Management of Skin and Soft-Tissue Infections: Application of Antimicrobial Stewardship Principles

Presented by:
Trevor C. Van Schooneveld, MD, FACP
Associate Professor
Department of Internal Medicine – Infectious Diseases
Conflicts of Interest

Research funding – Merck, Rebiotrix
Consultant – BioMerieux
Objectives

• Describe the opportunities for stewardship in skin and soft-tissue infections (SSTI)
• Identify bacterial pathogens associated with various skin and soft tissue infections and choose a treatment regimen to target these pathogens
• Recognize SSTI mimics
Skin and Soft Tissue Infection

Relationship of Age and Sex with Incidence of Cellulitis

Incidence nearly doubles in summer

Annual Rates of Outpaient Visits for SSTI 1997-2005

Skin and Soft Tissue Infection

• Common infections
  • Superficial → Deep
  • Epidemiology, approach and therapy choices

• Uncommon infections
  • Exposures, bites, etc.

• Infectious mimics
Retrospective analysis of 322 SSTI

*S. aureus* or Streptococci isolated from 97% cultures

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Cellulitis (N=66)</th>
<th>Cutaneous Abscess (N=103)</th>
<th>SSTI with Complicating Factors (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad-spectrum Gram-negative therapy</td>
<td>61%</td>
<td>67%</td>
<td>80%</td>
</tr>
<tr>
<td>Anaerobic therapy</td>
<td>74%</td>
<td>73%</td>
<td>83%</td>
</tr>
<tr>
<td>Gram-positive therapy only</td>
<td>38%</td>
<td>33%</td>
<td>17%</td>
</tr>
<tr>
<td>Three or more antibiotics</td>
<td>52%</td>
<td>40%</td>
<td>48%</td>
</tr>
<tr>
<td>Median Duration Therapy (days)</td>
<td>11</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

Avoidable antibiotic exposure occurred in 46% of outpatient SSTI
### Utilization of Imaging in SSTI

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Cellulitis (N=66)</th>
<th>Cutaneous Abscess (N=103)</th>
<th>SSTI with Complicating Factors (N=153)</th>
<th>Yield of Image for Deep Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any imaging</td>
<td>94%</td>
<td>69%</td>
<td>86%</td>
<td>4%</td>
</tr>
<tr>
<td>Plain film</td>
<td>94%</td>
<td>69%</td>
<td>86%</td>
<td>1%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>42%</td>
<td>14%</td>
<td>26%</td>
<td>0.3%</td>
</tr>
<tr>
<td>CT image</td>
<td>9%</td>
<td>15%</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>MRI</td>
<td>8%</td>
<td>3%</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>CT or MRI</td>
<td>17%</td>
<td>17%</td>
<td>24%</td>
<td>NR</td>
</tr>
</tbody>
</table>
Cellulitis Misdiagnosis

- Patients admitted with cellulitis from ED (N=259)
  - 30.5% (N=79) did not have cellulitis
    - Vascular disorders 61%, Inflammatory 19%, Other 20%
    - 44 of 79 (56%) admitted for treatment of cellulitis did not need admission

Impact of cellulitis misdiagnosis across US!

- Estimated 50-130K unnecessary hospitalization
- $195-515 million avoidable costs
- Thousands nosocomial infections and CDI cases

Principles of SSTI Treatment

1. Is this really an infection?
2. Based on the appearance what type of skin infection is it?
3. What is the expected bacterial epidemiology of the infection?
   A. Are there exposures suggesting an unusual pathogen?
   B. What is the immune status of the patient?
4. How deep or severe is it?
Impetigo

• Epidermis only
  • *S. aureus* and *S. pyogenes*

• Macule → Small vesicles → pustule rapidly ruptures
  • Golden-yellow crust, painless

• Topical therapy for limited disease
  • Mupirocin, retapamulin

• No response, severe, or bullous
  • Cephalexin or dicloxacillin
  • MRSA concern =
    • Clindamycin alone
    • Add doxycycline or TMP-SMX to above
Folliculitis

- Inflamed hair follicle with eruption of pustules/papules centered on follicles
  - Bacterial – normal skin flora and/or *Staphylococcus aureus*
  - Hot tub folliculitis – *Pseudomonas*
  - Dermatophytes, *Candida*
  - Drug induced
  - Irritant

- Treatment
  - Warm compresses, usually resolves on own
  - Topical antibiotics targeting Staph
    - Duration 5 days
  - Culture if not responding
Erysipelas

• Upper dermis and lymphatics
• Painful, fiery red, **well demarcated**, **raised**, indurated
  • Face and lower extremity
  • Fevers, chills
• Epidemiology
  • Young children, elderly
  • Lymphedema and venous stasis predispose
• Beta-hemolytic Strep (GAS)
• Penicillin drug of choice
• Duration = 5-7 days
Skin Abscess

- **Furuncle** = Painful, tender, fluctuant nodule that extends into the subcutaneous tissue
- **Carbuncle** = multiple coalescent into fat
- **Areas of friction and hair follicles**
  - Neck, face, axillae, buttocks
Skin Abscesses and Cellulitis: Consider the Epidemiology

Prevalence of MRSA Among 422 ED Patients With SSTI

- 7/13 (54%)
- 11/28 (39%)
- 24/47 (51%)
- 26/42 (62%)
- 18/30 (60%)
- 17/25 (68%)
- 43/58 (74%)
- 4/20 (20%)
- 32/58 (55%)
- 23/32 (72%)
- 46/69 (67%)

MSSA 17%

Skin Abscess

• Painful, tender, fluctuant nodule(s)
• Risk Factors – obesity, steroids, diabetes
• *S. aureus*, especially MRSA
  • If severe get a culture
  • Consider other pathogens depending on location and/or injury
• Treatment = incision and drainage
  • Furuncle – moist heat may be adequate
  • Carbuncles always need I&D
• What is the role of antimicrobials?
Small Placebo-Controlled, Randomized Trials of Antibiotics in Skin Abscesses

Percent Clinical Cure

Rejendran

Duong

Schmitz

Cephalexin
N=166

P=.25

TMP/SMX
N=161

P=.12

TMP/SMX
N=212

P=.52

Some suggestion of decreased recurrence with TMP/SMX

Large Placebo-Controlled, Randomized Trials of Antibiotics in Skin Abscesses

**Percent Clinical Cure**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TMP-SMX</th>
<th>Clindamycin</th>
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</thead>
<tbody>
<tr>
<td>Talan, et al (N=1265)</td>
<td>73.6</td>
<td>80.5</td>
<td></td>
</tr>
<tr>
<td>Daum, et al (N=786)</td>
<td>68.9</td>
<td>81.7</td>
<td>83.1</td>
</tr>
</tbody>
</table>

- **P=0.005**
- **P<0.001**

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Talan, et al (N=1265)</td>
<td>ED patients &gt;12 yrs. old</td>
<td>Placebo vs. TMP-SMX 2 DS tabs BID</td>
<td>TMP-SMX decreased subsequent surgical intervention, new skin infection, and infection in a household member</td>
</tr>
<tr>
<td>Daum, et al (N=786)</td>
<td>ED/clinic/urgent care patients &gt;6 mo. old</td>
<td>Placebo vs. TMP-SMX 1 DS tab BID vs. Clindamycin 300mg TID</td>
<td>Subsequent infections decreased (6.8% vs. 12-13%) with clindamycin only but more adverse events with clindamycin (21.9% vs. 11-12%)</td>
</tr>
</tbody>
</table>

**Talan, et al. NEJM. 2016;374:823-32.**
**Daum RS, et al. NEJM. 2017;376:2545-55**
Skin Abscesses

• **I&D primary therapy but many benefit from antibiotics**

• Use antibiotics when:
  - Multiple lesions
  - Lesion >2 cm (risk vs. benefit in smaller)
  - Can’t drain easily or sensitive area (face, hand, genitals)
  - Immunocompromised or extremes age
  - Systemic signs infection (fever, etc.)
  - Severe, extensive, or rapidly progressive disease with associated cellulitis or septic phlebitis
  - Failure of I&D

• **Agents – must be active against MRSA**
  - Moderate disease = TMP/SMX or Doxycycline (clinda?)
  - Severe disease = Vancomycin, Daptomycin, Linezolid

• **Duration – 5 to 7 days**

Clindamycin as Primary Therapy?

**S. aureus Clindamycin Susceptibility at NM**

<table>
<thead>
<tr>
<th>Year</th>
<th>Percent Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>83</td>
</tr>
<tr>
<td>2015</td>
<td>80</td>
</tr>
<tr>
<td>2016</td>
<td>82</td>
</tr>
<tr>
<td>2017</td>
<td>73</td>
</tr>
<tr>
<td>2018</td>
<td>73</td>
</tr>
</tbody>
</table>

Clindamycin Susceptibility in S. aureus
Cellulitis

- Involves deeper dermis and subcutaneous tissues
  - Tender, painful, spreading erythema with swelling
  - Not elevated with indistinct borders, can be patchy

- Fevers, chills common

- Lymphadenitis or lymphangitis

- Etiology
  - Beta-hemolytic Strep
    - Groups A/B/C/G Streptococci
  - Difficult to ascertain
    - Blood cultures low yield
    - Nothing to culture
Epidemiology of Cellulitis

• Prospective study “nonculturable cellulitis” (N=179)
  • What % due to β-hemolytic Streptococci (BHS)
    • 73% diagnosed with BHS infection (serology, BCX)
    • 96% response rate to beta-lactams
      • 91% (21/23) specifically tested negative for Strep

• Conclusion → Cellulitis primarily caused by BHS

• Treatment
  • 1st generation ceph (cephalexin, cefazolin)
  • Anti-staphylococcal PCN (dicloxacillin, oxacillin)

• Duration = 5-7 days
  • Can go longer if respond poorly
  • Factors associated with slow response not related to antibiotic choice

What about MRSA treatment in cellulitis?

- Two multicenter RCT evaluated TMP-SMX added to beta-lactam in uncomplicated cellulitis
  - No abscess, immunosuppression, PVD, device present
- Treated with cephalexin; randomized TMP-SMX OR placebo
  - Various dosing regimens and durations

<table>
<thead>
<tr>
<th>Outcomes (TMP-SMX vs. Placebo)</th>
<th>Pallin, et al. (N=146)</th>
<th>Moran, et al. (N=496)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Cure Rate</td>
<td>85% vs. 82% (95%CI, -9.3%-15%, P=.66)</td>
<td>83.5% vs. 85.5% (95%CI, -9.7%-5.7%, P=.5)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>49% vs. 53% (P=.62)</td>
<td>41.1% vs. 36.3%, P=NS</td>
</tr>
</tbody>
</table>

No benefit to adding anti-MRSA therapy to cellulitis

Moran GJ. *JAMA*. 2017;317:2088-96
What about Clindamycin in cellulitis?

- Blinded randomized trial of oral beta-lactam PLUS clindamycin
  - ED patients with limb cellulitis
  - Outcome = improvement at day 5

<table>
<thead>
<tr>
<th></th>
<th>Clindamycin (N=203)</th>
<th>Placebo (N=207)</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>67% (136/203)</td>
<td>68% (140/172)</td>
<td>0.97</td>
<td>0.92</td>
</tr>
<tr>
<td>(entire population)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>87% (136/156)</td>
<td>81% (140/172)</td>
<td>1.55</td>
<td>0.17</td>
</tr>
<tr>
<td>(evaluable population)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21.5%</td>
<td>9.3%</td>
<td></td>
<td>.002</td>
</tr>
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</table>

Abscess and Cellulitis Summary

• Treat based on infectious syndrome
  • Non-purulent cellulitis → treat for strep using beta-lactam
    • Use high doses in obese or severe edema
  • Abscess → drainage required, but antibiotics indicated in most
  • Purulence present → treat for MRSA
    • Mild-Moderate = TMP/SMX or Doxy/Mino (Clinda??)
      • Recent trials suggested no difference between TMP-SMX and Clindamycin in outcomes
    • Severe = Vancomycin or others
  • Complicated infections (burns, wounds, etc.) = same as purulent infections

• Don’t routinely cover gram-negatives/anaerobes
  • When should I cover them?

Diabetic Foot Infection

• Diabetic neuropathy and vascular insufficiency predispose to ulcer

• Infections
  • Mild-Moderate infections = Strep and Staph
  • Severe = Often polymicrobial and require broad-spectrum therapy

• Adequate surgical debridement essential

• PO therapy possible in many cases
  • Fluoroquinolones, metronidazole, clindamycin, linezolid, TMP-SMX

• Duration depends on:
  • Underlying osteomyelitis
  • Adequate debridement
DFI Nebraska Medicine

- 138 Diabetic Foot Infections over 2 years at NM
  - 30% superficial swabs
  - 57% with surgical debridement and deep tissue/bone cultures

Deep Culture Epidemiology

- B-HEMOLYTIC STREP: 46%
- MSSA: 44%
- STREP VIRIDANS: 10%
- MRSA: 10%
- ENTEROCOCCUS: 10%
- PROTEUS: 10%
- KLEBSIELLA: 7%
- ANAEROBES: 5%
- MORGANELLA: 5%
- E. COLI: 5%
- PSEUDOMONAS: 2%
- ENTEROBACTER: 2%

Empiric Coverage vs % Isolated

- MRSA: 90%
- PSEUDOMONAS: 78%

N=63 cases
<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Suspected Organisms</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Foot Infections</td>
<td><strong>Mild</strong>: &gt;2 of the following signs of local infection: Induration, erythema, tenderness warmth, pus</td>
<td><strong>First rule out deep tissue infection/osteomyelitis</strong>&lt;br&gt;<strong>Mild</strong>: Cephalexin 1000mg PO TID OR Amoxicillin-clavulanate 875/125 mg PO q12h If there is history of MRSA colonization/infection add: Doxycycline 100 mg PO q12h OR TMP/SMX DS 1 tab PO q12h</td>
</tr>
<tr>
<td></td>
<td><strong>Moderate</strong>: Mild infection + abscess, osteomyelitis, septic arthritis, &gt;2 cm erythema or lymphangitis, without systemic signs of inflammation</td>
<td><strong>Severe Penicillin Allergy</strong>: Clindamycin 300 mg PO q8h</td>
</tr>
<tr>
<td></td>
<td><strong>Severe</strong>: Moderate + systemic signs of infection (fever, tachycardia, leukocytosis, hypotension, sepsis Syndrome)</td>
<td><strong>Moderate - PO</strong>: Amoxicillin-clavulanate 875/125 mg PO q12h If there is history of MRSA colonization/infection add: Doxycycline 100 mg PO q12h OR TMP/SMX DS 1 tab PO q12h <strong>Severe Penicillin Allergy</strong>: Levofloxacin 750 mg PO daily PLUS Doxycycline 100 mg PO q12h</td>
</tr>
</tbody>
</table>

**Pseudomonas** infection very rare: cover only with risk factors (history of MRSA infection or colonization)<br><br>**Moderate - IV**: Ceftriaxone 2g IV daily PLUS Metronidazole 500mg IV q8h OR Ampicillin/sulbactam 3g q6h OR Ertapenem 1g daily<br><br>**Severe Penicillin Allergy**: Levofloxacin 750 mg IV daily PLUS Clindamycin 900 mg IV q8h

If there is history of MRSA colonization/infection: Vancomycin 10-15 mg/kg IV q12h# [Consult pharmacy for patient-specific dosing].

**Severe**: [Consult pharmacy for patient-specific vancomycin 15 mg/kg IV q12h dosing]<br>• Vancomycin PLUS Ceftriaxone 2g IV daily PLUS Metronidazole 500mg IV q8h (PREFERRED); OR • Vancomycin PLUS Ertapenem 1g daily; OR • Vancomycin PLUS Piperacillin/tazobactam 4.5g IV q8h

(Click here for complete DFI guideline on the ASP Website)
Necrotizing Fasciitis

• Polymicrobial (Type I)
  • Mixed infection caused by aerobic and anaerobic bacteria
  • Diabetes and peripheral vascular disease

• Monomicrobial (Type II)
  • *Streptococcus pyogenes*

• Clostridial Myonecrosis
  • Inadequately debrided surgical or traumatic wounds
  • *Clostridium perfringens*
Necrotizing Infections: Therapy

- **Surgical debridement!!!**
- Antimicrobials
  - Broad spectrum until culture data available
  - Vancomycin + Pip/Tazo
- Adjunctive Therapy??
  - IVIG
  - HBO
Surgical Site Infection

• Most costly nosocomial infection
  • Affects roughly 2.6% of surgeries
  • Accounts for 38% of all nosocomial infections

• Pain, swelling, erythema, purulent drainage
  • Fever common
    • Early fever (first 48-72 hours) rarely from infection
Surgical Site Infection

- Treatment = Incision/wound opening adequate for most

- Consider antibiotics when:
  - Fever >38.5°C, >5 cm surrounding erythema, or leukocytosis
  - If using antibiotics get a culture!!

- Antibiotic choice depends on surgery site
  - Clean site = trunk, head, neck, extremity
    - Cover Gram positives only (Staph and Strep)
    - Cefazolin or Vancomycin (if MRSA concern)
  - Contaminated site = GI tract or female genital tract
    - Cover gram positive, gram negative and anaerobe
    - Ceftriaxone + metronidazole OR piperacillin/tazobactam OR FQ + metronidazole
Question

• Which animal bite is most likely to get infected?
  1. Dog
  2. Cat
  3. Human
  4. Zombie
  5. Chupacabra
Unusual SSTI Exposures: Human Bites

• Polymicrobial
  • *Streptococci*, *S. aureus*, *Eikenella*, *Fusobacterium*, *Peptostreptococcus*, *Prevotella*

• Treatment
  • Prophylaxis for 3-5 days with Amox/clav
  • Infection
    • Ampicillin-sulbactam
Unusual SSTI Exposures: Animal Bites

• Consider animal (cat 80% infected, dog 5%)
  • *Pasteurella, S. aureus, Streptococci, Fusobacterium, Capnocytophaga*

• When to use prophylaxis
  • Deep puncture (especially cats)
  • Moderate or severe with crush injury
  • On hand or genitals
  • Near prosthetic material
  • Involves bone, joint, or poorly vascularized area
  • Patient is immunocompromised

• Treatment/prophylaxis
  • Amox/clav
Unusual SSTI Exposures

- 56 yo male with chronic Hepatitis C presents with severe cellulitis of left leg and septic shock. He returned from a trip to Gulf Coast yesterday where sustained a scrape on a sea wall while swimming.

*Vibrio vulnificus*
Unusual SSTI Exposures

• 44 yo male presents with infection of a left knee laceration
  • Occurred while swimming in a local lake
  • The infection is severe and rapidly progressive

*Aeromonas hydrophila*
Unusual SSTI Exposures

- 28 yo female from Mexico
- Progressive skin lesions over last 3-6 months
  - Non-tender
  - Father had similar issue in Mexico
- Palpable nodules posterior arms, face
- No fevers, chills
- No nail salons

Lepromatous leprosy
28 year-old male recently returned from Iraq with these lesions that have not healed despite multiple courses of antibiotics. They are not tender.

Cutaneous Leishmaniasis
Unusual SSTI Exposures

37 you non-breast feeding female who presented with bilateral breast infections which have not responded to doxycycline or TMP/SMX

Mycobacterium fortuitum infection due to IVDU
What is the Immune Status?

• 46 yo male with AML undergoing allogeneic bone marrow transplant
  • Neutropenic 23 days with progressive lesion on forearm

Mucormycosis
SSTI Mimics

Patient admitted 2 days ago for CAP. Now with left deltoid cellulitis. What is the cause of this painful, red, hot, swollen left deltoid?

Influenza vaccine reaction
SSTI Mimics

Patient with chronic liver and kidney disease transferred with these lesions which have been progressive over the last 3 weeks. No fevers, clinically stable.

Calciphylaxis due to renal failure
SSTI Mimics

Patient admitted with fever, high WBC, left shift and high eosinophil count. Rash on feet non-blanching. Similar erythema covers arms, trunk, face and thighs.

Drug Reaction to Allopurinol
SSTI Mimics

Pain, swelling, redness right arm at site of previous PIV

Right leg swollen, tender especially posteriorly 2 days after returning from European vacation. Low grade fever

Superficial thrombophlebitis

Deep Vein Thrombosis
SSTI Mimics

Patient referred for recalcitrant cellulitis despite prolonged IV and oral antibiotics active against Strep, MRSA, gram-negatives.

Mild leg pain and moderately tender, edematous, no fever or WBC. CRP normal.

Dependent Rubor
SSTI Mimics

Patient with bilateral cellulitis which is recurrent, left worse than right

Chronic Venous Stasis
SSTI Mimics

Patient with this rash despite multiple courses antibiotics. Severe pain, wants it cut off. Indurated and tender. Doesn’t resolve with elevation.

Lipodermatosclerosis

Fibrosing panniculitis due to chronic venous stasis
SSTI Mimics

- Contact dermatitis
- Acute tophaceous gout
SSTI Mimics

• Vascular disorders
  • Superficial and deep venous thrombophlebitis

• Dermatologic disorders
  • Contact dermatitis
  • Insect bites
  • Drug reactions

• Rheumatologic disorders
  • Gout
  • Vasculitis and other forms of panniculitis

• Malignant disorders
  • Sweet’s syndrome
  • Carcinoma erysipelatoides

• Foreign-body reactions
  • Metallic implants, mesh, foreign body granulomas

• Familial Syndromes
  • Familial Mediterranean and Hibernian fevers
Conclusions

• SSTI are often misdiagnosed and antimicrobial use can be improved
• Consider the epidemiology when making treatment decisions
  • Abscess = MRSA, drain, consider abx
  • Cellulitis = Streptococci and beta-lactam
  • Necrotizing infection = polymicrobial until proven otherwise
• Consider the patient factors when evaluating SSTI
• Don’t forget SSTI mimics
Questions?