Beyond the Red Leg:
Cellulitis and Its Mimickers

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose
Overview

• Cellulitis & Pseudocellulitis: Background

• Diagnosis: Typical vs. Variant vs. Pseudocellulitis

• Pseudocellulitis
Cellulitis

- Deep skin and subcutaneous fat infection

- Poorly-demarcated erythema, warmth, tenderness, edema
  - Rubor, calor, dolor, tumor: inflammation

- 2.2% of all general practitioner office visits
  - US Outpatient + ED 2006: 14.5 million cases, $3.7 billion
  - 4.6 million cases in 1997

Cellulitis

• 10% of infectious disease-related US hospitalizations ‘98-’06
• Average length of stay 7-10 days, 15 days if recurrent cellulitis
• 400,000 days/ year in the English National Health Service

• 73% increased rate of hospitalization in US from 1997-2011
  – Five-fold increased hospitalization from 54yo to >=85yo
  – Over 650,000 admissions

Cellulitis at MGH: #15 Admission, #1 Readmission

Diagnosis Group

- Cellulitis & Rash
- Pulmonary
- Other
- Esophageal
- GI Other
- Cardiac/Other
- Musculoskeletal
- Vascular/Blood
- UTI
- CHF
- Other
- Pneumonia
- Neuro
- Pain
- Endocrine
- Renal
- ID
- IBS
- Pancreas
- Psycho-social
- Liver
- AML

% Total Readmissions

FY11 Qty

Table courtesy of D. Mari
Pseudocellulitis: The Problems

• Preliminary data: 7% of 500 inpatient consults over nine months for unresponsive cellulitis
  – 85% = pseudocellulitis

• Very little agreement on the ‘gold standard’
  – No laboratory criteria exist to confirm dx

• Dermatologist expertise facilitates the identification and proper treatment of actual mimicking diagnoses, reduced antibiotic use

Cellulitis vs Pseudocellulitis

- Up to 33% represent ‘pseudocellulitis’, or other mimicking inflammatory skin conditions
- Diagnostic criteria are unclearly defined, variably applied
- Poorly-demarcated erythema, warmth, tenderness, edema
  - Rubor, calor, dolor, tumor: *inflammation* (*Celsus, 1st century AD*)
- Per year, cellulitis misdiagnosis, hospitalization, and antibiosis leads to an estimated:
  - 50,000 unnecessary hospitalizations
  - $195 million in avoidable health care spending
  - 9,000 nosocomial infections, 1,000 C. difficile infections
- Dermatology or Infectious Diseases consultation proposed as clinical gold standard

Associated Risk Factors

- 1+ known risk factor
- H/O skin disease
- Active cancer
- Diabetes
- High-Dose Immunosupp.
- H/O Transplant
- Tinea pedis
- ESRD
- Known trauma
- Chronic Lymphedema
- Neutropenia
- Onychomycosis
- AIDS
- Low-dose Immunosupp.

Local Risk Factors Are More Significant in the Development of Leg Cellulitis Than Systemic Risk Factors

- A systematic review and meta-analysis over 70y
- Local significant risk factors: prior cellulitis, prior leg surgery, a ‘site of bacterial entry’ from wound, ulceration, excoriating skin disease or toe-web disease, chronic leg edema
- Obesity was the only potentially significant global health factor
- Evaluation and management of predisposing factors via regular follow-up visits may minimize risk

Multidisciplinary Approach to Cellulitis at MGH

- Dermatology consultation for patients presenting for presumed cellulitis within 24 hours of IV antibiotic initiation
- 31% misdiagnosis rate
- Decrease in IV antibiotic use (<4 days: 86.3 versus 72.5; p=0.04) as well as total duration of antibiotic use
- Decrease in hospital stay (<4 days: 76.1% versus 64.4%; p=0.14)
- Improvement at 2 week assessment (89.3% versus 68.3% p<0.01) with no complications or increased risk of readmission


- 210/635 referrals for lower limb cellulitis (33%) had other diagnoses which did not require admission

- 96% true cellulitis pts managed entirely as outpatients, many at home

- 28% patients with cellulitis had an underlying skin disease identified and treated → reduced the risk of recurrent cellulitis, leg ulceration, and lymphedema

- 18/635 patients referred with lower limb cellulitis required hospital admission for conventional treatment (3%)
Microbiology: Common Pathogens

• Adults:
  - Streptococcus pyogenes, Staphylococcus aureus
  - MSSA>>>MRSA, unless traumatic

• Children:
  • Staphylococcus aureus
    – Previously Haemophilus influenzae
Microbiology: Immunosuppression

• Mild/Moderate: DM, ESRD, Cirrhosis, PDN<20mg
  – Staphylococci, streptococci
  – Gram Negative Rods (GNR)

• Severe: neutropenic, PDN >20mg, other immunosuppressives, AIDS
  – Staphylococci, streptococci, GNR
  – Atypical mycobacteria, deep fungal, nosocomials

Adapted from Bologna Dermatology Fig 73.7
Multidisciplinary Approach to Cellulitis at MGH: Antibiotic Stewardship

- Mean number of antibiotics used: 2.8 (SD 1.3)

- 57.7% of all patients given longer than IDSA recommended maximum antibiotic courses
  
  - 68% of control patients given >=10 days of antibiotics vs. 49% of intervention patients (p<0.01)
    - Specialist recommendations often ignored; antibiotics ‘just in case’

- 20% of patients at MGH are on vancomycin

Vancomycin in the Emergency Department

Weight based vancomycin dosing

- Correct: 24%
- Overdose: 3%
- Underdose: 73%

Number of ED vancomycin doses administered prior to discharge

- Dose 1: 68%
- Dose 2: 27%
- Dose 3: 5%

Antibiotic Stewardship: Treatment Algorithm for Nonpurulent Cellulitis

Adapted from: Raff AB, Kroshinsky D. Cellulitis: A Review. JAMA. 2016 Jul 19;316(3):
Antibiotic Stewardship: Treatment Algorithm for Purulent Cellulitis

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult Dosing</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSSA and <em>Streptococcus</em> Coverage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>875mg, 2times/dorally</td>
<td>Streptococcal and MSSA coverage</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1g every 8h intravenously</td>
<td>For true penicillin-allergic patients, less bone marrow suppression than nafcillin</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>600mg every 12h intravenously</td>
<td>Adjust for reduced creatinine clearance</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1-2g/dorally/intravenously</td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>500mg, 4times/dorally</td>
<td>Except in true penicillin-allergic patients with immediate hypersensitivity reactions</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>250-500mg, 4times/dorally</td>
<td>Oral agent of choice for MSSA</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td>500mg every 6h intravenously</td>
<td>Not to exceed 50 mg/kg or 4 g/d, whichever is lower</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1g every 8h intravenously</td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td>1-2g every 4h intravenously</td>
<td>Parenteral drug of choice in MSSA</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>1-2g every 4h intravenously</td>
<td>Parenteral drug of choice in MSSA</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>2-4 million U every 4-6h intravenously</td>
<td></td>
</tr>
<tr>
<td>Penicillin VK</td>
<td>250-500mg every 6h orally</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>3.375g every 6h intravenously</td>
<td></td>
</tr>
<tr>
<td><strong>MRSA Coverage</strong></td>
<td></td>
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</tr>
<tr>
<td>Clindamycin</td>
<td>300-450mg 4 times/d orally</td>
<td>Potential inducible resistance in MRSA</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>4mg/kg every 24h intravenously</td>
<td>Costly (500 mg, $534.59&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100mg, 2times/dorally</td>
<td>Possible photosensitivity Variable antistreptococcal activity</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600mg every 12h orally</td>
<td>Costly (600-mg tablet, $184; 2 mg/mL [300 mL], $96&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100mg, 2times/dorally</td>
<td>Variable antistreptococcal coverage</td>
</tr>
<tr>
<td>Telavancin</td>
<td>10mg/kg every 24h intravenously (infused during 1h)</td>
<td>Costly (250 mg, $238.96&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100mg followed by 50mg every 12h intravenously</td>
<td>Adjust for severe liver impairment</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>1-2 double-strength tablets 2 times/d orally</td>
<td>Increased risk of blistering skin reactions Poor streptococcal coverage</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15mg/kg every 12h intravenously</td>
<td>Parenteral agent of choice for MRSA infections</td>
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TMP/SMX: 2 DS tabs BID for patients >100kg, immunosuppression, trauma-induced SSTI
Multicenter, double-blind, randomized superiority trial in 5 US EDs

500 cellulitis outpatients > 12 yo with no wound, purulent drainage, or abscess (confirmed by bedside ultrasound)

Randomized to two treatment arms:
- Cephalexin, 500 mg 4 times daily, plus SMX-TMP, 320 mg/1600 mg twice daily, for 7 days or
- Cephalexin plus placebo for 7 days

Clinical cure in 83.5% of cephalexin plus SMX-TMP group vs 85.5% in the cephalexin group (95% CI, −9.7% to 5.7%; P = 0.50)

Predisposing Factors to Cellulitis

- Trauma:
  - Piercings
  - IVDA/‘popping’
  - Bites
  - Self-induced

- Tinea pedis/ onychomycosis
- Uncontrolled edema

Chronic Ulcers & Infection

- Diabetic, stasis, decubitus

- Culture usually
  - Polymicrobial
  - Not involved in cellulitis
  - Unnecessarily broad coverage


Chronic Ulcers & Infection

- Signs of infection:
  - New onset pain
  - Increased erythema

- Usually multiorganism
  - Anaerobes, Gram-negative aerobes
Predisposing Factors for Recurrence

- Peripheral vascular disease
- LN dissection
- XRT
- Liposuction
- Leg vein harvesting for CABG
- IVDA, skin popping
- Tinea pedis, onychomycosis
- Underlying vascular and lymphatic disease due to prior episodes
Possible Complications of Typical Cellulitis

- Bacteremia
- Lymphadenitis
- Subacute bacterial endocarditis
- Glomerulonephritis
- Elephantiasis nostra verrucosa
Evaluation

• History
  – Onset and duration: first or recurrent episode
  – Local symptoms: pain/ pruritus/ burning/ dysesthesia
  – Associated symptoms: SOB, arthritis, diarrhea, headache, cough, chills, fever
  – Course/ progression

• Past medical, family, social history

• Medications
Evaluation: Objective

• General appearance

• Vital Signs:
  – Fever: infection or systemic inflammation
    • Pattern of fever (ie diurnal- Still’s disease)
  – Tachycardia, hypotension

• LAD: infectious, inflammatory, neoplastic
Atypical Features or Unresponsive to Treatment:

- Resistant pathogens
- Cellulitis variant (ie- necrotizing, fungal)
- Pseudocellulitis
Diagnostic Testing for Cellulitis

- Labs
- Cultures
- Biopsy
- Imaging
- Special tests directed at pseudocellulitis
Diagnostic Testing for Cellulitis

• Labs: CBC w/ differential, CMP

• Cultures:
  – Blood: 91% negative and usually not helpful
    • 19% *S.pyogenes*, 38% other β-hemolytic streptococci, 14% *S.aureus*,
      28% Gram-negative
    • ~50% of positive blood cultures represent contaminants
  – Skin swabs, biopsy, aspiration usually low yield
    • Highly variable results
  – Not recommended for uncomplicated/routine cellulitis


Inability of PCR, Pyrosequencing, and Culture to Identify the Cause of Cellulitis

- US ED evaluation of 49 subjects
  - Samples taken from infected and unaffected skin
  - No statistically significant differences between sides
  - S. pyogenes > MSSA, no MRSA

- Conclusions: bacterial cause cannot be determined by comparison of prevalence and quantity of pathogens

Blood Cultures in Cellulitis

- 183 patients presenting to the MGH ED 10/2014 – 2/2016 with a presumed diagnosis of cellulitis

- 32.8% (60) patients received blood cultures
  - 90% (54/60) did not meet IDSA guidelines
  - 96.7% (58/60) no growth (1 growth, 1 contaminant)

- Extrapolated annual national cost of diagnostic imaging and blood cultures for presumed cellulitis: $226.9 million dollars

Ko L, Kroshinsky D. JAMA Internal Medicine.
When to Biopsy

- Atypical case in immunosuppressed patient
- Concern about non-bacterial etiology
  - Special stains, cultures
- Concern for pseudocellulitis
Differential Diagnosis for Cellulitis

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<thead>
<tr>
<th></th>
<th>Infectious</th>
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<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Erythema migrans, herpes simplex, herpes zoster, cutaneous abscess</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Bacterial (eg, erysipelas, necrotizing fasciitis); viral (eg, parvovirus B19, CMV); fungal (eg, Cryptococcus neoformans, Sporothrix schenckii, mucormycosis); mycobacterial; parasites (eg, Trypanosoma cruzi, Dermatobia hominis [myiasis]); osteomyelitis; septic joint</td>
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<thead>
<tr>
<th></th>
<th>Inflammatory</th>
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<tr>
<td><strong>Common</strong></td>
<td>Drug reactions; contact dermatitis; angioedema; Sweet syndrome; gout; acute bursitis; erythema nodosum</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Fixed drug reaction; pyoderma gangrenosum; sarcoidosis; eosinophilic cellulitis (Well syndrome); relapsing polychondritis; familial Mediterranean fever; polyarteritis nodosa; panniculitis (eg, lipodermatosclerosis, morphea, eosinophilic fasciitis, traumatic, pancreatic, lupus); cutaneous GVHD</td>
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<th>Vascular</th>
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<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Venous stasis dermatitis; lymphedema; deep vein thrombosis; superficial thrombophlebitis; hematoma</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Erythromelalgia; calciphylaxis</td>
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<tr>
<th></th>
<th>Neoplastic</th>
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<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Carcinoma erysipelois; Paget disease of the breast; extramammary Paget disease; inflammatory breast carcinoma; lymphoma; leukemia</td>
</tr>
</tbody>
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<thead>
<tr>
<th></th>
<th>Miscellaneous</th>
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<tr>
<td><strong>Common</strong></td>
<td>Insect bites/stings; reaction to foreign body implant (eg, metal, mesh, silicone or paraffin injections); postcutaneous injection; intravenous line infiltration</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Compartment syndrome; radiation recall; pressure/coma bullae</td>
</tr>
</tbody>
</table>

Imaging: Only to Rule Out Other Conditions

- X-ray
  - Osteomyelitis (chronic), foreign body

- Ultrasound
  - Abscess, pyomyositis

- CT
  - Osteomyelitis, pyomyositis*, necrotizing fasciitis*

- MRI
  - Osteomyelitis*, pyomyositis, necrotizing fasciitis

### Imaging in Cellulitis

- 183 patients presenting to the MGH ED 10/2014 – 2/2016 with a presumed diagnosis of cellulitis
  - 67.8% received imaging
  - 22.3% received more than one test, up to four

<table>
<thead>
<tr>
<th>Test</th>
<th>Total Tests Obtained</th>
<th>Tests Changing Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound - N(%)</td>
<td>85 (46.4)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Plain Radiograph - N(%)</td>
<td>53 (29.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Computed Tomography - N(%)</td>
<td>29 (15.8)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Magnetic Resonance - N(%)</td>
<td>11 (6.0)</td>
<td>4 (36.4)</td>
</tr>
</tbody>
</table>

Ko L, Kroshinsky D. JAMA Internal Medicine.
Conclusions

• Cellulitis is a common, costly, frequently overdiagnosed condition

• Consider alternate diagnoses in atypical cases or cases unresponsive to standard treatment

• Limit use of biopsies, imaging, ulcer and blood cultures

• Review antibiotic stewardship guidelines