Cellulitis is defined as an acute inflammation of the skin and subcutaneous tissue which is commonly caused by Streptococcus pyogenes or Staphylococcus aureus (Morton and Swartz, 2004). The lower leg is the most affected site, accounting for 75–90% of all cases (Tsao and Johnson, 1997). The true incidence of cellulitis is hard to estimate but a review of all hospital admissions in a UK district general hospital showed that about 3% of all admissions were for cellulitis (Morris, 2004), thereby constituting a huge financial burden on healthcare resources. The NHS Institute for Innovation and Improvement noted that there were 45,522 inpatient admissions for cellulitis in 2003–2004, costing the NHS £87m (Carter et al, 2007).

Symptoms of cellulitis vary depending on the severity, which can range from mild to a more severe form with systemic involvement in the form of tachycardia, hypotension, and general malaise with a marked inflammatory response (Morton and Swartz, 2004). A typical presentation is painful swelling with erythema that is hot and tender to touch, often preceded by ‘flu-like’ symptoms. Potential long-term consequences of cellulitis include lymphoedema and leg ulceration (Cox, 2002).

Various risk factors have been shown to be associated with cellulitis, with lymphoedema showing the strongest association (Dupuy et al, 1999). This is particularly the case in recurrent cellulitis. Streptococcal cellulitis associated with lymphoedema can be aggressive with severe symptoms and morbidity (Bonnetblanc and Bedane, 2003).

Identifying cellulitis

Cellulitis is often clinically apparent due to the presence of tender erythematous swelling of the affected limb and systemic symptoms of malaise (Morton and Swartz, 2004). Fever and raised inflammatory markers may also be present. Blistering and ulceration occur in severe forms of cellulitis, often associated with marked oedema (Cox, 2002). Various laboratory investigations have been used for diagnosis of cellulitis by microbiological culture, but overall these tests have a relatively low diagnostic yield. Skin swabs for culture from intact skin are not helpful, but the yield of positive results increases if a likely portal of entry is present or if there is secondary blistering (Dupuy et al, 1999; Tsao and Johnson, 1997). Swabs from erosions, exudate and ulcerations, if present, may be more helpful (Tsao and Johnson, 1997). However, such lesions may have secondary staphylococcal colonisation and may not identify the primary cause, and swabs from pre-existing ulcers may reveal several different bacteria.

The main reason for the low rate of identification of streptococci in cellulitis is that the infection is of the dermis, not of the skin surface, so it is difficult to identify. Another possible reason is that treatment has often been initiated at an early stage and may mask symptoms of fever, making microbiological identification more difficult. A review of 50 patients with cellulitis showed that only 26% had fever at the time of active cellulitis (Hook et al, 1986). A study performed by one of the authors showed that 40% of patients with cellulitis admitted to hospital were apyrexial and systemically well (Cox et al, 1998). Hospital clinicians are aware that some patients are referred because they are ‘not getting better’ despite antibiotic treatment, but this will often refer to redness or swelling which can persist for some time after antibiotic treatment.

Cellulitis is a relatively common infection of the skin and subcutaneous tissue associated with high morbidity and a burden on healthcare resources. Lymphoedema — the accumulation of fluid in interstitial spaces — can occur as a consequence of cellulitis. Similarly, the presence of chronic lymphoedema can predispose to recurrent episodes of cellulitis. This article explores the relationship between lymphoedema and cellulitis, with emphasis on diagnosis, management and methods of prevention.
Blood cultures have been shown to give a low yield for diagnosis in the absence of bacteraemia. A retrospective study among 757 patients with community-acquired cellulitis showed that only 2% of patients had a significant patient-specific microbial strain isolated (Perl et al, 1999). A slightly higher rate of positive blood cultures in patients with leg lymphoedema has been demonstrated (Baddour and Bono, 1985). The authors believe that blood cultures have a marginal impact on clinical management in the absence of systemic symptoms and raised inflammatory markers, and therefore do not appear to be cost-effective. This does not however apply for necrotising fasciitis, which is a more serious infection affecting the deeper tissue structures associated with high mortality and systemic sepsis. Although less common than cellulitis, necrotising fasciitis is often confused with cellulitis, particularly at its early phase of presentation where blood cultures have a higher diagnostic yield (Cox, 2002).

Antistreptolysin titre (ASOT) levels may confirm a streptococcal aetiology in retrospect, as this blood test result is often raised as early as 7–10 days following a streptococcal infection, and takes several weeks to subside (Cox, 2002; Eriksson et al, 1996). This investigation is particularly useful in patients who are less likely to have a non-streptococcal aetiology (e.g. patients with excoriated eczema, carbuncles, abscesses or leg ulcers), as a negative test helps to exclude a streptococcal cause. Conversely, confirming streptococcal infections can be useful when choosing antibiotic therapy for patients with recurrent cellulitis.

Skin biopsy and/or aspirate have been shown to be of limited value in the diagnosis of cellulitis, but may have a role in excluding some differential diagnoses such as vasculitis or eosinophilic cellulitis in those with atypical presentations (Tsao and Johnson, 1997; Morton and Swartz, 2004; Cox, 2002).

Treatment with antibiotics (oral or intravenous) will be discussed later; however, elimination and treatment of potential risk factors such as onychomycosis, tinea pedis or leg ulcers and the control of lymphoedema, all contribute to the reduction in morbidity as well as future recurrence (Collins et al, 1989; Carter et al, 2007).

Risk factors for cellulitis
Local factors in the affected limb are strongly associated with a predisposition for cellulitis. General factors that might be regarded as risk factors include obesity, smoking, alcohol misuse and diabetes mellitus. The association with diabetes, smoking and alcohol has not been proven in retrospective studies (Dupuy et al, 1999), but obesity has been shown to be linked with an increased risk (Scheinfield, 2004).

Local factors causing defects in the skin barrier may increase the risk of developing cellulitis by acting as a portal of entry for micro-organisms (Morton and Swartz, 2004; Cox, 2002; Dupuy et al, 1999). Skin trauma, lacerations, puncture wounds, leg ulcers, dermatitis, toe web maceration and tinea pedis fall into this group. In a study involving 647 patients, 77% had local barrier defects that may have acted as portals of entry, 50% of which were fungal infections (mostly of the toe web) (Morr, 2004). Among the aforementioned factors, leg ulcers form the strongest risk (Dupuy et al, 1999).

Previous episodes of cellulitis are associated with a higher risk for recurrence, possibly due to local soft tissue and lymphatic damage (de Godoy et al, 2000). This risk increases particularly if other factors are present (Boomsdott et al, 2005).

A retrospective study among patients with cellulitis who were followed for up to three years showed that 47% had a history of recurrent episodes (Cox, 2006). Another study (n=233) showed that 29% of patients had a recurrence within the first three years after their initial cellulitis (Jonup-Ronstrom, 1986).

Lymphoedema has been shown in several studies to be the strongest risk factor for cellulitis (Dupuy et al, 1999; Duvanel et al, 1989), particularly in recurrent cellulitis. This is specifically linked to leg oedema secondary to lymphoedema and is much less the case with oedema secondary to venous insufficiency. In an epidemiological study in London involving 823 patients, 28% of patients with lymphoedema had had an episode of cellulitis within the previous 12 months (Moffatt et al, 2003).

Dupuy et al (1999) found that lymphoedema was present in 18% of their patients affected with cellulitis involving 167 patients with 294 controls. A different study in which patients who had two or more episodes of leg cellulitis were investigated with lymphoscintigraphy (n=15) found significant lymphatic abnormalities, suggesting a link with infective episodes (Soo et al, 2008). Sixty percent of those patients also had abnormal lymphoscintigrams in the leg that had not been affected by cellulitis, suggesting that pre-existing lymphatic abnormalities can precede the occurrence of clinical cellulitis. Stober et al (1987) found similar findings of abnormal lymphatic ducts among patients with cellulitis of the leg, and Damstra et al (2008) showed that 79% of 33 patients with impaired lymph drainage in the affected limb also had evidence of impaired drainage in the unaffected limb.

These studies support the increasingly accepted concept that previously undetected lymphatic abnormalities may be present among patients with cellulitis. Early detection of lymphatic abnormalities through lymphoscintigraphy — the gold standard method for detecting lymphatic abnormalities — and lymphoedema, and treatment of any abnormalities detected, may therefore reduce future episodes of cellulitis. However, there are obvious practical limitations to this, as the abnormalities demonstrated are often not easy to treat.

Management of cellulitis
The aim of treatment in cellulitis is resolution of the symptoms, reducing the duration of hospital admission and the avoidance of sequelae such as oedema and ulceration. General measures such as bed rest, elevation of the affected leg skin and wound care and analgesia are the first-line treatments for cellulitis (Morton and Swartz, 2004; Cox, 2002). Antibiotics are required to eradicate the causative organism, however, national prescribing advice on choice and duration of antibiotic therapy for cellulitis varies.
Generally, oral antibiotics are used for the milder forms of cellulitis where systemic involvement is minimal. Currently, recommendations for antibiotic choice vary with three different guidelines/recommendations currently existing in the UK (Clinical Resource Efficiency Support Team [CREST], 2005; Clinical Knowledge Summaries [CKS], 2006; Mortimer et al, 2006).

The CREST guidance (2005) suggests flucloxacillin as the first-line antibiotic (intravenously in severe cases), with the macrolide clindamycin for patients who are allergic to penicillin. In severe cases, intravenous clindamycin can be used as a substitute for clindamycin in cases of penicillin allergy.

CKS (2006) guidance recommends flucloxacillin as first-line and erythromycin or clindamycin in the case of penicillin allergy. The suggested duration of treatment is for seven days for mild infections and 10 days for more severe forms. There is limited evidence available for the estimated duration of treatment. One study with levofloxacin (which is rarely used for cellulitis in the UK) showed that if response to treatment occurs after five days, further treatment may not provide any additional benefit (Hepburn et al, 2004).

Treatment of cellulitis in patients with lymphoedema differs slightly as the causative organism is most likely to be streptococcal. Based on this, the British Lymphology Society (BLS) recommends amoxicillin as first-line therapy for cellulitis with lymphoedema. Clindamycin is recommended as second-line for those allergic to penicillin (Mortimer et al, 2006).

The review of response after 48 hours is recommended in all the guidelines (CREST, 2005; CKS, 2006; Mortimer et al, 2006).

In France, benzyl penicillin is the first-line recommended treatment for uncomplicated cellulitis (Societe Francaise de Dermatologue, 2001). Benzyl penicillin or phenoxymethyl penicillin both have a low minimal inhibitory concentration (MIC) against streptococci (i.e. low concentrations of the drug will inhibit the bacteria). However, penicillin alone is not recommended as first-line therapy in the UK, due to its limited effect against staphylococci (CREST, 2005; CKS, 2006; Mortimer et al, 2006). This is potentially important as clinical diagnosis of the infective organism may be difficult, especially in early localised cellulitis or in cellulitis with a wound as the portal of entry. Flucloxacillin as first-line treatment, as recommended by CREST and CKS, also has a low MIC for streptococci and in addition has anti-staphylococcal action. Although the MIC of penicillin is more favourable than that of flucloxacillin for streptococci, flucloxacillin’s MIC is sufficiently low that the addition of benzyl penicillin to flucloxacillin in patients who do not respond to the latter is unlikely to produce added beneficial value. This has been proven by a study that showed no difference in outcome when comparing a group of patients treated with flucloxacillin versus a group treated with flucloxacillin and benzyl penicillin (Leman and Mukherjee, 2005).

Treatment of recurrent cellulitis Despite the current limited evidence regarding long-term treatment for recurrent cellulitis, prophylactic therapy is widely used. Small studies suggest that oral antibiotic prophylaxis can be beneficial and cost-effective (Jorup-Ronstrom, 1986; Pavlotsky et al, 2004), and a small study (36 patients in the study randomised to two groups of 18 patients each) showed that prophylactic erythromycin for 18 months resulted in no recurrences in cellulitis compared with a placebo (Kremer et al, 1991). A large multi-centre national study, being coordinated by the UK Dermatology Clinical Trials Network, has already enrolled five times as many patients as the largest of the above studies (170 to date), and will hopefully provide useful evidence about the role of penicillin prophylaxis. Called PATCH (Prophylactic Antibiotics for the Treatment of Cellulitis at Home), the study is a randomised multi-centre clinical trial assessing whether prophylactic penicillin reduces episodes of cellulitis in patients who had recurrent (at least two episodes within the preceding 36 months) episodes of cellulitis (UK Dermatology Clinical Trials Network’s PATCH Study Group, 2007).

Current guidance regarding prophylaxis in cellulitis is suggested by the BLS if two or more episodes of cellulitis occur annually. The recommendation for phenoxymethylpenicillin is partly due to its long-term safety profile — as opposed to flucloxacillin which carries the risk of hepatic toxicity if used long term (Mortimer et al, 2006) — and also because recurrent cellulitis, with or without a background of lymphoedema, is most likely to be streptococcal infection.

Lymphoedema

Oedema is defined as excessive interstitial fluid which develops when there is a discrepancy between the microvascular filtration rate (in the capillaries and venules) and lymph drainage. Increases in interstitial fluid pressures and volume stimulate lymph flow through the collecting lymphatics. This is the main process responsible for interstitial fluid drainage. Impairment of the lymphatic drainage in the face of normal filtration will result in oedema (lymphoedema). In healthy lymphatic ducts, the lymph flow increases when capillary filtration increases, thus preventing the formation of oedema (Mortimer and Levick, 2004).

The process of lymph transport in the leg is mainly an active process achieved through contraction. This contractile mechanism of the smooth muscle walls of the collecting ducts is under the influence of the sympathetic system as well as the influx of calcium ions (Levick, 2004). Oedema related to calcium channel blockers is, therefore, likely to be partly through their effect on lymphatics. Activation of the calf muscle pump through contraction is generally believed to contribute to an increase in lymph transport.

The term lymphoedema covers a range of pathologies, all of which present clinically as chronic swelling or more limb(s) arising from a defect in the lymphatic channels. This implies a fundamental failure in lymph transport, as opposed to filtration oedema which is caused by increased capillary filtration (Mortimer and Levick, 2004).

Primary lymphoedema is the term used for lymphoedema that arises from...
an abnormality of lymphatic development, either due to genetic or congenital malformations in the collecting ducts (such as Milroy disease and Klippel-Trenaunay syndrome), or due to acquired abnormalities such as lymphangio-obliterative lymphoedemas (Consensus Document of the International Society of Lymphology Executive Committee, 2003). This represents a small percentage of lymphoedemas that often present after puberty.

Secondary lymphoedema refers to lymphoedema that is caused by an extrinsic process such as infection, malignancy or surgery which damages a previously well-functioning lymphatic system (Consensus Document of the International Society of Lymphology Executive Committee, 2003).

Generally, if oedema is symmetrical a systemic cause is likely to be found (e.g. hypoalbuminaemia, nephrotic syndrome), whereas unilateral limb oedema is often the result of local pathology to the lymphatic system.

Clinical lymphoedema manifests with swelling, pitting and thickening of the skin, which leads in time to a characteristic papillomatous appearance and a warty (hyperkeratotic) texture.

Treatment of lymphoedema
The main component in the treatment of lymphoedema is an improvement in lymph drainage. This can be attempted through several measures which will be explained briefly.

Exercise induces changes in interstitial fluid pressure which leads to an increase in both the lymphatic filling and pressure, with a consequential increase in the contractility of the lymphatic ducts. An increase in the flow of the non-contractile lymph ducts is likely to be influenced by exercise which leads to the passive movement of lymph.

Compression through bandaging or stockings aims to generate an increased interstitial pressure by opposing capillary filtration, leading to an increased venous return as well as to an increase in the contractility of the lymphatic ducts. Multi-layer bandaging is often used in combination with exercise in cases of severe lymphoedema.

Elevation of the affected leg may contribute by reducing the venous pressure and subsequently the filtration. It is often used in conjunction with other measures, as leg elevation on its own has little effect on the lymphatic drainage.

Manual lymphatic drainage (MLD) in the form of massaging the affected limb may stimulate lymph drainage from the root of the limb to the draining lymphatic basins. This is often combined with the aforementioned techniques.

Pneumatic compression therapy can be used to soften and reduce the limb volume but may displace fluid into adjacent areas and its use is therefore limited. The equipment used for this method is designed to inflate and deflate around a swollen limb, exerting a pressure of 30–40mmHg. Although it increases the reabsorption of interstitial fluid, it has no effect on the reabsorption of proteins. This leads to an increase in the concentration of interstitial protein and results in hardening of the treated limb (Mortimer and Levick, 2004). Furthermore, single chambered pumps have no direct effect on lymph flow, and the high pressures can damage the superficial lymphatics.

It is well known that diuretics do not play a role in the treatment of lymphoedema and should only be used in oedema secondary to salt and water retention (Mortimer and Levick, 2004).

The emergence of lymphoedema clinics led by nurses, physiotherapists and doctors from various specialties has allowed for an integrated service which in turn constitutes an increased risk for cellulitis (Collins et al, 1989; Woo et al, 2000). In unpublished original data referred to in a Cochrane review, about a quarter of patients with lymphoedema will have at least one episode of cellulitis or related skin infection in the affected limb (Badger et al, 2004).

This vicious cycle is independent from the primary aetiology of the lymphoedema and is thought to be multifactorial. The protein-rich lymphatic fluid serves as an excellent medium for bacteria to grow, and stagnation of the lymphatic fluid due to impaired lymph drainage with consequent reduction in lymphatic clearance creates a state of local immune deficiency, which, in turn, can increase the risk of local cellulitis (Baddour and Bisno, 1985; Mortimer and Levick, 2004).

In patients without lymphoedema, bacterial components released from bacteria are eliminated by phagocytosis and/or antibiotics and are cleared efficiently by lymphatic drainage (Jeffs, 1998).

Baddour and Bisno (1985) postulated that bacterial toxins which were ‘pooled’ in insufficiently drained lymphatic tissue contribute to the systemic symptoms found in some patients with cellulitis, complicating lymphoedema. This is largely attributable to the release of cytokines as a host response to the presence of excessive lymph. It is unclear why there seems to be a great individual variance in the manifestation of systemic symptoms, but it is likely that other host immune mechanisms play a role.

Mortimer et al (2006) suggested that once bacteria have gained entry to oedematous tissue, eradication proves difficult and there is a risk of reactivation of cellulitis if the local immune system is impaired (Mortimer and Levick, 2004). The involvement of such mechanisms may provide an additional explanation for the benefit of agents such as clindamycin and macrolides, as these have immunomodulatory actions as well as...
anti-streptococcal activity and therefore may have a role in the treatment of patients with recurrent cellulitis that complicates lymphoedema (Ritts, 1990).

Conclusion

Cellulitis is a common and potentially serious infection associated with a huge cost to the healthcare system and morbidity to the patient. Various risk factors have been found to predispose to cellulitis, with lymphoedema showing the strongest link. The relationship between cellulitis and lymphoedema appears to be a vicious cycle; a pre-existing lymphatic defect predisposes to cellulitis, episodes of cellulitis damage the lymphatic system, and either the primary or post-cellulitic lymphoedema predispose to recurrent episodes of cellulitis. It is therefore important that both cellulitis and lymphoedema are treated appropriately to reduce the risk of worsening lymphoedema and recurrent cellulitis.

Prophylactic antibiotics do appear to be beneficial in reducing the recurrence rate of cellulitis and are currently recommended, although without a strong evidence base, particularly when cellulitis is associated with lymphoedema. The large, ongoing multi-centre trial described earlier, investigating the use of prophylactic antibiotics in cellulitis (PATCH study), may in time provide this evidence.

References


