TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

Katie Gordon
PGY1 Resident

and Brian Malecek
PGY1 Resident

OBJECTIVES

- Recognize the most common pathogens associated with acute bacterial skin and soft tissue infections.
- Explain the main resistance mechanisms of Staphylococcus aureus and differentiate between MSSA, MRSA, hVISA and VRSA.
- Investigate new medications that may be useful in the treatment of MRSA skin and soft tissue infections and formulate a patient specific regimen

2014 SSTI GUIDELINES

CASE 1

- CC: "I have this itchy red thing on my leg and it is starting to hurt."
- HPI: CP is a 63 yom presenting with purulent LLE cellulitis. He is 74" and 112 kg. CP received TMP-SMX outpatient 3 weeks prior with a suspected community acquired-MRSA cellulitis on his right arm.
- Vitals: Tmax 101.2°F, BP 121/82, HR 105, RR 18
- NKDA
- Labs: 4.2 25 0.7 14.2 93 426

- What should CP be treated with empirically upon admission?
  A. Nothing he received TMP-SMX already
  B. Vancomycin 1500 mg IV Q12 hours
  C. Clindamycin 300 mg IV Q8 hours
  D. Linezolid 600 mg PO Q12 hours

COMMON CAUSATIVE PATHOGENS
**STAPHYLOCOCCUS AUREUS**

- **Morphology:** Gram positive cocci in pairs and clusters
- **Resistance Mechanism:**
  - Penicillinase: type of beta lactamase
  - MRSA: mediated by the mec-A gene → PBP2a
- **Clinical Presentation with SSTI:**
  - Often associated with purulent drainage
  - Red pimple, boil or spider bite appearance
  - Swollen
  - Painful
- **MRSA Guidelines published by Infectious Disease Society of America (IDSA) in 2011.**

---

**STREPTOCOCCI PYOGENES (GROUP A STREP)**

- **Morphology:** Gram positive cocci in pairs and chains
- **Clinical Presentation with SSTI:**
  - Non-purulent
  - Pain
  - Edema
  - Erythema
  - Poorly defined borders
  - Malaise, Fever, Chills
- **Group B, C or G Streptococcus spp.** may also be present, but are less common than Group A Strep

---

**OTHERS**

- **Gram negative bacilli**
  - Enteric Gram negatives
  - Pseudomonas aeruginosa
- **Anaerobes (Bacteroides spp.)**
  - Often seen in diabetic foot infections or patients that are chronically colonized versus actively infected

---

**CLINDAMYCIN**

- **Mechanism of Action**
  - Reversibly binds to 50S ribosomal subunits preventing peptide bond formation → inhibits bacterial protein synthesis
- **Bacteriostatic**
- **Standard Dosing**
  - 300-450 mg PO TID
  - 600 mg IV or PO TID
- **Additional Information**
  - D-zone test is recommended for detection of inducible resistance
- **Caveats**
  - Covers ~70% of all of our Staphylococcus aureus and only 71% of MRSA
  - Poor urinary concentrations (~10% excretion)
  - Increased risk of C. difficile

---

**SULFAMETHOXAZOLE/TRIMETHOPRIM**

- **Mechanism of Action**
  - Sulfamethoxazole: interferes with bacterial folic acid synthesis and growth by inhibiting dihydrofolate acid formation from para-amino benzoic acid
  - Trimethoprim: inhibits dihydrofolate acid reduction to tetrahydrofolate → inhibits enzymes of folic acid pathway
- **Bactericidal**
- **Standard Dosing**
  - 1-2.5 DS tablets Q12 hours (community acquired MRSA)
  - 3.5-4 mg TMP/kg/dose Q8-12 hours (Osteomyelitis)
  - 15 mg TMP/kg/day divided Q6-8 hours (PCP treatment)
- **Special Toxicities**
  - Potential for SJS and TENS
  - Immune mediated thrombocytopenia - typically worse in elderly
**Mechanism of Action**
- Inhibits bacterial protein synthesis by binding to 23S ribosomal RNA of the 50S subunit
- Bacteriostatic against Enterococcus spp. and Staphylococcus spp.
- Bactericidal against Streptococci spp.

**Standard Dosing**
- 600 mg IV or PO BID

**Special Toxicities**
- >2 weeks of therapy monitor for myelosuppression, specifically thrombocytopenia
- Monitor for visual changes with chronic therapy (>3 months)

**Caveats**
- Risk of serotonin syndrome
- No hepatic or renal dose adjustments needed
- 100% oral bioavailability
- Limited use in bloodstream infections and endocarditis

**Additional Information**
- If using IV monitor for extravasation (preferable to give via central line)
- CYP3A4 drug interactions possible

---

**Vancomycin**

**Mechanism of Action**
- Binds to D-alal-D-alal tightly and inhibits synthesis of the cell wall
- Slowly bactericidal

**Dosed: Dosing based on pharmacokinetic evaluation**
- AUC/MIC Pharmacodynamic

**Benefits:**
- Measurable troughs to aid in assessing therapy outcomes

**Drawbacks:**
- Potential nephrotoxicity (5-40% depending on risk factors)
- Patient specific dosing based on pharmacokinetic evaluation
- Goal troughs (at steady state) vary by disease state: *per MRSA guidelines established by IDSA*
  - 10-15: Skin and soft tissue infections
  - 15-20: Meningitis, Endocarditis, Pneumonia, Bacteremia, Osteomyelitis, Severe SSTI (necrotizing fasciitis)

---

**Daptomycin**

**Mechanism of Action**
- Binds to components of the cell membrane and causes rapid depolarization inhibiting synthesis of DNA, RNA, and protein
- Bactericidal – concentration dependent manner

**Standard Dosing**
- 4 mg/kg daily (complicated SSSI)
- 6 mg/kg daily (endocarditis)
- 8-10 mg/kg daily has been studied for BSI, Endocarditis, OM

**Special Toxicities**
- Rhabdomyolysis risk - CPK should be monitored weekly

**Caveats**
- Not to be used for PNA - inactivated by surfactant in the lungs.
- Not great bone and joint penetration, higher doses needed
- Doses clinically used are higher than approved doses

**Benefits:**
- Measurable troughs to aid in assessing therapy outcomes

**Drawbacks:**
- Potential nephrotoxicity (5-40% depending on risk factors)
- Patient specific dosing based on pharmacokinetic evaluation
- Goal troughs (at steady state) vary by disease state: *per MRSA guidelines established by IDSA*
  - 10-15: Skin and soft tissue infections
  - 15-20: Meningitis, Endocarditis, Pneumonia, Bacteremia, Osteomyelitis, Severe SSTI (necrotizing fasciitis)

---

**Zephyr**

**Mechanism of Action**
- Binds to components of the cell membrane and causes rapid depolarization inhibiting synthesis of DNA, RNA, and protein
- Bactericidal – concentration dependent manner

**Standard Dosing**
- 600 mg IV or PO BID

**Special Toxicities**
- Possibilities for SJS/TENS
- Photosensitivity
- Teeth staining
- Calcium binding

**Additional Information**
- If using IV monitor for extravasation (preferable to give via central line)
- CYP3A4 drug interactions possible

---

**Vancomycin Intermediate mechanism not well understood, but thicker cell walls have been found with more subunits, leading to the thought that vancomycin has less interaction with D-alal-D-alal**

**Vancomycin Resistant Staphylococcus mechanism via vanA gene**

---

**Doxycycline**

**Mechanism of Action**
- Inhibits protein synthesis by binding to 30S subunit
- Bacteriostatic

**Standard Dosing**
- 100 mg BID (CA-MRSA cellulitis)

**Special Toxicities**
- Possibilities for SJS/TENS
- Photosensitivity
- Teeth staining
- Calcium binding

**Additional Information**
- If using IV monitor for extravasation (preferable to give via central line)
- CYP3A4 drug interactions possible

---

**Linezolid**

**Mechanism of Action**
- Inhibits protein synthesis by binding to 30S subunit
- Bacteriostatic

**Standard Dosing**
- 600 mg IV or PO BID

**Special Toxicities**
- Possibilities for SJS/TENS
- Photosensitivity
- Teeth staining
- Calcium binding

**Additional Information**
- If using IV monitor for extravasation (preferable to give via central line)
- CYP3A4 drug interactions possible
**Newly Approved Agents**

- **Tedizolid**
- **Dalbavancin**
- **Oritavancin**
- **Ceftaroline**

**New Antimicrobials**

**Vancomycin and Resistance**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total cases reported for previous years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIVRSA</td>
<td></td>
</tr>
<tr>
<td>VRSA</td>
<td></td>
</tr>
</tbody>
</table>

Testing methods have varying degrees of accuracy, e-tests should be used to confirm results on Vitek-2 or Microscan.

**Case 2**

- KG is a 45 yof presenting with severe, purulent cellulitis and cultures grew MRSA resistant to Clindamycin and Bactrim. Allergies to medications include: Vancomycin and penicillins.
- KG’s family is present and brought in her home medication bottles and it is discovered that she takes phenelzine (an MAOI). The attending physician wants to restart this medication.
- Current therapy includes linezolid 600 mg PO BID
- What changes need to be made to CP’s treatment?
  A. No adjustments need to be made
  B. DC linezolid if he is completed with therapy
  C. DC linezolid, switch to daptomycin 8 mg/kg Q24 hours

**Antibiotic Shortage**

- Not in the traditional sense of a drug shortage, but rather a shortage in new agents in addition to an increase in resistance.
- In 2010, FDA issued draft guidance for development of systemic drugs treating ABSSIs
  - Clinical response criteria
  - Non-inferiority trial design
- Qualified Infectious Disease Program (QIDP)
  - Allows for quick release of antibiotics “before” resistance is present in the hospitals or community to the new agents
  - 3 drugs currently have been approved via this program for ABSSI

**Tedizolid Phosphate (Sivextro)**

- **Class:** Oxazolidinone
- **MOA:** Prodrug converted by phosphatases, active tedizolid binds to 50S bacterial ribosomal subunit, inhibits formation of 70S which is essential for translation.
  - **Bacteriostatic**
- **Cost:** $235 per tablet
- **Dosage Forms:** 200 mg tablets, 200 mg reconstituted solution
- **Dosing:** 200 mg PO/IV daily for 6 days (only FDA approved for ABSSI)
  - **PK/PD:**
  - **Time dependent**
  - **Oral bioavailability:** 91%
- **Place in therapy:** acute bacterial SSTI, including cellulitis and erysipelas
  - Has shown some efficacy in isolates that are resistant to linezolid and vancomycin due to chloramphenicol-florfenicol resistance methyltransferase gene
  - No SSRI interaction and no bone marrow suppression

*Source: Sivextro [package insert], Lexington, MA: Cubist; 2014.*
**ESTABLISH-1**

**Design**
- Randomized, double blind, double dummy, multicenter, multinational, phase 3 noninferiority trial
- Inclusion: >18 yo, cellulitis/erysipelas, major cutaneous abscess, or wound infection and gram positive pathogen suspected
- 200 mg of tedizolid phosphate daily for 6 days or 600 mg of linezolid Q12 hours for 10 days

**Outcomes**
- Assessed at 48-72 hours after first dose of study drug, EOT (day 11), post therapy evaluation (7-14 days after EOT)
- 10% non-inferiority margin was defined

**Results**
- 48-72 hour response rates: 79.5% (n=322) Tedizolid and 79.4% (n=335) Linezolid
- EOT (day 11): 69.3% Tedizolid and 71.9% Linezolid (ITT)
- Safety: 40.8% Tedizolid and 43.3% Linezolid reported treatment-emergent adverse events

**Conclusions**
- Tedizolid 200 mg daily for 6 days is noninferior to linezolid 600 mg Q12 hours for 10 days

**DALBAVANCIN (DALVANCE)**

- Class: Lipoglycopeptide
- MOA: Inhibits cell wall cross-linking by binding to D-ala-D-ala.
- Bactericidal
- Cost: $1788 (per 500 mg vial)
- Dosage Forms: 500 mg IV reconstituted solution
- Dosing: 1000 mg IV as single dose, followed by 500 mg IV 1 week later (only FDA approved for ABSSSI)
- Renal dose adjustments needed (750 mg IV → 375 mg 1 week later)
- PK/PD:
  - AUC/MIC
  - Half life: 2 weeks
- Place in therapy: ABSSSI
- First drug to be approved as Qualified Infectious Disease Product (QIDP)
- Caveat: May precipitate with saline based products

**DISCOVER-1 AND DISCOVER-2**

**Design**
- Double blind, double dummy, international, multicenter, randomized trials from 2011 through 2012
- Inclusion: cellulitis, major abscess, wound infection each associated with at least 75 cm² of erythema. Adults thought to require at least 3 days IV therapy
- Excluded: Patient receiving abx within 14 days
- Dalbavancin 1 g IV day 1 followed by 500 mg IV day 8 or Vancomycin 1 g (or 15 mg/kg) IV Q12 hours for 10-14 days (may switch to linezolid 600 mg PO Q12 hours after at least 3 days of vancomycin to complete 10-14 days)

**Outcomes**
- Treatment success at 48-72 hours of therapy

**Results**
- DISCOVER-1: early clinical response 83.3% (n=288) dalbavancin vs 81.8% (n=285) vancomycin-linezolid
- DISCOVER-2: early clinical response 76.8% (n=371) dalbavancin vs 78.3% (n=368) vancomycin-linezolid
- Pooled analysis: 79.7% (n=659) dalbavancin vs 79.8% (n=653) vancomycin-linezolid

**Conclusions**
- Dalbavancin is non-inferior to vancomycin-linezolid

**ORITAVANCIN (ORBACTIV)**

- Class: Lipoglycopeptide
- MOA: Inhibits cell wall synthesis by binding to D-ala-D-ala. In addition, disrupts membrane potential of cell wall and changes cell permeability.
- Bactericidal
- Cost: $1160
- Dosage Forms: 400 mg IV powder for reconstitution (40mL)
- Dosing: 1200 mg IV over 3 hours once (only FDA approved for ABSSSI)
- Renal dosing not needed, not studied in severe renal impairment
- PK/PD: AUC/MIC
- Half life 245 hours
- Place in therapy: ABSSSI
- Approved August 6, 2014
- Caveats:
  - Use of IV UFH is contraindicated 48 hours after Orbactiv dose due to aPTT false elevation
  - Package insert recommends against use with OM
  - Incompatible with saline solutions. Dilute with D5.
  - Potential CYP drug interactions (inducer of 3A4, 2D6; weak inhibitor 2C9, 2C19)

**Results**
- DISCOVER-1: early clinical response 83.3% (n=288) dalbavancin vs 81.8% (n=285) vancomycin-linezolid
- DISCOVER-2: early clinical response 76.8% (n=371) dalbavancin vs 78.3% (n=368) vancomycin-linezolid
- Pooled analysis: 79.7% (n=659) dalbavancin vs 79.8% (n=653) vancomycin-linezolid

**Conclusions**
- Dalbavancin is non-inferior to vancomycin-linezolid
Design
• International, randomized, double-blind study
• Inclusion: adults with ABSSSI (wound infection, cellulitis, major cutaneous abscesses)
• Single IV dose (1200 mg) oritavancin vs Vancomycin IV for 7-10 days

Outcomes
• Early clinical evaluation (48-72 hours after initiation of study treatment), EOT clinical evaluation (day 7 to day 10), day patient stopped therapy or switched to non-study drug

Results
• Early clinical evaluation: 82.3% oritavancin vs 78.9% vancomycin
• Post-therapy evaluation: 79.6% oritavancin vs 80% vancomycin
• Reduction in lesion size ≥20% at early clinical evaluation: 86.9% oritavancin vs 82.9% vancomycin

Conclusion
• Oritavancin is non-inferior to vancomycin

SOLO-1

Class: “5th generation” cephalosporin
• MOA: Inhibits cell wall synthesis by binding to PBP1 through 3, this blocks final transpeptidation of peptidoglycan synthesis in bacteria cell walls. Strong affinity for PBP2a and PBP2x
• Bactericidal
• Cost: $75.80 (400 mg or 600 mg)
• Dosage Forms: 400 mg IV and 600 mg IV
• Dosing: 600 mg IV Q12
• Renal dosing: 400 mg IV Q12 (CrCl 30-50); 300 mg IV Q12 (CrCl <15 or HD, give after HD)
• PK/PD: Time dependent
• Place in therapy:
  • PNA 600 mg Q12 hours for 5-7 days
  • SSSI (MRSA), complicated 600 mg IV Q12 hours 5-14 days

CEFTAROLINE (TEFLARO)

IN THE PIPELINE

Gram-positive Agents
• Solithromycin
• Eravacycline
• Delafloxacin

Gram-negative Agents
• Ceftolozane/tazobactam
• Ceftazidime/avibactam
• Ceftaroline/avibactam
• Imipenem/cilastatin/relebactam
• Meropenem/RPX-7009
• Plazomicin
• Eravacycline
• Delafloxacin
• Brilacidin

CASE 1 CONTINUED

CP was started on Vancomycin 1500 mg IV Q12 hours
CP develops a high fever of 102.4 F on day 2 of admission and a BC show a GPC in clusters, WBC rises to 14.5
Susceptibilities come back from a wound culture and are as follows:

TMP-SMX 16 Resistant
Usualite 2R Resistant
Oxacillin 4S Susceptible
Clindamycin 4S Susceptible
Vancomycin 1S Susceptible
Daptomycin 0.5 Susceptible
Linezolid 2S Susceptible

How should therapy be adjusted?
A. Continue vancomycin
B. Continue vancomycin, start clindamycin 300 mg IV Q8 hours
C. DC vancomycin, start daptomycin 8 mg/kg IV Q24 hours
D. DC vancomycin, start linezolid 600 mg IV Q12 hours
E. Panic and call the AMS pharmacist because this is not possible

CASE 1 CONTINUED

What should be done next with this patient? (Select all that apply)
A. TTE or TEE depending on risk factors
B. E-test on blood isolate
C. ID Consult
D. Repeat blood cultures daily until negative

An E-test on blood isolate is performed and the MIC to vancomycin is 2.

How should therapy be adjusted?
A. Continue vancomycin
B. Continue vancomycin, start clindamycin 300 mg IV Q8 hours
C. DC vancomycin, start daptomycin 6 mg/kg IV Q24 hours
D. DC vancomycin, start linezolid 600 mg IV Q12 hours
E. Panic and call the AMS pharmacist because this is not possible
CASE 3

- PT is a 37 yof presenting with an ABSSSI and dehydration. The medical resident in the ER does not want to admit her and heard about a new medication that is a one time dose and wants to know more information on this product. Patient is on warfarin at home for A.fib.

- What key counseling points should be given to the ER resident? (Select all that apply)
  A. Should not be given in combination with saline based products as it can cause precipitation
  B. Dilution is not necessary with the product and can be given IV push
  C. The infusion should run over 3 hours
  D. Heparin use within 48 hours is contraindicated with this product in the event Warfarin INR could be elevated for 24 hours
  E. Medication is expensive and should not be used as first line agent since more appropriate agents are available for use at this time

OBJECTIVES

- Recognize the most common pathogens associated with acute bacterial skin and soft tissue infections.
- Explain the main resistance mechanisms of Staphylococcus aureus and differentiate between MSSA, MRSA, hVISA and VRSA.
- Investigate new medications that may be useful in the treatment of MRSA skin and soft tissue infections and formulate a patient specific regimen

CONCLUSIONS/SUMMARY

- Understanding resistance mechanisms can aid in antibiotic selection
- MRSA treatment can be complex with increasing resistance and constantly emerging resistance mechanisms to newer antibiotics.
- Treatment needs to be tailored to account for drug interactions, adverse drug reactions, clinical improvement and if possible cost considerations.
- Newer agents should have educational pieces to nursing and physicians before use is initiated. Limiting use should also be considered due to cost and reserving for resistant infections.

REFERENCES