evidence for their use is generally weak[6]. It is usually advisable to seek the help of a specialist urticaria clinic at this stage to define the urticarial subgroup. Some types may be more likely to respond to novel approaches, including the use of immunosuppressive drugs for patients with the most severe forms of autoimmune urticaria.

Prognosis

Many cases of urticaria are short-lived, lasting days or weeks. About 50% of patients with ordinary urticaria can be expected to have cleared by six months. The outlook for those with urticaria and angio-oedema is less encouraging since 50% will still have their condition five years later[7]. Urticarial vasculitis is likely to persist or recur over many years.

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Management of lower leg cellulitis

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Lower leg cellulitis is a common reason for urgent medical admission; it often results in prolonged hospitalisation and significant long-term morbidity[1–5].

Clinical features

Cellulitis is deeply situated inflammation of the skin and subcutaneous tissue, usually due to an infection. The distinction from erysipelas, which is more superficial and thus has more sharply demarcated margins, is somewhat artificial on the leg.

Typical lower leg cellulitis is characterised by progressive painful swelling and erythema (Fig 1) with pyrexia and general malaise which are often present before the localising signs. Blistering and ulceration may occur, usually if oedema is marked.

Bacteriology

Most patients with proximally spreading lower leg cellulitis have streptococcal infection[1–5]. Group A streptococci are most important but groups C and G organisms are also common at this site. Staphylococcal cellulitis is usually more localised but can mimic streptococcal disease. Other infections[1,3] are much less common at this site but should be considered, particularly in the following situations:

- diabetes, immunosuppression or hepatic cirrhosis
- localised cellulitis
- penetrating injury or animal bite
- preceding ulceration
- recent foreign travel
- cellulitis at other body sites or in children.

Predisposing factors

Toeweb maceration is a common portal of entry for streptococci in lower leg cellulitis (Fig 2), while tinea pedis is a major factor in patients with recurrent episodes[5,6]. Mycology cultures from macerated toewebs are important (note that athlete's foot fungi do not fluoresce and cannot be detected using Wood's light).

Lower leg oedema of any causation is a risk factor. Lymphoedema is especially important as a cause of recurrent episodes[6] and is a situation in which streptococcal cellulitis can be particularly aggressive.

Other risk factors include obesity, recent surgery (especially venectomy for coronary artery bypass grafting) and preceding venous eczema or leg ulceration[6]. Blunt injury[5] is reported sufficiently

Key Points

Most acute lower leg cellulitis is due to streptococcal infection

A diagnosis of bilateral lower leg cellulitis is likely to be incorrect

Antistreptolysin-O titre is extremely useful to confirm the cause of cellulitis but is unreliable in the first week

In resistant cases of streptococcal cellulitis, clindamycin is the best antibiotic choice

Treatment of associated tinea pedis and persistent oedema is critical to reduce the risk of recurrent episodes

KEY WORDS: CPD, cellulitis, erysipelas, necrotising fasciitis, streptococcal infection, lower leg

frequently by patients, often with an interval of several weeks, that it is probably a true risk factor. It perhaps acts by trapping circulating streptococci in damaged vessels.

Streptococcal virulence

Numerous studies have suggested a recent increase in the frequency and virulence of streptococcal infection[7,8]. Several cell wall and extracellular factors act as superantigens or contribute in some other way to this virulence (Table 1)[7–10].

Differential diagnosis

Differential diagnoses of lower leg cellulitis (Table 2) are not all mutually exclusive. For example, deep venous thrombosis (DVT) or thrombophlebitis may coexist with cellulitis and treatment may need to cover both possibilities whilst awaiting results of investigations.

Diagnostic problems

Suspected bilateral cellulitis is a frequent diagnostic pitfall. Although occasionally recorded in large series[6], this author's experience is that bilateral cellulitis is vanishingly rare – if it occurs at all. Most patients with a suggested diagnosis of bilateral cellulitis in fact have erythema due to bilateral venous disease, acute or chronic oedema, or lymphoedema. It may be correct that one leg also has cellulitis (all those conditions predispose to infection), but the important point is that there will be residual physical signs when any infection has been treated, thus erroneously suggesting lack of response of cellulitis. Acute oedema or lymphoedema may cause blisters as well as erythema[11]. Misdiagnosis of venous disease as cellulitis is common and well known to all dermatologists[12].

Another diagnostic problem is the patient who appears to have cellulitis but is apyrexial and systemically well. This applied to over 40% of patients in a recent audit by the author, and presumably reflects the effect of antibiotic therapy before referral to hospital. The failure of the redness and swelling to respond is probably due to immunological responses and cytokine release rather than reflecting significant numbers of viable organisms. Serological testing (see below) may confirm the diagnosis in such instances.

Necrotising fasciitis

It is particularly important to identify necrotising fasciitis which may evolve from cellulitis. Features such as blistering or superficial necrosis (Fig 3) are suspicious but may occur in either disorder and in isolation do not warrant surgical intervention. Marked local tenderness and increasing 'crescendo' pain are important indicators of possible fasciitis, while neutrophilia is an early laboratory feature. Blood cultures are positive in about 60% of patients with streptococcal necrotising fasciitis (compared with 5–10% of patients with cellulitis), and hypotension due to associated streptococcal toxic shock syndrome (STSS) is common. Laboratory criteria for STSS include creatinine above 177 μmol/l, platelets below 100×10^9/l and a twofold elevation of hepatic transaminases. Magnetic resonance imaging (MRI) is the most useful investigation to distinguish

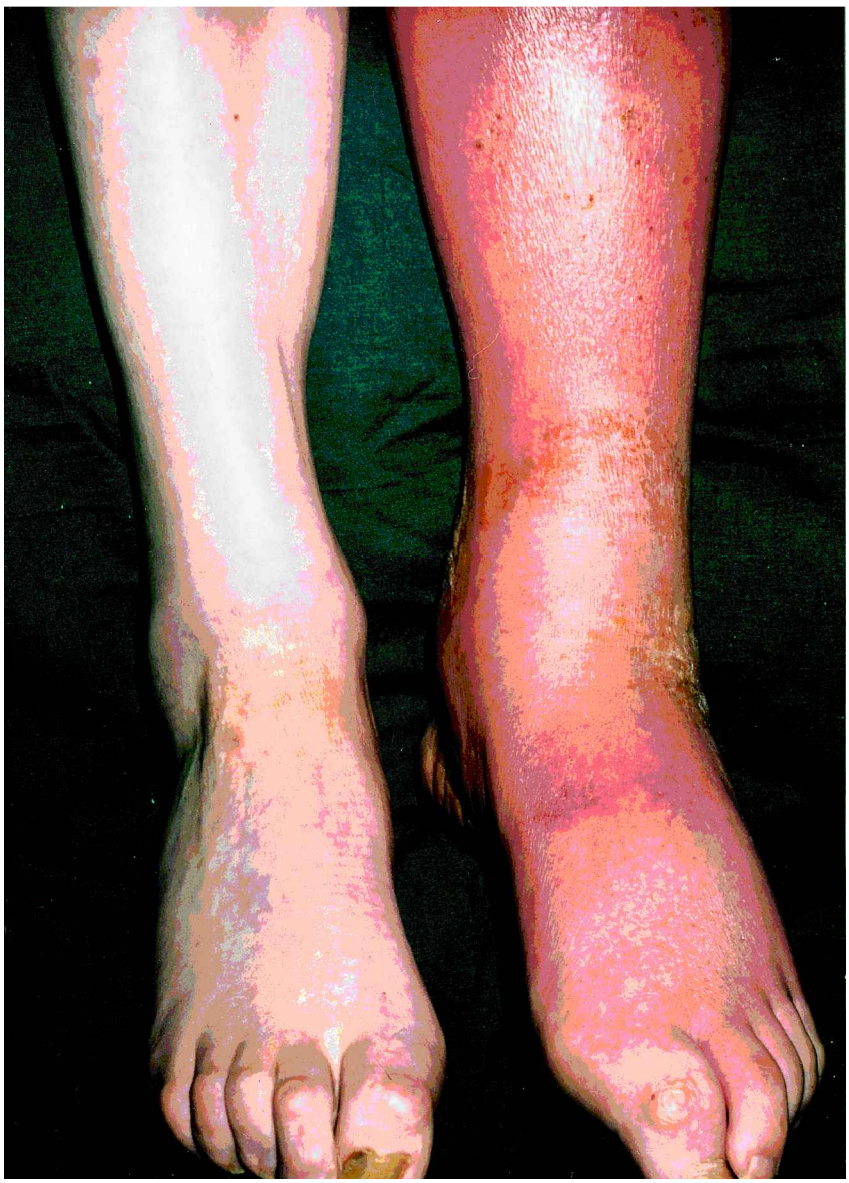

Fig 1. Red swollen leg due to streptococcal cellulitis.

cellulitis and necrotising fasciitis, but surgical intervention should not be delayed for the sake of investigations in a patient with worsening symptoms.

Investigations

It is difficult to obtain prompt bacteriological proof of streptococcal causation as there is usually no obvious focus of infection from which to obtain samples. Needle aspiration from the edge of the cellulitic area (usually with prior injection of a small volume of saline) has a yield of 10–20%, as does aspiration of blister fluid. Skin biopsy with immunofluorescent detection of streptococci has a higher yield but is a research technique and not routinely available. Samples for microbiological culture should be taken from any leg ulceration as many bacteria which colonise ulcers may cause cellulitis. The following investigations are recommended:

- *'Routine bloods'*, especially to detect leukocytosis and features of STSS.
- *Antistreptolysin-O (ASO) titre*: useful to confirm the diagnosis retrospectively as this may influence ongoing antibiotic therapy. This test is usually normal until about a week after onset (it is due to the host antibody response and does not parallel bacterial or toxin load at the time the sample is taken). It may be negative in patients in whom treatment is started promptly.
- *Bacteriology swab* from any ulcer and moist toewebs; culture blister fluid.
- *Blood culture*: usually negative, but higher positive rate in necrotising fasciitis.
- *Aspirate* (see above) if any unusual features or reason to suspect other organisms.
- *Mycology cultures* from toeweb maceration to identify tinea pedis as a portal of entry.
- *MRI or surgical intervention* if pain increases (to exclude necrotising infection).
- *Other investigations* to exclude differential diagnoses (eg d-dimer for DVT).

Table 1. Streptococcal proteins and virulence factors.

Factor	Comment
M proteins (group A, similar proteins in group C and G)	Cell surface proteins Related to virulence (M1 and M3 mostly implicated), antiphagocytic
T proteins	Cell surface proteins Used for typing, not pathogenic
Streptococcal pyrogenic exotoxins (SPE) A, B, C, F	Exotoxins, superantigenic
Streptococcal superantigen	Exotoxin, superantigenic
Streptolysin-O	Exotoxin Antigenic, antiphagocytic, toxic to polymorphonuclear leukocytes and platelets, synergistic with SPE-A, stimulates release of tumour necrosis factor
Mitogenic factor	Exotoxin
Other exotoxins	Including DNAses, streptokinase, proteases, hyaluronidase

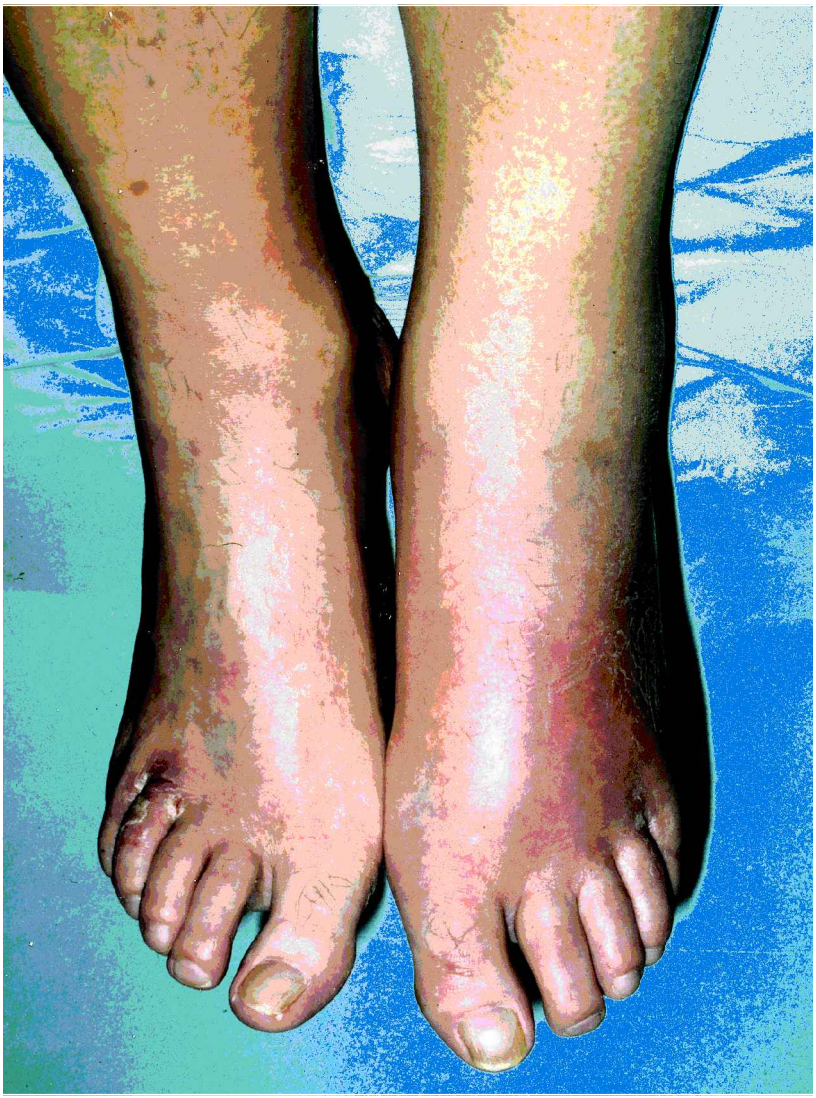

Fig 2. Pedal oedema is an early feature of lower leg cellulitis. Note the bilateral tinea pedis, a common cause of recurrent episodes.

Management

Some patients respond to oral antibiotic therapy but most patients attending an emergency medical unit are treated with intravenous antibiotics. In typical lower leg cellulitis it is generally recommended that the antibiotic choice should cover streptococcal and staphylococcal disease. Penicillin is usually recommended for known streptococcal infection as it has a low minimum inhibitory concentration (MIC) for streptococci. A logical approach is to use benzylpenicillin with flucloxacillin, stopping the latter once streptococcal infection has been confirmed by the ASO test. Cephalosporins (especially cefuroxime or ceftriaxone), macrolides, vancomycin, fluoroquinolones, teicoplanin and clindamycin may also be used[1–3] .

Table 2. Differential diagnosis of lower leg cellulitis.

Differential diagnosis	Discriminatory features and comments
Lower leg eczema (usually venous or acute contact dermatitis)	Longer history, itch rather than tenderness, supramalleolar site, presence of scaling or crusting, associated varicose veins and pigmentation Preceding eczema may be a portal of entry for bacterial cellulitis
Acute oedema/blisters	Erythema is not as pronounced as in cellulitis with blistering Usually bilateral No pyrexia/malaise
Chronic oedema and lymphoedema	Marked erythema may be a feature of prolonged oedema Usually symmetrical No pyrexia/malaise but these conditions are important risk factors for cellulitis
Deep venous thrombosis	Usually calf tenderness, usually not well demarcated proximal margin of erythema Can coexist with cellulitis
Compartment syndrome	Usually sharply localised and extreme tenderness
Bursitis, arthritis	Localised bursitis is present adjacent to a joint or bony prominence Ruptured popliteal bursa affects the calf Inflammatory or infective joint disease is localised
Haematoma	Usually obvious trauma, but may be difficult to identify in patients with chronic lymphoedema
Necrotising fasciitis	(see text)
Eosinophilic fasciitis	Usually bilateral, slower evolution, not toxic, may be blood eosinophilia
Pyoderma gangrenosum	May be a diagnostic problem in the pre-ulceration phase Generally mid-shin and radially expanding rather than spreading proximally Malaise may occur, but significant pyrexia unlikely
Erythema nodosum and other panniculitides	Localised tender lesions, usually symmetrical Pyrexia and malaise, if present, generally reflect the causative disorder
Non-infective cellulitis (eg Wells syndrome)	Wells syndrome causes localised cellulitis with tissue and blood eosinophilia
Pretibial myxoedema	Erythema, swelling and cobblestoned or *peau d'orange* morphology Slow evolution, not toxic
Artefact	Cellulitis due to injection of irritant or infective material More common in the arms Usually affects several sites sequentially Erythema and systemic features are absent in artefactual lower limb swelling due to tourniquet (Secretan's syndrome, *oedème bleu*)

Erythromycin or azithromycin is suitable for patients who are allergic to penicillin. In resistant streptococcal cellulitis or streptococcal necrotising fasciitis, clindamycin with either penicillin or vancomycin should be used. The rationale for clindamycin in these situations is that a high bacterial density may be associated with decreased expression of penicillin-binding proteins and poor therapeutic response to penicillin, whereas clindamycin inhibits protein synthesis and is not affected by inoculum size. Other actions of clindamycin are:

- suppression of streptococcal toxin production
- reduction of M protein synthesis (thereby increasing phagocytosis of bacteria)
- reduction of cell wall synthesis
- suppression of cytokine production by mononuclear cells[7].

Azithromycin shares some of these properties and newer agents such as linezolid may also have a role.

The intensity of local symptoms in cellulitis is unlikely to be simply due to bacterial load. Prolonged redness and oedema – which are common after resolution of fever and improvement in general malaise – suggest an ongoing immunological response for which corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) might theoretically be useful. However, there has been controversy about using NSAIDs in cellulitis because studies indicate a higher frequency of fatal necrotising fasciitis in patients treated with these agents. Recent animal studies suggest that NSAIDs may mask symptoms of increasing bacterial load and should therefore be avoided.

Long-term morbidity

The significant long-term morbidity of lower leg cellulitis[5] is due to one or more of the following:

- recurrent episodes
- persistent oedema
- ulceration (Fig 3).

These factors may often be interrelated. Ulceration provides a portal of entry for infection, leading to further episodes. Chronic oedema is a risk factor for cellulitis (as described above), and repeated episodes of cellulitis cause further lymphatic damage. In an unpublished study of 171 cases by the author, the presence of persistent oedema was strongly correlated with the occurrence of two or more episodes of cellulitis.

To prevent recurrences, it is imperative to consider and treat:

- tinea pedis, usually with intermittent topical imidazole or allylamine compounds
- ulceration, with compression bandaging
- oedema, with adequate long-term support stockings.

Prophylaxis

Antibiotic prophylaxis is a less certain area. Several small series have reported benefit from prophylaxis with low dose penicillin V or erythromycin (both typically 250 mg bd) or with intermittent intramuscular depot penicillin. This appears to be safe[13,14]. However, it is not proven whether a prolonged course of antibiotics after an acute episode will prevent future recurrences. Each episode of streptococcal cellulitis adds to lymphatic damage, so it seems appropriate to consider prophylaxis for patients with either recurrent episodes or lymphoedema.

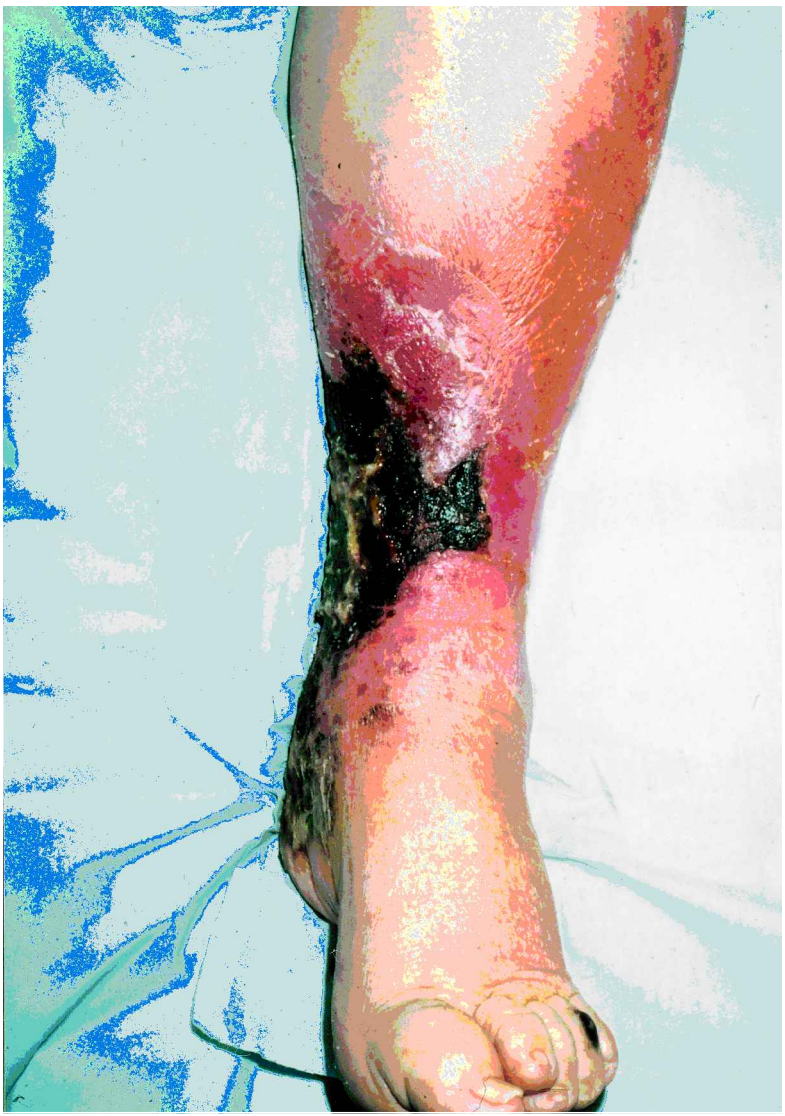

Fig 3. Necrosis leading to ulceration in a patient with cellulitis and elevated antistreptolysin-O titre (720 U/ml; normal <200 U/ml), but no evidence of necrotising fasciitis.

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