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.[1]

Microbiology

Gram-positive cocci such as *Streptococcus* spp and *Staphylococcus aureus* are thought to be the predominant cause of cellulitis.[2]

Positive blood cultures are found in less than 10% of cases. Wound or tissue cultures are negative in up to 70% cases,[3] with *S aureus*, group A streptococci and group G streptococci being the most common isolates from wound cultures.[4] Serological studies suggest group A streptococcal infection is an important cause of culture negative cellulitis.[5] Skin infection with pus is strongly associated with *S aureus*.[6]

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.[2]

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.[2]

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 fulminant 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.[7] Timing and evolution of the skin findings may differentiate cellulitis from

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Key points

Making the correct diagnosis is key to management. Non-infectious conditions should be considered

Narrow spectrum penicillins targeting streptococci and staphylococci (in the case of purulent infection) should be the mainstay of antimicrobial therapy

The natural history of cellulitis is one of slow resolution. Fever and inflammation often persist during the first 72 hours of treatment. Management should include limb elevation and continuing narrow-spectrum antimicrobial therapy alongside treatment of comorbid conditions exacerbating the cellulitis (oedema, diabetes, vascular disease)

Outpatient parenteral antimicrobial therapy (OPAT) (including ambulatory care) is often appropriate in patients requiring intravenous therapy, but presents challenges in terms of antimicrobial agents used. Daily review and early switch to oral therapies is optimal

In patients with recurrent episodes of cellulitis, risk factors should be addressed and consideration given to prophylaxis

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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.[5] 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 sepsis 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

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Box 2. Dundee classification – markers of sepsis

The presence of infection with two or more of:

> white blood cell count <4 or >12/mm^3

> 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.[17] 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

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Box 1. Key points in history taking[a]

> 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)

[a]Adapted from reference 2

Box 3. Suspected sepsis – high-risk criteria[a]

> Objective evidence of new altered mental state

> Respiratory rate: ≥25 breaths per minute *or* new need for oxygen (≥40% 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 ≥40 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

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Table 1. Cellulitis severity classification[a]

	Eron/CREST classification	Modified 'Dundee' classification
Class I	No or well-controlled comorbidities, systemically well	No sepsis, no comorbidities and SEWS <4
Class II	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	Documentation of one or more significant comorbidities (eg obesity, peripheral vascular disease or venous insufficiency), no sepsis, SEWS <4
Class III	Marked systemic inflammatory response (altered mental status, tachypnoea, tachycardia, hypotension etc) or may have very poorly controlled comorbities which may affect their response to treatment or have a limb-threatening infection due to vascular compromise	Sepsis but SEWS <4
Class IV	Septic shock or life threatening presentations such as necrotising fasciitis requiring urgent critical care and surgical input	Sepsis and SEWS ≥4

[a]Left-hand column adapted from reference 16, right-hand column adapted from reference 17.
CREST = Clinical Resource Efficiency Support Team; SEWS = Standardised Early Warning Score

outcomes between class I and II severity patients, suggesting that these two groups could be merged, further simplifying the classification. Other severity and prognostic scoring systems for skin and soft tissue infections have been proposed but have yet to be validated.[18] 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.[19]

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.[12]

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 outpatient 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.[12]

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.[12] Guidance from UK CREST recommends an agent with both anti-streptococcal and anti-staphylococcal activity, such as flucloxacillin.[16] 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.[12,15] 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.[12] 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.[20]

There is little evidence to support the historical practice of adding benzylpenicillin to flucloxacillin in the treatment of cellulitis.[21] 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.[22] Brunn *et al* found that early antimicrobial escalation (during the

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

	No penicillin allergy	Non-severe[a] penicillin allergy	Severe[a] penicillin allergy
Initial PO therapy	Flucloxacillin 500 mg – 1 g qds PO	As for severe pen allergy or cephalexin 500 mg qds PO	Clarithromycin 500 mg bd PO or Doxycycline 100 mg bd PO
Initial IV therapy	Flucloxacillin 1–2 g 6-hourly IV	Ceftriaxone 1–2 g OD	Clindamycin 600 mg – 1.2 g IV qds IV or IV vancomycin

[a]Severe penicillin allergy: anaphylaxis, angioedema, stridor, immediate onset urticarial
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.
bd = twice daily; PO = oral; IV = intravenous; qds = four times daily

first 3 days of therapy) did not result in improved outcomes and addressing non-antibiotic factors such as limb elevation and treatment of comorbidities should be considered as an integrated part of the clinical management of cellulitis.[23]

Outpatient parenteral antimicrobial therapy has become an increasingly important means of delivering ambulatory care. Cellulitis was the most common primary infective diagnosis in UK OPAT Outcomes registry in 2015.[24] Outpatient parenteral antimicrobial therapy may be considered as initial management in suitable patients with moderate (Dundee grade II) cellulitis without evidence of necrotising infection or sepsis;[12,15] alternatively, it may be used to facilitate early discharge in patients with improving parameters. Treatment success rates are almost 90%.[25]

The optimal duration of antimicrobial therapy in cellulitis remains unclear. Most cases of uncomplicated cellulitis are traditionally treated with 1–2 weeks of antimicrobial therapy.[15] However, evidence now exists to suggest that such prolonged courses may be unnecessary, and that 5 days treatment may be sufficient in cases of uncomplicated cellulitis.[26] Provided there are no concerns about absorption and there has been some clinical improvement, most patients with uncomplicated SSTIs can be safely switched to oral antibiotics after 1–4 days of parenteral therapy.[15,16] The CREST guidance suggests settling pyrexia, stable comorbidities, less intense erythema and falling inflammatory markers as criteria for an oral switch.[16] Any predisposing factors (eg tinea pedis, lymphoedema etc) should be addressed to reduce the risk of recurrent cellulitis.

Prophylaxis

Patients with a history of cellulitis, particularly of the lower limbs, have an estimated recurrence rate of 8–20%.[12] Patients with recurrent cellulitis should be carefully evaluated for any predisposing factors such as lower limb oedema, lymphoedema, dermatitis, tinea pedis, and measures taken to address them. Patients with three to four episodes of cellulitis per year despite addressing predisposing factors could be considered for prophylactic antimicrobial therapy so long as those factors persist.[12] A randomised controlled trial of phenoxymethylpenicillin prophylaxis in patients with a history of recurrent cellulitis showed a reduced rate of recurrence in the treatment group (hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.35–0.86, p=0.001). The number needed to treat (NNT) was five (95% CI 4–9).[27] ∎

References

1 NHS Digital. *Hospital Episode Statistics for England 2014–15* https://digital.nhs.uk/catalogue/PUB19124 [Accessed 9 April 2017].

2 Bennett JE, Dolin R, Blaser MJ, Mandell GL. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, 7th edn. Philadelphia: Churchill Livingstone/Elsevier, 2010.

3 Eron LJ, Lipsky BA. Use of cultures in cellulitis: when, how, and why? *Eur J Clin Microbiol Infect Dis* 2006;25:615–17.

4 Bläckberg A, Trell K, Rasmussen M. Erysipelas, a large retrospective study of aetiology and clinical presentation. *BMC Infect Dis* 2015;15:402.

5 Eriksson B, Jorup-Rönström C, Karkkonen K, Sjöblom AC, Holm SE. Erysipelas: clinical and bacteriologic spectrum and serological aspects. *Clin Infect Dis* 1996;23:1091–8.

6 Chambers HF. Cellulitis, by any other name. *Clin Infect Dis* 2013;56:1763–4.

7 Borschitz T, Schlicht S, Siegel E, Hanke E, von Stebut E. Improvement of a clinical score for necrotizing fasciitis: 'Pain out of proportion' and high CRP levels aid the diagnosis. *PLoS One* 2015;10:e0132775.

8 Keller EC, Tomecki KJ, Alraies MC. Distinguishing cellulitis from its mimics. *Cleve Clin J Med*. 2012;79:547–52.

9 Dupuy A, Benchikhi H, Roujeau JC *et al*. Risk factors for erysipelas of the leg (cellulitis): case-control study. *BMJ* 1999;318:1591–4.

10 Björnsdóttir S, Gottfredsson M, Thórisdóttir AS *et al*. Risk factors for acute cellulitis of the lower limb: a prospective case-control study. *Clin Infect Dis* 2005;41:1416–22.

11 Semel JD, Goldin H. Association of athlete's foot with cellulitis of the lower extremities: diagnostic value of bacterial cultures of ipsilateral interdigital space samples. *Clin Infect Dis* 1996;23:1162–4.

12 Stevens DL, Bisno AL, Chambers HF *et al*. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2014;59:e10–52.

13 Weng QY, Raff AB, Cohen JM *et al*. Costs and consequences associated with misdiagnosed lower extremity cellulitis. *JAMA Dermatol* 2017;153:141–6.

14 Levell NJ, Wingfield CG, Garioch JJ. Severe lower limb cellulitis is best diagnosed by dermatologists and managed with shared care between primary and secondary care. *Br J Dermatol* 2011;164:1326–8.

15 Eron LJ, Lipsky BA, Low DE *et al*. Managing skin and soft tissue infections: expert panel recommendations on key decision points. *J Antimicrob Chemother* 2003;52(Suppl 1):i3–17.

16 Fulton R, Doherty L, Gill D *et al*. *Guidelines on the management of cellulitis in adults*. Northern Ireland: CREST, 2005.

17 Marwick C, Broomhall J, McCowan C *et al*. Severity assessment of skin and soft tissue infections: cohort study of management and outcomes for hospitalized patients. *J Antimicrob Chemother* 2011;66:387–97.

18 Raff AB, Weng QY, Cohen JM *et al*. A predictive model for diagnosis of lower extremity cellulitis: A cross-sectional study. *J Am Acad Dermatol* 2017;76:618–25.

19 National Institute for Health and Care Excellence. *Sepsis: recognition, diagnosis and early management*. London: NICE, 2016.

20 Pallin DJ, Binder WD, Allen MB *et al*. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. *Clin Infect Dis* 2013;56:1754–62.

21 Leman P, Mukherjee D. Flucloxacillin alone or combined with benzylpenicillin to treat lower limb cellulitis: a randomised controlled trial. *Emerg Med J* 2005;22:342–6.

22 Brindle R, Williams OM, Davies P *et al*. Adjunctive clindamycin for cellulitis: a clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis. *BMJ Open* 2017;7:e013260.

23 Bruun T, Oppegaard O, Hufthammer KO, Langeland N, Skrede S. Early response in cellulitis: A prospective study of dynamics and predictors. *Clin Infect Dis* 2016;63:1034–41.

24 Gilchrist DM. A new approach to the National Outcomes Registry. National OPAT Conference, 2015 Apr 13; Business Design Centre, London. http://bsac.org.uk/meetings/2015-national-opat-conference-2/

25 Seaton RA, Sharp E, Bezlyak V, Weir CJ. Factors associated with outcome and duration of therapy in outpatient parenteral antibiotic therapy (OPAT) patients with skin and soft-tissue infections. *Int J Antimicrob Agents* 2011;38:243–8.

26 Hepburn MJ, Dooley DP, Skidmore PJ *et al*. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med* 2004;164:1669–74.

27 Thomas KS, Crook AM, Nunn AJ *et al*. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med* 2013;368:1695–703.

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