OUTPATIENT MANAGEMENT OF NON-PURULENT CELLULITIS

Ayesha Arrine, MD
OBJECTIVES

• Understand the definition and epidemiology of uncomplicated, non-purulent cellulitis.
• Understand the most common microbial causes of non-purulent cellulitis.
• Review the 2014 IDSA guidelines for management of mild, non-purulent cellulitis.
• Review the HFH guidelines for management of skin and soft tissue infections.
• Review the literature regarding the management and treatment options of non-purulent cellulitis.
• Review our current practice patterns in the ED and integrate evidence-based information into our daily practice.
CELLULITIS DEFINITION

• Cellulitis, as defined by IDSA, is a diffuse spreading infection with inflammation of the deeper dermis and subcutaneous fat and excludes infections associated with underlying suppurative foci, such as cutaneous abscesses, necrotizing fasciitis, septic arthritis, and osteomyelitis

• It can develop as a result of bacterial entry via breaches in the skin barrier

• Predisposing factors include disruption to the skin barrier as a result of trauma (insect bites, abrasions, penetrating wounds, or injection drug use), inflammation (eczema or radiation therapy), pre-existing skin infections (impetigo or tinea pedis), and edema (venous insufficiency)
CELLULITIS DIAGNOSIS

• The diagnosis of cellulitis is a clinical one
• Most cases of cellulitis are not amenable to identification of a pathogen
• Studies of cultures of biopsy specimens from cutaneous cellulitis found only 28.5% of needle aspiration and 18% of punch biopsy cultures were positive\(^1\)
• Studies have shown blood cultures are even less likely to be positive with <5% being positive \(^2\)
• Other techniques for pathogen identification include serologic and antigen studies, which have shown better results
CELLULITIS MICROBIOLOGY

- The vast majority of cellulitis pathogens are beta-hemolytic streptococci (groups A, B, C, G, and F) with staphylococcus aureus being a minority
- Gram-negative bacilli are rare
CELLULITIS MICROBIOLOGY: STREP

- BETA-HEMOLYTIC STREP
  - Group A Strep (S. pyogenes)
  - Group B Strep (S. agalactiae)
  - Group C Strep
  - Group G Strep
Methicillin-resistant staph aureus (MRSA) has become the dominant strain of staph aureus in many communities in the US

As a result, many clinicians are now empirically covering for this pathogen in the treatment of various skin and soft-tissue infections
2014 IDSA GUIDELINES

• Typical cases of cellulitis without systemic signs of infection (mild, non-purulent cellulitis), should receive an antimicrobial agent that is active against streptococci (strong, moderate)

• For cellulitis with systemic signs of infections (moderate, non-purulent cellulitis), systemic antibiotics against streptococci are indicated. Many clinicians could include coverage against MSSA (weak, low)

• For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe, non-purulent), vancomycin or another antimicrobial against both MRSA and streptococci is recommended (strong, moderate)
2014 IDSA GUIDELINES

• The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period (strong, high)

• Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended (strong, moderate)

• Outpatient therapy is recommended for patients who do not have SIRS, altered mental status, or hemodynamic instability (strong, moderate)
NONPURULENT
Necrotizing Infection /Cellulitis /Erysipelas

MANAGEMENT OF SSTIs

PURULENT
Furuncle / Carbuncle / Abscess

Severe
Moderate
Mild

Severe
Moderate
Mild

EMERGENT SURGICAL INSPECTION / DEBRIDEMENT
- Rule out necrotizing process

EMPIRIC Rx
- Vancomycin PLUS Piperacillin/Tazobactam

C & S

INTRAVENOUS Rx
- Penicillin or Ceftriaxone or Cefazolin or Clindamycin

DEFINEd Rx (Necrotizing Infections)
Monomicrobial Streptococcus pyogenes
- Penicillin PLUS Clindamycin
- Clostridial sp.
- Penicillin PLUS Clindamycin
- Vibrio vulnificus
- Doxycycline PLUS Ceftazidime
- Aeromonas hydrophila
- Doxycycline PLUS Ciprofloxacin

Polymicrobial
- Vancomycin PLUS Piperacillin/Tazobactam

DEFINEd Rx MRSA
- See Empiric

DEFINEd Rx MSSA
- Nafcillin or Cefazolin or Clindamycin

ORAL Rx
- Penicillin VK or Cephalosporin or Dicloxacillin or Clindamycin

I & D C & S

EMPIRIC Rx
- Vancomycin or Daptomycin or Linezolid or Televancin or Ceftaroline

DEFINED Rx MRSA
- TMP/SMX or Doxycycline

DEFINED Rx MSSA
- TMP/SMX
- MSSA
- Dicloxacillin or Cephalexin

I & D

\[1\] Since daptomycin and televancin are not approved for use in children, vancomycin is recommended; clindamycin may be used if clindamycin resistance is <10-15% at the institution.
Cellulitis, Outpatient Preferred Therapy

- Dicloxacillin 500mg qid for 5-10 days
- Cephalexin 500mg PO qid for 5-10 days
- Clindamycin 450mg PO tid for 5-10 days
WHAT IS THE BASIS OF THESE GUIDELINES?

- In the presence of a culturable source (abscess, wound, ulcer), etiologic pathogen can be identified, but soft-tissue infections without a culturable source, such as non-purulent cellulitis, pose a problem.
- The overall body of evidence suggests that streptococci are the most common single pathogen in cellulitis BHS to be the predominant cause of such infections, with S. aureus making up a minority.
- However, since the recent emergence of CA-MRSA in the 1990s, there had been no new studies to evaluate if BHS remains the main etiologic agent of non-culturable cellulitis.
The role of beta-hemolytic streptococci in causing diffuse, non-culturable cellulitis: a prospective investigation.

Jeng A¹, Beheshti M, Li J, Nathan R.

- A prospective investigation between 2004 and 2007 of patients admitted to inpatient service with diffuse, non-culturable cellulitis
- 179 patients had blood cultures and acute and convalescent serologies of anti-streptolysin O and anti-DNase-B antibodies drawn and were analyzed for response to B-lactam antibiotics
- The primary outcome being the proportion of these cases caused by BHS as diagnosed by serologies and/or blood cultures and the secondary outcome was the response rate of these patients to B-lactam antibiotics
• Of the 179 patients, 73% of non-culturable cellulitis was caused by BHS (+ASO/ADB positive or +blood cultures)

• Analysis of outcomes to B-lactam therapy revealed that patients diagnosed with BHS proven cellulitis had a 97% response while those who did not have BHS proven cellulitis had a 91% response, with an overall response rate of 95.8%

• Results of this large, prospective study show that diffuse, non-culturable cellulitis is still mainly caused by BHS, despite the MRSA epidemic, and that for this infection type, treatment with a B-lactam antibiotic is still effective
• A randomized, multicenter, double-blind placebo-controlled trial from 2007 to 2011 of patients with cellulitis presenting to the one of three EDs located in an area endemic for CA-MRSA

• All patients received cephalexin + placebo or cephalexin + TMP/SMX for 14 days and participants were instructed to continue therapy for at least a week then stop 3 days after they felt the infection to be cured

• The primary outcome was the risk difference for treatment success determined in patient at 2 weeks
• Of 146 patients, 85% (62/73) of those who received cephalexin + TMP/SMX were cured versus 82% (60/73) of the control who received only cephalexin, with a risk difference of 2.7% (95% CI, -9.3% to 15%, p=0.66)
• Of the 146 patients, 16% (11 in intervention group and 13 in control group) failed therapy. Reasons for failure included:
  • 21 were prescribed additional antibiotics due to clinicians’ perception of treatment failure
  • 6 required I&D
  • 3 had drug intolerance (allergy/side effects)
• Results of this large multi-center trial showed that among patients diagnosed with cellulitis without abscess, the addition of TMP-SMX to cephalexin did not improve the overall outcomes
A multi-center retrospective cohort study of outpatients treated for uncomplicated cellulitis was conducted between 2004 and 2005 to compare clinical failure rates of oral B-lactam and non-B-lactam treatments.

861 patients were included with 631 receiving B-lactam therapy (cephalexin being the most common) and 230 receiving non-B-lactam therapy with activity against CA-MRSA (clindamycin and TMP/SMX being the most common).

The primary end point was clinical failure, which was defined as:
- Antibiotic refill beyond initial prescribed duration or
- The addition of another antibiotic within 21 days of diagnosis or
- Return visit for cellulitis requiring I&D occurring between 48 hours and 21 days of diagnosis.
• Failure rates were 14.7% for B-lactam-therapy and 17% for non-B-lactam therapy (OR 0.85, 95% CI 0.56-1.31)
• Factors associated with failure were:
  • Age
  • Symptom severity
• Results of this retrospective study showed that there was no significant difference in clinical failure between B-lactam and non-B-lactam antibiotics for the treatment of uncomplicated cellulitis
<table>
<thead>
<tr>
<th>Antibiotic or Antibiotic Group</th>
<th>Clinical Failures/Patients Treated (% Failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All β-lactams</td>
<td>93/631 (14.7)</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>54/359 (15.1)</td>
</tr>
<tr>
<td>All other β-lactams</td>
<td>39/272 (14.3)</td>
</tr>
<tr>
<td>Dicloxicillin</td>
<td>25/169 (14.8)</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>13/88 (14.8)</td>
</tr>
<tr>
<td>Other β-lactams</td>
<td>1/15 (6.7)</td>
</tr>
<tr>
<td>Non-β-lactams</td>
<td>39/230 (17.0)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>14/86 (16.3)</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>8/43 (18.6)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>8/33 (24.2)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>3/16 (18.8)</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>1/11 (9.1)</td>
</tr>
<tr>
<td>Combinations</td>
<td>5/41 (12.2)</td>
</tr>
</tbody>
</table>
A 3-year retrospective cohort study of outpatients with cellulitis empirically treated at a teaching clinic of a tertiary-care medical center in Hawaii between 2005 and 2007 with treatment success rates being compared for cephalexin, TMP-SMX, and clindamycin.

405 patients were included with 180 receiving cephalexin, 152 TMP-SMX, 40 clindamycin, and 33 other antibiotics (including augmentin, dicloxacillin, doxycycline).

The primary outcome measured was treatment success, defined as clinical improvement or resolution of signs and symptoms of cellulitis occurring at the first follow-up visit without a change in antibiotics, hospitalization, or surgical intervention.
• Overall treatment success rate was higher in TMP-SMX group at 91% compared to cephalexin group at 74% (OR 2.28; 95% CI 1.79-6.39, p<0.001)

• Clindamycin had a higher success rate at 85% compared to cephalexin at 74%, but this was not statistically significant (OR 1.96; 95% CI 0.79-4.80, p<0.22)
• This is the only study that included patient’s with associated abscesses that did or did not require I&D, 40% of patients had cellulitis with abscess, 36% had simple cellulitis, and the remainder had cellulitis with an ulcer. Just by this alone, you are increasing your likelihood of MRSA.

• The investigators reported that the higher success rates of TMP-SMX compared with cephalexin were consistent regardless of the presence of wound or abscess, the severity of cellulitis, or whether drainage was performed, however when looking at the subgroup analysis data, these numbers were not statistically significant.

• The only numbers that were statistically significant in this study was the overall treatment success of all cellulitis and TMP-SMX having higher success rates than cephalexin in those cases with positive MRSA cultures.
Table 3. Comparison of Treatment Success Rates among Patients Treated with Cefalexin, Trimethoprim-Sulfamethoxazole, or Clindamycin with Subgroup Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cefalexin</th>
<th>TMP-SMX</th>
<th>Clindamycin</th>
<th>Odds Ratio (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients: n</td>
<td>180</td>
<td>152</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>124 (74)</td>
<td>138 (91)</td>
<td>34 (85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: n</td>
<td>108</td>
<td>92</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>79 (73)</td>
<td>84 (91)</td>
<td>17 (89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacific Islander: n</td>
<td>90</td>
<td>74</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>68 (76)</td>
<td>70 (95)</td>
<td>25 (93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity (body mass index ( \geq 30 )): n</td>
<td>99</td>
<td>74</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>67 (68)</td>
<td>65 (88)</td>
<td>19 (90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus: n</td>
<td>64</td>
<td>54</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>43 (67)</td>
<td>50 (93)</td>
<td>14 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoker: n</td>
<td>54</td>
<td>55</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>40 (74)</td>
<td>58 (89)</td>
<td>10 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis only: n</td>
<td>72</td>
<td>45</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>57 (78)</td>
<td>43 (96)</td>
<td>11 (85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis with abscess: n</td>
<td>28</td>
<td>40</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>18 (64)</td>
<td>35 (93)</td>
<td>10 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis with abscess: n</td>
<td>81</td>
<td>70</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>59 (73)</td>
<td>62 (89)</td>
<td>13 (83)</td>
<td></td>
<td></td>
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<tr>
<td>Mild disease severity: n</td>
<td>137</td>
<td>98</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>113 (82)</td>
<td>91 (97)</td>
<td>25 (83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate disease severity: n</td>
<td>43</td>
<td>56</td>
<td>10</td>
<td></td>
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<tr>
<td>Treatment success</td>
<td>21 (48)</td>
<td>45 (80)</td>
<td>9 (90)</td>
<td></td>
<td></td>
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<tr>
<td>Positive culture for MRSA: n</td>
<td>25</td>
<td>40</td>
<td>6</td>
<td></td>
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<tr>
<td>Treatment success</td>
<td>6 (24)</td>
<td>36 (30)</td>
<td>5 (33)</td>
<td></td>
<td></td>
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<tr>
<td>Receiving only oral antibiotic: n</td>
<td>126</td>
<td>103</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>88 (70)</td>
<td>92 (88)</td>
<td>23 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiving oral antibiotic and I&amp;D: n</td>
<td>53</td>
<td>43</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>45 (85)</td>
<td>44 (98)</td>
<td>10 (91)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A retrospective chart review of patient’s seen in the ED with cellulitis in 2000 and 2005

A total of 319 patients met study criteria in 200 and 432 met criteria in 2005

The objective was to determine antibiotic prescribing patterns and treatment failure rates for cellulitis in pre- and post-CAMRSA eras
• B-lactam antibiotics accounted for 83.7% of prescriptions in 2000 and 64.6% of prescription in 2005, resulting in a significant change in B-lactam use (p<0.0001)

• CA-MRSA effective antibiotics accounted for 1.25% of prescriptions in 2000 and 28.9% in 2005, resulting in a significant change in CAMRSA effective antibiotic use (p<0.0001)

• Treatment failure rates of individual antibiotics were determined for antibiotics used more than 10 times per year. In 2000, the overall, B-lactam group treatment failure rate was 17.23% and in 2005 it was 16.8%, this was not statistically significant (p<0.9)

• CAMRSA effective antibiotics were used only 4 times in 2000, precluding determination of a treatment failure rate. In 2005, the treatment failure rate for this group was 21.3%
Fig. 1  Percentage of single-agent prescriptions in 2000 (n = 319).
Fig. 2  Percentage of single-agent prescriptions in 2005 (n = 432).

- Cephalexin (46.5%)
- Clindamycin (18.5%)
- Amox/Clav (15%)
- TMP/SMZ (10.4%)
- Dicloxacillin (3%)
- Ciprofloxacin (3%)
- Other (3.5%)
WHAT ARE ED PHYSICIANS AT HENRY FORD HOSPITAL PRESCRIBING FOR NON-PURULENT CELLULITIS?

- Keflex: 5%
- Keflex + Bactrim: 50%
- Bactrim: 10%
- Clindamycin: 5%
- Doxycycline: 0%
HENRY FORD HOSPITAL MICROBIOLOGY DIVISION OUTPATIENT ANTIBIOTIC SUSCEPTIBILITY REPORT 2013

<table>
<thead>
<tr>
<th>Antibiotic Susceptibility Report</th>
<th>OUTPATIENT</th>
<th>Jan – Dec 2013</th>
<th>1st Isolate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Strains</td>
<td>Amoxicillin</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Acinetobacter sp.</td>
<td>49</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>87</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Citrobacter koseri</td>
<td>139</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>118</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>193</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>6446</td>
<td>53</td>
<td>92</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>49</td>
<td>76</td>
<td>79</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>83</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>988</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>563</td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>337</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>67</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Methicillin resistant S. aureus</td>
<td>819</td>
<td>0</td>
<td>96</td>
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<tr>
<td>Methicillin susceptible S. aureus</td>
<td>765</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Coagulase (-) staphylococci</td>
<td>124</td>
<td>44</td>
<td>88</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>147</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>36</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>52</td>
<td>97/0</td>
<td>100</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>52</td>
<td>78/0</td>
<td>100</td>
</tr>
</tbody>
</table>
COST & COMPLIANCE CONSIDERATIONS

CLINDAMYCIN

150mg capsules

3 capsules, 3x/day=9 capsules/day

9 capsules/day x 10 days= 90 capsules

Average Cash Cost: $79

Compliance:

3 capsules at 9am, 3 capsules at 3pm, 3 capsules at 9pm

Continue for 10 days
COST & COMPLIANCE CONSIDERATIONS

DOXYCYCLINE

100mg capsules

1 capsule, 2x/day = 2 capsules/day

2 capsules/day x 10 days = 20 capsules

Average Cash Cost: $92

Compliance:

1 capsule at 9am and 1 capsule at 9pm

Continue for 10 days
## COST & COMPLIANCE CONSIDERATIONS

<table>
<thead>
<tr>
<th></th>
<th>BACTRIM</th>
<th>KEFLEX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOSAGE</strong></td>
<td>1 DS tablet</td>
<td>500mg tablets</td>
</tr>
<tr>
<td></td>
<td>2 tablets, 2x/day= 4 tablets/day</td>
<td>1 tablet, 4x/day= 4 tablets/day</td>
</tr>
<tr>
<td></td>
<td>4 tablets/day x 10 days= 40 tablets</td>
<td>4 tablets/day x 10 days= 40 tablets</td>
</tr>
<tr>
<td><strong>Average Cash Cost:</strong></td>
<td>$33</td>
<td>$20</td>
</tr>
<tr>
<td><strong>Availability:</strong></td>
<td>Free at Meijer</td>
<td>Free at Meijer</td>
</tr>
<tr>
<td></td>
<td>$4 at Kroger</td>
<td>$4 at Kroger</td>
</tr>
</tbody>
</table>

**Compliance:**

3 tablets at 9am, 1 tablet at 1pm, 1 tablet at 4pm, 3 tablets at 9pm

Continue for 10 days
CONCLUSIONS

• Non-purulent cellulitis is usually caused by strep, which is susceptible to B-lactams

• MRSA coverage should be considered in patients with abscesses or other co-morbid conditions

• Single antibiotic use decreases risk of side effects, increases chances of compliance, decreases chances of antibiotic resistance, and decreases health care costs, so it should be strongly considered where applicable
1 Duvanel T, Auckenthaler R, Rohner P, harms M, Saurat JH. Quantitative cultures of biopsy specimens from cutaneous cellulitis, Arch Intern Med. 1989; 149: 293-6


REFERENCES


QUESTIONS?!