin (n=73)</th>
<th>Cephalaxin (n=73)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Cure at 30 days</td>
<td>85%</td>
<td>82%</td>
<td>0.66</td>
</tr>
<tr>
<td>Progression to abscess</td>
<td>7%</td>
<td>7%</td>
<td>1.0</td>
</tr>
<tr>
<td>At</td>
<td>49%</td>
<td>57%</td>
<td>0.63</td>
</tr>
<tr>
<td>Cdiff</td>
<td>0</td>
<td>2%</td>
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</tbody>
</table>

Clinical Trial: Comparative Effectiveness of Cephalaxin Plus Trimethoprim-Sulfamethoxazole Versus Cephalaxin Alone for Treatment of Uncomplicated Cellulitis: A Randomized Controlled Trial

D zone test for inducible resistance
Positive test as blunting of the clindamycin zone of inhibition
Uncomplicated MRSA ABSSTI

- TMP-SMX: 2-3 DS tabs p.o. BID
  - ≥ 95% of CA-MRSA strains are sensitive
  - Drug rash / hypersensitivity
  - Hematologic suppression
  - Hyperkalemia
  - Avoid in the third trimester
  - May be preferred agent in HIV

Other agents...

- Linezolid is effective but expensive and toxic with prolonged use
- Rifampin is bactericidal and penetrates biofilms
  - Low barrier for resistance
  - Unclear dosing
  - Possible role in decolonization?

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Back to Eli...

- Assess for I&D
- Post-I&D, would give antibiotics given his recurrent skin lesions
- Oral therapy with TMP-SMX, doxycycline, or clindamycin
- No other antimicrobial indicated as purulent disease so strep unlikely
Complicated MRSA (cABSSTI)

• Deep soft-tissue infection, surgical/traumatic wound, major abscesses, spreading cellulitis, infected ulcer, burn
• If systemic toxicity or worsening despite oral antibiotics, consider inpatient management with surgical intervention or outpatient parenteral therapy

Treatment for MRSA cABSSTI

• Vancomycin 55-75 mg/kg/dose IV every 8-12 hr for invasive disease and/or bacteremia
  • No new agent has demonstrated clinical superiority
  • Slowly bactericidal with variable tissue penetration
  • MIC creep?
• Heteroresistant vancomycin-intermediate (HvVISA) / VISA associated with treatment failure
• Vancomycin resistance (VRSA) rare

Treatment for MRSA cABSSTI

• Linezolid 600 mg po/IV BID for MRSA ABSSTI and pneumonia
  • Broad activity including VISA / VRSA
  • 100% oral bioavailability with excellent tissue penetration
  • Bacteriostatic and expensive and...
  • After two weeks...
  • Hematologic toxicity
  • Often irreversible peripheral / optic neuropathy
  • Lactic acidosis
  • Serotonin syndrome

Treatment for MRSA cABSSTI

• Daptomycin 4-6 mg/kg/dose IV daily for bacteremia, right-sided endocarditis, complicated ABSSTI
  • Rapidly bactericidal
  • Alternative for severe infection with elevated MIC to vancomycin but cross-resistance
  • Elevations in CPK (2.8-6.7%) and eosinophilic pneumonia
  • Inactivated by pulmonary surfactant

Other agents for MRSA cABSSTI

• Quinupristin-Dalfopristin rarely used
• Telavancin is bactericidal for ABSSTI and pneumonia
  • MRSA, VISA, VRSA, daptomycin (DNS) and linezolid (LNS) non-susceptible strains
  • Promising efficacy in bacteremia (ATTAIN/ASSURE)
  • Significant renal toxicity and worse outcomes in renal dysfunction
  • Teratogenicity, QT prolongation, thrombocytopenia

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Ceftaroline

- 5th generation cephalosporin for ABSSSI and pneumonia
- Bactericidal, well-tolerated, broad-spectrum
- CANVAS compared ceftaroline to vancomycin/aztreonam for 9-12 days for ABSSSI
  - Clinical cure similar: 85.5% (C) vs 85.3% (VA)
  - Clinical cure for MRSA similar: 77.3% (C) vs 75.3% (VA)
  - <5% adverse effects

New FDA Criteria

- For ABSSSI, primary endpoint of clinical response at 48-72 hours after initiating antibiotic
- Absence of fever and stabilization in size of area
- Quantifiable, reproducible, and shows sensitivity to drug effect
- Requires a larger area of skin infection

Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections

- The ESTABLISH-1 Randomized Trial
  - Early 79.6% (T) vs 79.4% (L)
  - End of treatment 69.3%-85.5% (T) vs 71.9%-86% (L)
  - Similar response rates in MRSA
  - Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial
  - Early 85% (T) vs 83% (L)
  - Less gastrointestinal (GI) side effects with tedizolid

Conclusions

- Tedizolid statistically non-inferior to linezolid in early clinical response for ABSSSI including MRSA
- Once daily dosing with a shorter duration
- Less gastrointestinal side effects
- Less myelosuppression and lack of serotoninergic stimulation

DISCOVER 1 and DISCOVER 2

The NEW ENGLAND JOURNAL of MEDICINE

JUNE 5, 2014

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection

Helen W. Boucher, M.D., Mark Wilcox, M.D., George H. Talbot, M.D., Selja P. Patteguntas, M.D., Anita F. Das, Ph.D., and Michael W. Dunne, M.D.
Conclusions

• Once-weekly dalbavancin non-inferior to vancomycin -> linezolid for ABSSSI including MRSA
• Adverse events infrequent in dalbavancin
• Dalbavancin group had shorter duration of therapy and 25% treated entirely as outpatient
• On-going studies in osteomyelitis

Single-Dose Oritavancin Versus 7–10 Days of Vancomycin in the Treatment of Gram-Positive Acute Bacterial Skin and Skin Structure Infections: The SOLO II Noninferiority Study

Oritavancin x1 vs 7-10 days of vancomycin
Primary endpoint at 48-72 hrs and investigator-assessed clinical cure at 7-14 days

Conclusions

• Oritavancin x 1 is non-inferior to 7-10 days of vancomycin in ABSSSI
• Efficacy extended across subgroups, including MRSA
• Adverse effects were uncommon
• Potential to advance outpatient parenteral therapy and improve adherence

Duration of therapy

• Licensing trials treat for >14 days but individualized based on clinical response
• No differences in outcome in uncomplicated cellulitis receiving 5 vs 10 days
• 43 randomized to 5 additional days of levofloxacin vs placebo
• No difference in clinical cure (98% vs 98%)

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**Recurrent disease**

- Two or more MRSA ABSSTs at different sites over 6 months
- Interplay between pathogen, host colonization and behavior, and environmental exposure
- Don’t forget about hygiene...
  - Cover wounds
  - Avoid sharing personal items (towels, soaps)
  - Wash surfaces that come into frequent contact with bare skin

**Recurrent because of colonization?**

- CA-MRSA has virulence traits that enhance infectivity after colonization
  - 87% with ABSSTI remained colonized for median of 21 days
  - 19.8% never cleared over 6 months
- 1/4 - 1/3 harbor CA-MRSA in the nose at any time
  - If you eliminate nasal carriage, does colonization disappear from other sites?
  - If you eliminate colonization, do you decrease the risk for infection?

**Cluzet VC, CID. 2015**

**Data to support decolonization in prevention of recurrent infection not robust**

- The role of colonization at other sites in recurrent disease is unknown
- Regimen, frequency, duration of decolonization agents unclear
- Potential to select for more resistant or virulent strains

**Laupland KB, CID. 2003**

- Soldiers randomized to mupirocin vs placebo, or if MRSA colonized, treated with mupirocin vs placebo
  - 3.9% colonized: infection in 10.6%(M) vs 7.7%(P)
  - Non-colonized: infection in 3.5%(M) vs 4.3%(P)
  - New colonization in 1.4%(M) vs 1.6%(P)
  - No decrease in infection or prevention of new colonization for nasal mupirocin in this study

**Ellis MW et al. Antimicrob Agents Chem. 2007**

**Wertheim, HF, Ann Intern Med. 2004**

**Van Rijen, M, Cochrane Database Sys Rev. 2008**

**Mupirocin for decolonization**

- Review of 16 randomized controlled trials to assess mupirocin in eradication of MRSA colonization
  - 13% (M) vs 91.53% (P) in health care workers
  - 12.6% (M) vs 92.8% (P) in HIV positive persons
  - 2.4% (M) vs 90.6% of hemodialysis patients
  - Highly effective for eradication in short term but decreases in infection?

**Cluzet VC, CID. 2015**

**Mupirocin for infection prevention?**

- Soldiers randomized to mupirocin vs placebo, or if MRSA colonized, treated with mupirocin vs placebo
  - 3.9% colonized: infection in 10.6%(M) vs 7.7%(P)
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**Ellis MW et al. Antimicrob Agents Chem. 2007**

**Maybe a different population??**

- 1602 non-surgical carriers randomized to M vs P x 5 days
  - No difference in infection (2.6% M vs 2.8% P)
  - No difference in length of stay (86 both)
  - Mupirocin did not prevent MRSA infection in non-surgical patients who were MRSA colonized
  - Cochrane review found no decrease in MRSA infections with mupirocin in non-surgical patients...but other populations may benefit?
Surgical patients?

- 430 surgery patients randomized to pre-op M vs P
  - 2.9% M vs 4.4% P developed surgical site infection
  - If MRSA colonized, 4% M vs 7.4% P developed infection in general
  - Fewer infections if decolonized, but unrelated to surgical site

- 614 orthopedic patients randomized to pre-op M vs P
  - 16% M vs 21% P colonized 35 days after
  - No difference in surgical site infection (4.4% M vs 5.4%)
  - Good data for decolonization but unclear it prevents infection

Dialysis patients??

- Peritoneal dialysis patients randomized to monthly M vs P
  - No difference in catheter or exit site infections or peritonitis
  - Significant difference in staph exit site infections (14M vs 44P)

- Colonized hemodialysis patients randomized to M vs P x 9 mo
  - Decreased colonization (64%M vs 58%P) and significantly fewer infections (69%M vs 33%P)
  - Shorter follow up in mupirocin group

Repeated courses?

- Monthly M vs P for one year in MRSA colonized patients with recurrent infection
  - Significant reduction in skin infections (26M vs 52P)
  - Only 2/10 decolonized patients had recurrent infection vs 22/24 colonized patients
  - Monthly mupirocin in MRSA carriers reduced the incidence of colonization, which lowered the risk of skin infection

Any reason we shouldn’t?

- Mupirocin resistance has been reported in community settings but appears not to be widespread
  - Recolonization in 38-43% 4-6 weeks after
  - Other alternatives??

Skin antiseptics

- Chlorhexidine (CHG) demonstrates efficacy in bundles, but ineffective alone
  - Prospective military study randomized to standard (S), enhanced-standard (ES), or CHG
    - Overall 4% developed ABSSTI, 26% due to MRSA
    - ABSSTI rates 3.48(1.50) S vs 4.18 (1.29) ES vs 4.71 (0.97) CHG
    - Neither hygiene / education nor CHG prevented MRSA-related ABSSTI

- CHG vs control cloths over body thrice weekly
  - MRSA colonization in 2.6% CHG vs 6% control (p=0.034)
  - 0.094 CHG vs 0.071 control had ABSSTI (p=0.14)
  - CHG decreased MRSA colonization but did not reduce ABSSTI
  - Bleach baths??
    - Well tolerated but little data of effectiveness
    - In vitro does kill MRSA but as of now considered expert opinion
Oral antimicrobials??

- Review showed no difference in MRSA eradication with mupirocin vs oral/topical antibiotics vs placebo
- Did not examine infection rates
- Rifampin effective at eradication but not sustained at 90 days

- Review of rifampin-based regimens in MRSA eradication
  - Rifampin effective even as monotherapy
  - 2% toxicity with average of 17% resistance
  - Rifampin effective in eradication and addition of another antibiotic may decrease resistance

Combination therapy??

- Randomized to CHG, mupirocin, rifampin/doxycycline vs nothing
- Negative nasal swabs in 74% treated vs 32% untreated at 3 mo
- Mupirocin resistance in 5%

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Loeb, M et al. Cochrane Database Syst Rev. 2003
Falagas, ME et al. J Antimicrob Chemother. 2007

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Falagas, ME et al. J Antimicrob Chemother. 2007

IDSA recommendations

- Mupirocin alone or with topical CHG for decolonization
- Oral antibiotics not recommended unless failure of above
  - Consider rifampin-based combinations (TMP-SMX or doxycycline)
  - Can be used with topical antiseptics
  - Emphasize hygiene

Decolonize everyone??

- 183 colonized children with > 1 CA-MRSA ABSSTI randomized to index (I) vs household (H) decolonization
  - At 1 mo, 59% of patients in (I) and 51% in (H) eradicated MRSA colonization
  - ABSSTI reported in 72% of patients in (I) vs 53% in (H)
  - Household decolonization may reduce the incidence of subsequent ABSSTI

Simor, A et al., CID 2007
Fritz, S et al., CID 2012

Back to Eli...

- Start with hygiene
  - Stop picking!
  - Wash hands and launder clothes from the gym
  - 2% mupirocin to anterior nares daily x 5 days
  - 4% chlorhexidine total body wash x 5 days
  - Would not give systemic antibiotics unless he fails decolonization, then would consider rifampin-containing regimen

Conclusions

- Purulent ABSSTI are commonly caused by CA-MRSA
  - Virulence factors that allow it to persist in the environment
  - Increased risk of transmission and recurrent infection

- Treatment of infection includes I/D
  - Addition of antibiotics (oral or IV) based on severity of infection
  - New agents with longer half lives now exist

- Data for management of recurrent disease is conflicting
  - Start with mupirocin and CHG
  - If fail, consider systemic antibiotics, including rifampin
  - Decolonization of the household may be necessary