Diagnosis and management of cellulitis

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Cellulitis is a frequently encountered condition, but remains a challenging clinical entity. Under and overtreatment with antimicrobials frequently occurs and mimics cloud the diagnosis. Typical presentation, microbiology and management approaches are discussed.

Introduction
Definition
Cellulitis is simply defined as an acute infection of the skin involving the dermis and subcutaneous tissues. Erysipelas classically refers to a more superficial cellulitis of the face or extremities with lymphatic involvement, classically due to streptococcal infection. Diabetic foot infections and wound infections are specific entities. Although they may share some features with cellulitis, their management is different and beyond the scope of this article. This article will focus on cellulitis of the lower limb.

Burden of disease
In 2014–5, cellulitis was listed as a primary diagnosis for 114,190 completed consultant episodes in secondary care and 75,838 inpatient admissions with a median length of stay of 3 days with a mean patient age of 63. Many more cases are treated in primary care.

Microbiology
Gram-positive cocci such as Streptococcus spp and Staphylococcus aureus are thought to be the predominant cause of cellulitis. Positive blood cultures are found in less than 10% of cases. Wound or tissue cultures are negative in up to 70% cases, with S aureus, group A streptococci and group G streptococci being the most common isolates from wound cultures. Serological studies suggest group A streptococcal infection is an important cause of culture negative cellulitis. Skin infection with pus is strongly associated with S aureus. Animal bites can be associated with cellulitis due to Gram-negatives such as Pasteurella and Capnocytophaga. Exposure of a skin break to salt or fresh water is associated with Vibrio vulnificus and Aeromonas spp respectively.

Group A streptococci can be associated with the development of necrotising fasciitis, although this can also be due to mixed infection including Gram-negative and anaerobic organisms, particularly in the elderly and immunosuppressed.

Clinical presentation
The classic presentation of rubor (redness), dolor (pain), tumor (swelling), calor (heat) are the hallmarks of cellulitis. The spectrum of severity ranges from localised erythema in a systemically well patient to the rapidly spreading erythema and fulminating sepsis seen with necrotising fasciitis. Pain out of proportion to the clinical signs, in particular, if accompanied by a history of rapid progression should prompt consideration of a necrotising fasciitis. Timing and evolution of the skin findings may differentiate cellulitis from...
some of the common mimics with more chronic clinical course. Recent antibiotic exposure and hospital contact should prompt the consideration of antibiotic resistance in the causative organism. Careful clinical examination may reveal a portal of entry such as ulcers, trauma, eczema or cutaneous mycosis. The finding of bilateral lower limb erythema in an afebrile patient with normal inflammatory markers should prompt the clinician to reconsider the diagnosis of cellulitis.8 Systemic features and groin pain are common and may predate the onset of skin changes.5 Skin breaks, bullae or areas of necrotic tissue may be present in severe cellulitis. See Box 1 for key points in history taking.

Risk factors
Skin breaks, lymphedema, venous insufficiency, tinea pedis and obesity have been associated with an increased risk of lower limb cellulitis in case control studies.9–11

Management
Assessment of baseline liver and renal function may be useful for assessing end-organ dysfunction in patients with septis and for dosing of antimicrobials. Cultures of blood, aspirates or biopsies are not recommended but should be considered in patients who have systemic features of sepsis, who are immunosuppressed or for cases associated with immersion injuries or animal bites.12

Cellulitis mimics
Separate studies have concluded that approximately 30% of cellulitis patients are misdiagnosed.13,14 Commonly encountered alternate diagnoses included eczema, lymphoedema and lipodermatosclerosis. Of the misdiagnosed patients, 85% did not require hospital admission and 92% received unnecessary antibiotics.

Stratifying risk
While the British Society for Antimicrobial Chemotherapy (BSAC) expert panel recommendations and UK Clinical Resource Efficiency

Box 1. Key points in history taking6

- Pattern and speed of progression
- Age and medical comorbidities (diabetes, chronic kidney disease, hepatic disease, vascular disease, immunosuppression)
- Recent antimicrobial treatment
- Possible site of inoculation – trauma, fungal infections
- History of previous cellulitis
- Travel history
- Risk for atypical organisms:
  - profound immunosuppression
  - animal or human bites
  - sea or freshwater exposure (to broken skin) including pools and spas
  - exposure to animals, fish, or reptiles
- intravenous drug use (including skin-popping)

Box 2. Dundee classification – markers of sepsis

The presence of infection with two or more of:
- white blood cell count <4 or >12/mm3
- temperature <36°C or >38°C
- heart rate >90 beats/min
- respiratory rate >20 breaths/min

Support Team (CREST) guidelines recommend use of the Eron classification of cellulitis in order to grade severity.15,16 The lack of a clear definition of systemic sepsis and ambiguous and potentially overlapping categories have hampered its use in clinical practice. Marwick et al used a modified version of the Eron classification (the Dundee classification) to separate patients into distinct groups based on the presence or absence of defined systemic features of sepsis, the presence or absence of significant comorbidities and their Standardised Early Warning Score (SEWS).17 The markers of sepsis selected (see Box 2) were in line with the internationally recognised definition of the Systemic Inflammatory Response Syndrome (SIRS) at the time. The SEWS is a standardised form of early warning score, calculated from the patient’s routine clinical observations, with a threshold score of 4 selected to indicate the most severely unwell patients (class IV) in whom a clinical review was mandated at the site where the study was undertaken. See Table 1 for cellulitis severity classification.

Marwick et al used the Dundee criteria to grade severity and then assessed the appropriateness of the prescribed antimicrobial regimens.18 They found significant overtreatment of skin and soft tissue infections (SSTIs) (both in terms of spectrum and route of antimicrobial) particularly in the lowest severity group, where 65% of patients were deemed to have been over treated. Thirty day mortality and undertreatment increased with the class of disease severity, from 1% mortality and 14% undertreatment in the class I severity group to 33% mortality and 92% undertreatment in the class IV severity group. These findings suggest the currently used severity scoring system is not a robust means of guiding empirical therapy. There was no significant difference in antimicrobial therapy or treatment

Box 3. Suspected sepsis – high-risk criteria

- Objective evidence of new altered mental state
- Respiratory rate: ≥225 breaths per minute or new need for oxygen (≥60% FiO2) to maintain saturation ≥92% (or ≥88% in known chronic obstructive pulmonary disease)
- Heart rate: ≥130 beats per minute
- Systolic blood pressure ≤90 mmHg or ≤60 mmHg below normal
- Not passed urine in previous 18 hours, or for catheterised patients passed < 0.5 mL/kg of urine per hour
- Mottled or ashen appearance
- Cyanosis of skin, lips or tongue
- Non-blanching rash of skin

6Adapted from reference 2

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and consideration given to systemic antibiotics in patients with incised and drained. Samples should be sent for bacterial culture and soft tissue infections have been proposed but have yet to be validated. National Institute for Health and Care Excellence (NICE) moderate- and high-risk criteria (Box 3 shows the high-risk criteria) may help clinicians rapidly identify patients with sepsis due to cellulitis who require urgent admission and assessment.

### Treatment

Patients with purulent skin and soft tissue infections such as abscesses, furuncles or carbuncles should have those collections incised and drained. Samples should be sent for bacterial culture and consideration given to systemic antibiotics in patients with systemic signs of infection. Non-purulent skin and soft tissue infections generally require treatment with systemic antimicrobials. Oral antimicrobial therapy is adequate for patients with no systemic signs of infection and no comorbidities (Dundee class I), some Dundee class II patients may be suitable for oral antibiotics or may require an initial period of intravenous (IV) therapy either in hospital or via out patient antimicrobial therapy (OPAT). Intravenous agents should be used for those with evidence of systemic infection (Dundee class III and IV) or those who do not respond to initial oral therapy. Patients in whom there is a concern of a deep or necrotising infection should have an urgent surgical consultation for consideration of surgical inspection and debridement.

While recommendations regarding specific antimicrobial agents will vary depending on local practice and resistance rates, suggested empiric regimens are outlined in Table 2. Patients with mild to moderate cellulitis should be treated with an agent active against streptococci. In patients with a history of penetrating trauma or with a purulent infection, the addition of anti-staphylococcal cover is strongly advised. Guidance from UK CREST recommends an agent with both anti-streptococcal and anti-staphylococcal activity, such as flucloxacillin. Due to the increased risk of venous thromboembolism due to the acute inflammatory state and immobility, thromboprophylaxis with low-molecular-weight heparin should be considered in line with local and national guidelines. Specific situations, such as infections associated with human or animal bites, may require broader spectrum antimicrobial cover and should be discussed with an infection specialist, as should cellulitis involving atypical sites such as the face, torso and upper limb. Patients with severe or necrotising infections should have initial broad spectrum antimicrobial cover to include staphylococci, streptococci, Gram-negative organisms and also an agent with activity against toxin production in group A streptococci, such as clindamycin or linezolid. Treatment with an agent active against methicillin-resistant *S aureus* (MRSA) should be considered in patients with a known history of, or risk factors for, MRSA colonisation as well as in those with suspected necrotising fasciitis. Recent prospective trials in the USA have suggested that empiric use of agents active against MRSA may not be warranted in the treatment of non-purulent cellulitis. There is little evidence to support the historical practice of adding benzylpenicillin to flucloxacillin in the treatment of cellulitis. In a randomised double-blinded trial comparing flucloxacillin and clindamycin with flucloxacillin alone, there was no difference in clinical improvement or the resumption of normal daily activities, but there was increased diarrhoea in the clindamycin group.

### Table 1. Cellulitis severity classification

<table>
<thead>
<tr>
<th>Class I</th>
<th>No or well-controlled comorbidities, systemically well</th>
<th>Modified ‘Dundee’ classification</th>
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<tr>
<td>Class II</td>
<td>Systemically unwell with no uncontrolled comorbidities (eg obesity, peripheral vascular disease or venous insufficiency) or systemically well with poorly controlled comorbidities, which may delay their recovery</td>
<td>No sepsis, no comorbidities and SEWS &lt;4</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked systemic inflammatory response (altered mental status, tachypnoea, tachycardia, hypotension etc) or may have very poorly controlled comorbidities which may affect their response to treatment or have a limb-threatening infection due to vascular compromise</td>
<td>Documentation of one or more significant comorbidities (eg obesity, peripheral vascular disease or venous insufficiency), no sepsis, SEWS &lt;4</td>
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Note: MRSA colonised; consider adding vancomycin and discuss with local infectious diseases / microbiology team. Antimicrobial choice in suspected necrotising fasciitis or cellulitis with systemic sepsis syndrome should be discussed urgently with local infectious diseases / microbiology team.

### Table 2. Suggested initial oral and IV recommendations for treatment of cellulitis

<table>
<thead>
<tr>
<th>Initial PO therapy</th>
<th>Non-severe&lt;sup&gt;a&lt;/sup&gt; penicillin allergy</th>
<th>Severe&lt;sup&gt;a&lt;/sup&gt; penicillin allergy</th>
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<tbody>
<tr>
<td>No penicillin allergy</td>
<td>Flucloxacillin 500 mg – 1 g qds PO</td>
<td>Clarithromycin 500 mg bd PO or Doxycycline 100 mg bd PO</td>
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<tr>
<td>Initial IV therapy</td>
<td>As for severe pen allergy or cephalaxin 500 mg qds PO</td>
<td>Ceftriaxone 1–2 g OD</td>
</tr>
<tr>
<td>Flucloxacillin 1–2 g 6-hourly IV</td>
<td>Clindamycin 600 mg – 1.2 g IV qds IV or IV vancomycin</td>
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<sup>a</sup>Severe penicillin allergy: anaphylaxis, angioedema, stridor, immediate onset urticarial
number needed to treat (NNT) was five (95% CI 4–9). Any predisposing factors (eg tinea pedis, lymphoedema etc) should be addressed to reduce the risk of recurrent cellulitis. Patients with three to four episodes of cellulitis per year should be carefully evaluated for any aspects.

References


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