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Cellulitis of the leg

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DEFINITION

Cellulitis, in its strictest sense, is defined as an inflammation of loose connective tissue with or without infection. However, in clinical practice, it is a term used to denote a painful and potentially serious infection of the skin and subcutaneous tissue (Figure 1). The term 'erysipelas' is sometimes used to describe cellulitis that spreads more superficially higher into the dermis. As it is clinically challenging to differentiate the two, the general term cellulitis is more widely used. The infection is the most common dermatological reason for emergency treatment and its incidence is increasing.¹ In the USA, the condition is responsible for 2.3 million emergency room visits annually,² while in the UK secondary care alone treated over 104,000 cases in 2013.³

AETIOLOGY

For most typical cases of cellulitis occurring in the leg, the causative organisms are β -haemolytic streptococci (group A) bacteria (mainly *Streptococcus pyogenes*) and/or *Staphylococcus aureus*.⁴ Other streptococci including groups A, C and G have also been identified as a cause. Beyond this, other organisms should be suspected if:⁵

- The patient is very young or old
- The patient has diabetes or liver cirrhosis
- The patient is immunocompromised
- The infection has gained entry following a bite, pre-existing ulcer or penetrating injury.

In this group of patients, further investigations are warranted as alternative organisms are a strong possibility.



Figure 1. Cellulitis of the left leg with ulceration

Key point: Most cellulitis is caused by Group A streptococci or *Staphylococcus aureus*; however, in the patient with diabetes, different organisms may predominate.

CLINICAL FEATURES

Cellulitis can occur in the skin on any part of the body although the leg is the most commonly affected area.⁶ A review of 4 million US patients' medical records (aged 20–64) over an eight-year period

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reported 140,767 cases of the disease, in which 30% affected the leg, 14% the arm and forearm, 12% trunk, 8% face, 7% foot and 1.4% the toes.⁷ The condition affects males and females equally, with the incidence increasing with age,⁸ and being most common in the fourth to sixth decades.⁹

Cellulitis presents with a red, hot, swollen area of skin that is painful to the touch. Lymphangitis and lymphadenopathy may accompany the condition. Fever and malaise are common for all but the mildest cases and may precede visible changes in the skin. At the site of infection, particularly in the elderly, blisters may develop in severe cases, which may be haemorrhagic, resulting in superficial ulceration and necrosis. Presentation of the disease in the legs is virtually always unilateral and, as such, bilateral cases should raise suspicion as to the correct diagnosis.

Key point: Bilateral cellulitis of the leg is extremely rare, so alternative diagnoses should be considered.

INVESTIGATIONS

Despite its bacterial aetiology, confirming the presence of the infecting organism in cases of cellulitis is challenging. Swabs of open wounds and tissue samples may yield organisms in only 20–40% of cases. Needle aspiration of affected tissue and blood cultures are even more disappointing and frequently elicit positive results in fewer than 5% of cases.^{10, 11} Consequently, this is only advised when the patient is seriously unwell. Although non-specific, nearly all patients will show a raised white blood cell count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Blood results in the normal ranges would suggest the diagnosis of cellulitis is unlikely and other diagnoses should be considered.¹²

One recent study has investigated the use of thermal imaging and temperature measurement to assess differences in leg temperatures between the affected and unaffected limb in patients with presumed cellulitis. The results suggested that, in diagnosed cases of cellulitis, the temperature is 3.2°C higher in the affected limb and this had a positive predictive value of 96%. However, in the cases found not to be cellulitis, the temperature difference was only around 1°C between the affected and unaffected limbs.¹³

Key point: There are no laboratory tests that can confirm cellulitis. Each case requires careful clinical assessment.

DIFFERENTIAL DIAGNOSIS

Despite its clinical appearance, cellulitis is frequently misdiagnosed.¹⁴ Weng & colleagues reported results from a study showing that 79 patients (30%) of 259 patients had been wrongly diagnosed, with 90% of these patients receiving unnecessary antibiotics.¹⁵ As there are no confirmatory tests available, diagnosis is made on physical examination and history alone.

Varicose (or venous) eczema is one of the most commonly mistaken conditions mimicking cellulitis, particularly in the older patient, as they both give rise to inflammation of the legs. Although its cause is unknown, venous eczema is commonly associated with varicose veins or a history of deep vein thrombosis. The eczema is characterised by inflammation of the leg, with itching and crusting but with little oedema. Haemosiderin deposits may be observed in the area between the knees and ankles over time. Eczematous lesions may also be present on other parts of the body. The patient



Figure 2. Tinea pedis is a risk factor for the development of cellulitis

will generally otherwise feel well with no raised body temperature or leg tenderness. In contrast, although cellulitis may present as inflammation of the skin with a marked oedema, the condition is painful to the touch and the patient will be systemically unwell – feverish with increased temperature, and raised ESR and CRP on blood testing.¹⁶

Contact dermatitis (irritant and allergic) can simulate cellulitis. Erythematous plaques and patches normally arise in a geometric arrangement corresponding to the point of contact with the irritant/allergen, leading to pruritis and pain. Occasionally, lesions remote to the point of application can arise. A good history can help distinguish the condition from cellulitis.¹⁷

Lymphoedema is another clinical condition affecting the lower limb that can lead to severe swelling of the leg due to reduced lymphatic drainage. Although the swollen leg is more likely to develop secondary cellulitis, on its own lymphoedema is generally painless and without erythema or raised local temperature. For some causes, elevation of the leg will reduce the swelling and should reduce erythema. Erythema in the cellulitic leg will remain – even if elevated.

Key point: Venous eczema is the most frequent misdiagnosis for cellulitis. Itching and crusting occur in the affected limb with eczema, but a raised body temperature, localised pain and fever are absent.

Dependent rubor is a condition characterised by deep red discolouration of the legs when the patient is standing. The condition is associated with peripheral vascular disease, with many patients exhibiting rest pain or intermittent claudication. The temperature of affected limbs with the condition may be slightly raised, but elevation of the limb will cause the erythema to disappear. In an infected limb, the redness will remain on elevation.

Necrotising fasciitis may rarely develop from a cellulitic limb. Clinicians should be mindful as this always requires prompt surgical intervention. Characteristics that suggest a necrotising infection include:¹⁸

- Haemorrhagic blisters (may also present in cellulitis)
- Oedema and tenderness beyond the edges of the skin lesion

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Class	Definition
1	Patients who have no signs of systemic toxicity, have no uncontrolled co-morbidities and can usually be managed with oral antimicrobials on an outpatient basis.
2	Patients who are either systemically ill or systemically well but with a co-morbidity such as peripheral vascular disease, chronic venous insufficiency or morbid obesity, which may complicate or delay resolution of their infection.
3	Patients who may have a significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension or may have unstable co-morbidities that may interfere with a response to therapy or have a limb-threatening infection due to vascular compromise.
4	Patients who have sepsis syndrome or severe life-threatening infection such as necrotising fasciitis.

Table 1. Classification of patients with cellulitis adapted from the CREST guidelines¹²

- Severe pain (out of proportion to the clinical appearance)
- Bleeding into the skin (bruising)
- Cutaneous anaesthesia due to destruction of cutaneous nerves
- Foul smelling watery discharge due to the presence of anaerobic bacteria
- A patient who is seriously unwell (fever, chills, loss of consciousness, hypotension and tachycardia).

RISK FACTORS FOR LOWER-LIMB CELLULITIS

Identification of the risk factors predisposing the leg to cellulitis can help target patients at risk of the disease as well as prevent further episodes.

A recent systematic review of six studies identified the following as risk factors (highest risk factor first):¹⁹

- Previous episodes of cellulitis
- Open wounds
- Current leg ulcers
- Lymphoedema/chronic leg oedema
- Excoriating skin diseases
- Tinea pedis (see Figure 2)
- Increased body mass index (BMI >30 kg/m²).

Although highlighted as risk factors in previous studies, diabetes,^{20,21} previous varicose vein surgery²² and smoking²³ were not found to be significant risk factors in this review. For an infection to occur in the limb, it readily follows that a portal of entry is required (such as a bite, pre-existing ulcer, penetrating injury or skin disease) and studies have consistently demonstrated this as a major risk factor for the condition.

Key Point: Having one bout of cellulitis in the lower limb dramatically increases an individual's chances of further episodes of the condition.

From a podiatric perspective, work has focused on the role of

dermatophyte infection and its relationship to cellulitis.²⁴ Dupuy *et al*²⁵ in a case-controlled study of 167 patients with cellulitis identified the presence of web space intertrigo as a risk factor. Undertaking further work, Bjornsdottir *et al*²² calculated that the presence of web space intertrigo increased the risk of cellulitis occurring more than five-fold. In addition, the presence of *B*-haemolytic streptococci or *Staph aureus* within the web space increased the risk of developing cellulitis 28-fold.

Key Point: The presence of fungal foot infection (tinea pedis and onychomycosis) is a known risk factor for cellulitis.

This concept was explored further by Semel & Goldin²⁶ who examined 22 patients with episodes of leg cellulitis. Within this group, 20 (83%) with celluitic legs had positive cultures of dermatophytes from their web spaces. More interestingly, an analysis of bacteria recovered from the same web spaces demonstrated gram-positive bacteria present in 100% of cases. Seventeen (85%) of those celluitic web spaces were culture positive for *B*-haemolytic streptococci (group A in four cases, group B in three cases, group C in one and group G in nine cases).

The interdigital web space has a complex physiology. Studies have examined the process of web space maceration. In the absence of any dermatophytes, recovery from maceration is rapid and resolute, following removal of any occlusion. However, if dermatophytes are present, this leads to a soggy, white maceration. In addition, increases in the bacterial diversity have been measured. Under these circumstances, the fungus is able to invade deeper into the epidermis, weakening skin architecture and promoting fissure development²⁷ allowing the ingress of local bacteria.

Fungal foot infection is not just restricted to the interdigital areas. Roujeau & colleagues²⁸ studied 243 patients with lower-limb cellulitis and examined patients for the presence of fungal infection on the foot. Their results demonstrated that tinea infection on any part of the foot was a statistically significant risk factor for cellulitis, increasing the risk by a factor expressed as an odds ratio (OR)

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	First line	Second line
Class 1	Flucloxacillin 500mg qds (oral)	Penicillin allergy: Clarithromycin 500mg bd
Class 2	Flucloxacillin 2g qds (IV) or * Ceftriaxone 1g od (IV) (outpatient parenteral antimicrobial therapy [OPAT] only) (*Must not be used in penicillin allergy)	Penicillin allergy: Clarithromycin 500mg bd IV or Clindamycin 600mg tds IV
Class 3	Flucloxacillin 2g qds (IV)	Penicillin allergy: Clarithromycin 500mg bd IV or Clindamycin 900mg tds IV
Class 4	Benzympenicillin 2.4g 2-4 hourly IV + Ciprofloxacin 400mg bd IV + Clindamycin 900mg tds IV (If allergic to penicillin use Ciprofloxacin and Clindamycin only) Discuss with local microbiology service	

Table 2. Drug therapy for typical cellulitis¹²

of 2.5. This was examined further to geographic areas of the foot, resulting in the following risk factors: interdigital space (OR 3.2), plantar surface (OR 1.7) and onychomycosis (OR 2.2).

Key Point: Interdigital tinea pedis holds the greatest risk for the development of cellulitis, followed by nail and plantar skin dermatophyte infection, respectively.

Although the preceding studies associate tinea infection with the promotion of the ingress of bacterial infection through broken skin, only one study has shown a direct link between bacterial presence on the skin and cellulitis. By molecular typing, two patients with lower-limb cellulitis have been shown to have identical isolates from their web spaces and in their blood specimens.²⁹

TREATMENT

Current guidelines have been published for the management of acute cellulitis by the British Lymphology Society and Lymphoedema Support Network³⁰ and Clinical Resource Efficiency Support Team (CREST)¹² – the latter of which have been adapted by The National Institute for Health and Care Excellence (NICE), as part of the clinical knowledge summaries.³¹ Individual patients diagnosed with the condition should be graded as demonstrated in Table 1. General measures include antibiotics, elevation and analgesia, where required. Cellulitic areas should be outlined on the skin (with a biro/marker pen) and reviewed daily to assess progress and ascertain the effectiveness of antibiotics.

A Cochrane paper, published in 2010, reviewed 25 randomised controlled trials investigating the use of antibiotics and cellulitis³² but was unable to identify the best treatment based on the available

evidence as no study reported any one treatment being superior. In addition, although one study concluded that adding steroids to the antibiotic regime shortened hospital stays, it was unable to conclude if this was likely to be correct.

Following the CREST guidelines¹² outlined in Table 1, it is suggested that class 1 patients can be treated with oral antibiotics on an outpatient basis, while class 2 patients may require a short (48-hour) hospitalisation with intravenous antibiotics and discharge. Patients in classes 3 and 4 are recommended for hospitalisation until there is clear indication of improvement in their systemic condition, with evidence of reduced local infection (see Table 2).

Currently, there is no UK-wide policy for the treatment of cellulitis, so local policy guidelines should be followed on the principle that the infecting organism should be identified and treated accordingly. In the absence of local policy, CREST guidelines¹² suggest a regime based on the classification of the patient and their penicillin allergy status although it is noted there is slight variation with the guidelines offered by NICE³¹ (see Table 2).

POST-CELLULITIS CARE

Following cellulitis, post-cellulitic changes to the affected limb are a risk. The most common are chronic leg oedema, pain and haemosiderin deposits within the skin. Residual leg erythema can also be present beyond the acute episode and slow to subside. In one retrospective survey of 171 patients with cellulitis, chronic leg oedema (in the affected limb) was present in 46% of subjects and a latter risk of leg ulceration was reported in 13% of patients post-cellulitis.³³

Following an initial event, recurrent bouts of cellulitis are common. A systemic review of risk factors for cellulitis showed previous episodes to be the greatest predictor of recurrence –

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patients who have had previous episodes of cellulitis were 40 times more likely to succumb to the condition than patients who had never had cellulitis.¹⁹ Such patients need guidance on self-care to reduce the risk.

Measures include:

- Advice on skin care and the regular use of suitable emollients to the legs and feet
- Proper management of any pre-existing skin conditions³⁴
- Good foot care (effectively managing bouts of tinea pedis/ onychomycosis)
- Avoiding skin injury to the feet and legs
- Wearing compression hosiery where possible
- Weight reduction.³⁵

Active manual decompression of lymphoedema has been shown to reduce recurrence of the condition by around 67% in the lower limb.³⁴ Except for this study, there is no solid evidence to show that active modification of risk factors can prevent recurrence,³⁶ however an empirical approach is advised in the absence of suitable evidence.

Previously, the use of long-term antibiotics for patients suffering recurrence had been advocated. Current guidance only advocates the use of low-dose, long-term antibiotics if the patient has experienced two or more episodes of cellulitis in one year (Figure 3), with a suggestion that this should be discontinued if successful prophylaxis is achieved during the following two years.³⁷ Penicillin V 250mgs bd is suggested or erythromycin 250mgs bd in the case of penicillin allergy. Research has demonstrated that recurrence can be reduced by 84% a year in patients undergoing prophylactic antibiotics.³⁸

THE ROLE OF THE PODIATRIST

The podiatrist can play a significant role in the prevention of the disease and reducing the risk of further morbidity. The condition is known to occur more frequently in older patients,⁸ and those with diabetes are likely to suffer increased morbidity and prolonged hospital admissions than those without diabetes.³⁹

Basic skin care remains the tenet for patients with a history of the disease. As skin breakage remains a leading risk factor for cellulitis development, maintaining skin integrity should be paramount. As with prevention in the diabetic foot, the aim of treatment should be to prevent skin compromise and ulceration as this may allow the ingress of cellulitis-causing bacteria. Simple reduction of callus on the plantar surface and around the heels can prevent cracking and fissuring.

Education in the use of emollients to the feet and legs should also be utilised. Emollients containing urea are particularly effective in maintaining skin flexibility and enabling thinning of plantar and heel hyperkeratosis.⁴⁰ Interdigital hygiene cannot be over-emphasised. Evidence has highlighted how this area is a potential portal of entry. Reduction of any maceration is advised with simple astringents thereby reducing fungal and bacterial populations which are known to increase the risk of the disease. The use of topical miconazole has been shown to have efficacy against gram-positive organisms such as streptococci (including *Strep pyogenes*) and *Staphylococcus* at concentrations well below those found in off-the-shelf topical formulations [1%].⁴¹

Key point: In patients with a history of cellulitis, interdigital



Figure 3. Current guidance advocates the use of low-dose, long-term antibiotics if the patient has experienced two or more episodes of cellulitis

hygiene is of paramount importance.

Key point: The use of miconazole nitrate 2% has been shown to be effective against dermatophytes and gram-negative organisms responsible for causing cellulitis

In addition, patients should be educated to recognise the early signs of tinea pedis. Many patients are unaware of the presence of their infection⁴² due to the lack of symptoms such as itching.⁴³ Patients should be advised to pay attention to the interdigital areas where fungal infection has been shown to pose the highest risk for the development of lower-limb cellulitis^{22,25} but also include the plantar surface. Based on the evidence available, active treatment in patients with a history of cellulitis for any onychomycosis is advisable, when appropriate. Although not fully proven, the use of prophylactic antifungal agents on the foot may help reduce the recurrence of tinea.^{42,44,45} A typical regime would be fortnightly applications of two days of terbinafine hydrochloride 1% as it is able to reside in the skin longer after application than the imidazoles.

Key point: Patients with a history of lower-limb cellulitis should be encouraged to use regular emollients and educated on recognising the early signs of tinea pedis.

SUMMARY

Cellulitis is the most common dermatological emergency that requires prompt assessment and diagnosis. Most cases occur in the lower limb due to the spread of streptococcal and staphylococcal infection in the skin and subcutaneous tissues. Appropriate management with antibiotics is required to prevent further morbidity, and long-term management should be focused towards preventative strategies that aim to preserve skin integrity. On the foot, this includes patient education towards the use of urea-based emollients, good interdigital hygiene and the recognition of fungal foot infection, which is a significant risk factor in the development of the disease.

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