SKIN AND SOFT TISSUE INFECTIONS
OCTOBER 3-4, 2015
Steven Tran, PharmD
NEFSHP Fall Meeting 2015

Disclosures
• I have no financial conflicts of interest to disclose or report.

Objectives for Pharmacists
❖ Review the signs and symptoms of skin and soft tissue infections
❖ Recommend evidence-based antibiotic regimens for the treatment of skin and soft tissue infections
❖ Evaluate ongoing treatment regimens for appropriate continuation of therapy

Skin and Soft Tissue Infections (SSTI)
❖ Impetigo/Ecthyma
❖ Furuncles/Carbuncles/Abscesses
❖ Cellulitis/Erysipelas
❖ Wound Infections
❖ Necrotizing Infections
❖ Animal Bite Wounds
❖ SSTI with Neutropenic Fever

Scratching the Surface
Furuncles/Carbuncles/Abscesses
❖ Collection of pus within dermis or deeper with redness, edema and/or induration

Wound Infection
❖ Purulent drainage from wound with surrounding redness, edema and/or induration

Cellulitis/Erysipelas
❖ Diffuse skin infection with spreading area of redness, edema, and/or induration

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Cellulitis/Erysipelas
- Diffuse skin infection with spreading area of redness, edema, and/or induration

Skin and Soft Tissue Infections: A Focus
- Common reason for medical attention
  - Outpatient setting
    - Physician offices
    - Hospital outpatient departments
    - Emergency room visits
  - Inpatient setting
    - Hospital admissions
    - Surgical site complications

The Bugs of Interest
- Nonpurulent SSTI - Cellulitis
  - Beta-hemolytic streptococci
- Purulent SSTI - Abscess
  - Staphylococcus aureus, methicillin-sensitive and resistant
- Hospital-acquired SSTI or Site/Wound Infection
  - S. aureus, p. aeruginosa, e. coli, enterococcus spp.
- SSTI with Recent Water Contact
  - Aeromonas hydrophila, Vibrio vulnificus
- Necrotizing fasciitis
  - S. pyogenes, S. aureus, enterobactericeae, klebsiella spp., pseudomonas spp., anaerobes

Bacteria on the Loose
- Methicillin-resistant S. aureus (MRSA)
  - Presence first detected in 1961
  - Methicillin introduced 2 years earlier
- Major nosocomial pathogen
  - Hospital-acquired MRSA (HA-MRSA)
  - Frequent isolate from positive cultures
  - Blood stream and site infections
- Increasing community prevalence
  - Community-acquired MRSA (CA-MRSA)
  - Respiratory and skin and soft tissue infections

SENTRY: Complicated SSTIs

<table>
<thead>
<tr>
<th>S. aureus</th>
<th>P. aeruginosa</th>
<th>E. coli</th>
<th>S. pneumoniae</th>
<th>K. pneumoniae</th>
<th>S. pyogenes</th>
<th>S. aureus</th>
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</thead>
<tbody>
<tr>
<td>44.6</td>
<td>11.1</td>
<td>9.3</td>
<td>7.2</td>
<td>4.8</td>
<td>4.2</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Infectious Disease Society of America (IDSA) Guidelines
- 2014 Guidelines for SSTI
  - Update and refine 2005 guidelines
  - Organization and weighting of recommendations
  - Recognize the emergent issue of MRSA for SSTIs
  - Provide systematic management to providers for different classifications of SSTI
  - Evidence-based treatment options
  - Simple diagnostic algorithms for appropriate therapy

Nonpurulent SSTIs

• Emergency surgical inspection/drainage
  
  • Prescribe or + placebo or + Penicillin G
  
  • Intravenous + Penicillin + Chloramphenicol
  
  • Intravenous + Penicillin + Gentamicin
  
  • Intravenous + Penicillin + Metronidazole

• Outpatient intramuscular
  
  • Benzathine Penicillin
  
  • Ceftriaxone

Background

Multicenter from 2007 to 2011

Design

Randomized, double-blind, placebo controlled trial

Participants

• Inclusion
  
  • Emergency room
  
  • Uncomplicated cellulitis

• Exclusion
  
  • Symptoms > 1 week
  
  • Diabetes
  
  • Abscess > 3 mm
  
  • Purulence > 1 cc

Intervention

Cephalexin + placebo versus Cephalexin + trimethoprim/sulfamethoxazole

Outcome

Primary: Risk difference for cure at 1 month

• Follow-up at 2 weeks and 1 month

Results

• 153 (146) patients
  
  • Control: previous antibiotic use, crowded contact, spider bite
  
  • Intervention: healthcare worker, MRSA contact, cellulitis with edema

• Clinical cure
  
  • Control: 60/73 (82%)  
  
  • Intervention: 62/73 (85%)

• 2.7% (95% CI, -9.3% to 15%)

Subsequent per-protocol analysis

• 4 non-cellulitis patients
  
  • 4.2 (95% CI, -7.4 to 16%)

Discussion

• No benefit from trimethoprim-sulfamethoxazole
  
  • IDSA guidelines
  
  • Non-purulent cellulitis
  
  • Microbiological data?
  
  • CA-MRSA exotoxin?
  
  • Diabetics excluded
  
  • CA-MRSA risk factors
  
  • Epidemiological correlations
  
  • Duration of therapy
  
  • Effectiveness versus efficacy

Implications

• First evidence-based trial for IDSA guideline
  
  • 2 ongoing trials

References

Pallin et al. (2013) Uncomplicated Cellulitis


Pallin et al. (2013) Uncomplicated Cellulitis


Schmitz et al. (2010) Uncomplicated Abscess

<table>
<thead>
<tr>
<th>Schmitz et al. (2010)</th>
<th>Uncomplicated Abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong></td>
<td>Role of CA-MRSA coverage after incision and drainage (I/D) of uncomplicated skin abscesses</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Multi-center, double-blind, randomized placebo controlled trial</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>* Inclusion: ED patients ≥16yo, Abscess with I/D</td>
</tr>
<tr>
<td></td>
<td>* Exclusion: Immunocompromised, Fever/systic signs, Previous antibiotics, Deeper structure abscess</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Trimethoprim-sulfamethoxazole 160/800 mg BID for 7 days post-I/D versus placebo</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Primary: Treatment failure within 7 days, Secondary: Development of new lesions, abscess, or pusule within 30 days</td>
</tr>
</tbody>
</table>


Schmitz et al. (2010) Uncomplicated Abscess

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<th>Uncomplicated Abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Results</strong></td>
<td>220 patients enrolled, 96 TMP-SMX, 116 placebo</td>
</tr>
<tr>
<td><strong>Culture results</strong></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>Placebo 47/100 (47%), TMP-SMX 50/84 (60%)</td>
</tr>
<tr>
<td>MSSA</td>
<td>Placebo 22/100 (22%), TMP-SMX 13/84 (15%)</td>
</tr>
<tr>
<td>S. viridans</td>
<td>Placebo 5/100 (5%), TMP-SMX 2/84 (2%)</td>
</tr>
<tr>
<td>Coag neg staph</td>
<td>Placebo 10/100 (10%), TMP-SMX 1/84 (1%)</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Treatment failure at 7 days Placebo 27 (26%), TMP-SMX 15 (17%) P value 0.12</td>
</tr>
</tbody>
</table>

Schmitz et al. (2010) Uncomplicated Abscess

Results

- 139 patients at 30-day follow-up

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=90)</th>
<th>TMP-SMX (n=46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New lesion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>within 30 days</td>
<td>14 (28%)</td>
<td>4 (9%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Discussion

- Similar rates of CA-MRSA
- Loss to follow-up for secondary outcome
- Previous trials
  - Cephalexin post-I/D
  - TMP-SMX in pediatrics
- Addition of TMP-SMX to I/D does not decrease failure rate

Cefazolin versus Oxacillin/Nafcillin

- Li et al. (2014)
- Complicated MSSA bacteremia
  - Tolerability
  - Outcomes
    - Primary: rate of clinical cure at end of therapy
    - Secondary: treatment failure, adverse events, discontinuation
- Results
  - 59 patients treated with cefazolin
    - 93% received 6 grams daily
  - 34 patients treated with oxacillin
    - 94% received 12 grams daily
  - Clinical cure: 95% (C) versus 88% (O) (p = 0.25)

Cefazolin versus Oxacillin

Cefazolin versus Nafcillin


Cefazolin versus Nafcillin


Cefazolin versus Nafcillin


What About MRSA?


Linezolid vs Vancomycin vs Daptomycin

Linezolid vs Vancomycin vs Daptomycin

- No difference in length of stay for empiric treatment
  - Vancomycin: 87% of troughs > 10 mg/mL

<table>
<thead>
<tr>
<th>MRSA Agent</th>
<th>Daily Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daptomycin (4 mg/kg)</td>
<td>$340</td>
</tr>
<tr>
<td>Linezolid</td>
<td>$222</td>
</tr>
<tr>
<td>Vancomycin (1g q12h)</td>
<td>$7</td>
</tr>
</tbody>
</table>

Antibiotics and Healthcare

“Every antibiotic prescribed has a potential health system impact caused by creation of selective pressures for multi-drug resistant organisms.”

–Stan Deresinski, MD

Resistance Timeline

- Quantity of Antibiotic Use
  - Continuation of empiric coverage with multiple agents
  - New agents for MRSA and multi-drug resistant organisms

- Quality of Antibiotic Use
  - Effective use of current antibiotics
  - Reserving newer therapies for resistant organisms

Narrow Spectrum of Approval
Food and Drug Administration (FDA) Guidance

- 2013: FDA and Industry
- Guidance for Industry: Developing Drugs for Treatment
- Acute bacterial skin and skin structure infections (ABSSSI)
- Resolution of signs and symptoms after completion of therapy
- Reliability of outcome measure?
- Previous research
- Treatment effects at 48-72 hours
- Applicable to modern circumstances and standards?

Foundation for National Institutes of Health (FNIH): A Helping Hand

- Interim Evaluation
- Analysis of modern trials for lesion size and control
- Tigecycline, daptomycin, ceftriaxone
- Response 48-72 hours after randomization
- Success defined as control of infected lesion spread
- Concerns
- Lack of rigorous justification for biomarker
- Lesion spread as related to functional status
- Future direction
- Evaluate content validity and measurement properties of endpoints
- Third phase of review: new trials based on interim recommendations

Arsenal of New Antimicrobials

<table>
<thead>
<tr>
<th></th>
<th>Tedizolid</th>
<th>Dalbavacin</th>
<th>Oritavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>June 2014</td>
<td>May 2014</td>
<td>August 2014</td>
</tr>
<tr>
<td>Indication</td>
<td>ABSSSI</td>
<td>MSSA/MRSA</td>
<td>ABSSSI</td>
</tr>
<tr>
<td></td>
<td>Strep. spp.</td>
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<td>MSSA/MRSA</td>
</tr>
<tr>
<td></td>
<td>E. faecalis</td>
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<td>Strep. spp.</td>
</tr>
<tr>
<td>Dose</td>
<td>200 mg IV or PO daily x 6 days</td>
<td>1000 mg IV x 1, then 500 mg IV 1 week later</td>
<td>1200 mg IV infusion x1</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Nausea, vomiting, diarrhea</td>
<td>Nausea, rash, Red-Man Syndrome</td>
<td>Nausea, vomiting, SSTI abscess formation</td>
</tr>
<tr>
<td>Half-life</td>
<td>12 hours</td>
<td>204 hours</td>
<td>393 hours</td>
</tr>
</tbody>
</table>

ESTABLISH-1 ESTABLISH-2

<table>
<thead>
<tr>
<th>Group</th>
<th>≥18 yo</th>
<th>≥12 yo</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>ABSSSI with local or systemic signs of infection</td>
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<tr>
<td>Dose</td>
<td>200 mg PO tedizolid daily x 6 days</td>
<td>200 mg IV tedizolid x daily 6 days</td>
</tr>
<tr>
<td></td>
<td>600 mg PO linezolid BID x 10 days</td>
<td>600 mg IV linezolid x BID 10 days</td>
</tr>
<tr>
<td>Outcome</td>
<td>Early response</td>
<td>Early response</td>
</tr>
<tr>
<td></td>
<td>Sustained response</td>
<td>Sustained response</td>
</tr>
<tr>
<td></td>
<td>Clinical success</td>
<td>Clinical success</td>
</tr>
<tr>
<td>Results</td>
<td>667 patients</td>
<td>666 patients</td>
</tr>
<tr>
<td></td>
<td>Early response</td>
<td>Early response</td>
</tr>
<tr>
<td></td>
<td>0.1% [-6.1 to -6.2%]</td>
<td>2.6% [3.0 to 8.2%]</td>
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<td></td>
<td>Sustained response</td>
<td>Sustained response</td>
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<tr>
<td></td>
<td>69.3% vs 71.5%</td>
<td>87% vs 88%</td>
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<td>Clinical success</td>
<td>Clinical success</td>
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<tr>
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<td>85.5% vs 86.0%</td>
<td>92% vs 96%</td>
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Tedizolid Dalbavancin Oritavancin

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Snodgrass WR, Anderson T. BMJ. 1937 July.


FNIH and FDA: Development of Endpoints

- Bridge Recommendations
- Cellulitis/erysipelas, major cutaneous abscesses, wound infections
- >75 cm² lesion size
- <30% trial population: abscess
- Secondary outcome: resolution of ABSSSI 7-14 days after therapy

FNIH: A Helping Hand

- Historical data suggests...
- Antibacterial versus ultraviolet light
- Cessation of lesion spread for cellulitis: day 2
- Clinical cure at 7 days
- Potential treatment response earlier in therapy?
- Effectiveness of modern agents vs. sulfonamides
Roles of New Agents

- Tedizolid
  - Shortened duration of therapy
  - Less side effects
- Dalbavancin
  - Convenient dosing
  - Long half-life
- Oritavancin
  - Convenient dosing
  - Long half-life
- But how do they compare?

Thom H et al. (2015)  
ABSSSI: Systemic Review and Meta-Analysis

<table>
<thead>
<tr>
<th>Outcome Focus</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td><strong>Clinical response</strong></td>
<td>Test-of-cure (TOC)</td>
<td>Early clinical response (ECR)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th></th>
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<tbody>
<tr>
<td>52 trials identified</td>
<td>26 trials included for TOC outcome</td>
<td>10 trials included enough data for ECR comparison</td>
</tr>
</tbody>
</table>

| Thom H et al. (2015)  
ABSSSI: Systemic Review and Meta-Analysis  
Background and Design Criteria |

- Previous meta-analyses did not include newer agents and excluded the presence of indirect evidence for treatments
- Systematic literature review and network meta-analysis
- Adult patients with ABSSSI treated with:
  - Vancomycin
  - Linezolid
  - Daptomycin
  - Tigecycline
  - Clindamycin
  - Telavancin
  - Dalbavancin
  - Oritavancin
  - Tedizolid
- Study data and outcomes must have conformed to new FDA guidelines on ABSSSI
- Exclusions: medical conditions affecting interpretation of early clinical response (ECR) e.g. neutropenia
- Intention to treat (ITT) and clinically evaluable (CE) patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TOC ITT*</th>
<th>TOC CE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline</td>
<td>1.07 (0.77-1.51)</td>
<td>12.92 (0.21-2.48)</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>0.91 (0.24-4.41)</td>
<td>1.62 (0.47-2.35)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>2.18 (0.90-6.42)</td>
<td>N/A</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1.55 (0.91-2.57)</td>
<td>1.65 (0.68-3.53)</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>1.06 (0.81-1.34)</td>
<td>1.24 (0.41-3.26)</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>1.51 (0.82-2.73)</td>
<td>N/A</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0.87 (0.61-1.26)</td>
<td>0.90 (0.31-1.79)</td>
</tr>
</tbody>
</table>

*Treatment effects are presented as odds ratio versus vancomycin. Ratios >1 indicate superior outcome for the comparator.

Thom H et al. (2015)  
ABSSSI: Systemic Review and Meta-Analysis

- Clinical response
- Test-of-cure (TOC)
- Early clinical response (ECR)
Thom H et al. (2015) ABSSSI: Systemic Review and Meta-Analysis

Discussion
- No statistically significant difference among approved agents for ABSSSI for TOC
- Limited ECR data suggests same results
- Previous two meta-analyses suggest superiority of linezolid over vancomycin
- No inclusion of indirect effects of treatment comparators

Limitations
- Unable to assess MRSA or MSSA confirmed subgroups due to lack of data
- Several studies lacked information to assess ECR

Conclusion
- Suggestion of equivalence for current use of agents for ABSSSI
- More ABSSSI studies are needed that confirm to recent FDA guidelines


Stevens DL, et al.

Narrowing Coverage to Suspected Pathogens

De-escalation to Defined Therapy

Antimicrobial Stewardship
- Right Drug
- Right Dose
- Right Duration
- Appropriate De-escalation
- Right Route of Delivery


Antimicrobial Stewardship Program
- Principles of Stewardship
  - Appropriate selection, dosing, route, and duration of antimicrobial therapy
  - Optimize clinical outcomes
  - Minimize unintended consequences of antimicrobial use:
    - Drug toxicity
    - Selection of pathogenic organisms
    - Emergence of resistance
  - Ensure quality assurance and patient safety

Pasquale et al. (2014) Antimicrobial Stewardship - ABSSSI

Background
- Summa Health System
- Historical data from 2011
  - ABSSSI average LOS: 6.2 days
  - 30-day ABSSSI readmission rate: 6.2%

Design
- Retrospective observational chart review

Participants
- Emergency department admits with ABSSSI
  - Reviewed within 24 hours
  - Cellulitis, abscess, surgical site/wound infections

Intervention
- Evaluation of patient by clinical pharmacist and ID physician
  - Prospective chart review and recommendation

Outcome
- Length of stay and 30-day ABSSSI readmission rate

Pasquale et al. (2014) Antimicrobial Stewardship - ABSSSI

Results
- 62 patients
  - 22 (35%) diabetics
  - 85 Interventions; 81 accepted
  - Dose change: 27 (44%)
  - De-escalation: 23 (37%)
  - Regimen change: 20 (24%)
  - ID consult: 6 (7%)
  - Other: 9 (11%)

Pasquale et al. (2014) Antimicrobial Stewardship - ABSSSI

Discussion
- Specific for ABSSSI
- Observational study
- Small patient size

Implications
- Interventions are readily available in various forms
- Antimicrobial stewardship implementation and focus


Intravenous to Oral Antibiotics

<table>
<thead>
<tr>
<th>Coverage</th>
<th>IV Therapy</th>
<th>PO Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus/ MSSA</td>
<td>Cefazolin/ Oxacillin/ Naclitcin/ Ceftriaxone</td>
<td>Amoxicillin-clavulinate/ Cephalexin/ Clindamycin</td>
</tr>
<tr>
<td>MRSA</td>
<td>Vancomycin/ Linezolin/ Ceftazoline/ Daptomycin</td>
<td>Doxycycline/ Minocycline/ TMP-SMX/ Clindamycin</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>Piperacillin-tazobactam/ vancomycin</td>
<td>TMP-SMX/ Cephalexin/ Clindamycin</td>
</tr>
</tbody>
</table>


Future Directions
- Duration of Antibiotic Therapy for Cellulitis (DANCE)
  - Prospective, multicenter, non-inferiority trial in the Netherlands
  - Short versus standard duration of inpatient cellulitis therapy
    - Primary outcome: resolution of cellulitis at day 14 without recurrence at day 28
    - Flucloxacillin IV/PO for 10-14 days for all cellulitis cases
    - Potential guidance for duration of therapy
    - Similar studies for respiratory tract infections, urinary tract infections, and bacteremia

Future Directions

- Omadacycline
  - Oral/IV, once-daily tetracycline derivative
  - Gram (+), gram (-), atypical, anaerobic, MRSA
  - ABSSSI, CABP, UTI undergoing phase 3 trials
- Iclaprim
  - IV dihydrofolate reductase inhibitor initially denied approval in 2008
  - Phase 3 trials approved on April 2015
  - ABSSSI and HABP caused by gram (+) pathogens
- Other investigational antibiotics
  - BC-3781 – semisynthetic pleuromutilin derivative
  - CEM-102/Fusidic acid – oral agent with high dose regimen
  - JNJ-Q2/Avarofloxacin – targets topoisomerase II and IV
  - TD-1792/1607 – glycopeptide-cephalosporin heterodimers

Conclusion

- Skin and soft tissue infections are common
- High antibiotic exposure for patients
- Appropriate empiric treatment with antibiotics, if indicated
  - Identification of most common pathogens for SSTI classification
    - Nonpurulent – Streptococcus spp., MSSA
    - Purulent – MSSA/MRSA
  - Bug-drug match
  - Consider local antibiogram

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SKIN AND SOFT TISSUE INFECTIONS
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