Managing the patient with recurring skin infections

**BACKGROUND**

Skin infections come in many forms. Most commonly, troublesome skin infection is synonymous with cellulitis, an entity that perfectly illustrates the cardinal signs of inflammation. Cellulitis is therefore an acute, usually noncontagious inflammation of the connective tissue of the skin, resulting from bacterial infection and characterized by localized warmth, erythema, pain and tenderness, swelling and reluctance to mobilize the affected area (Fig. PP4.1). When such a problem is recurrent, this can become extremely tiresome and even disabling for the afflicted individual.

Cellulitis is usually consequent upon a break developing in the skin surface or its appendages, such as a laceration, cut, fissure, puncture wound, insect bite, animal or human bite, scratch, abrasion, blisters or friction burn, such as might occur with shoes that are too tight. Organisms normally confined to the skin surface are admitted to the dermis where they proliferate and lead to cellulitis.

Erysipelas is a specific form of cellulitis usually caused by group A streptococci. The skin is red and very tender with a raised, well-demarcated area of inflammation often on the lower extremities or face. It is thought to be toxin mediated with intense superficial inflammation and lymphatic involvement. This can result in lymphatic obstruction and make the patient susceptible to recurrent episodes. Direct microbiologic cultures of skin and aspirate are often negative.

**RECURRENT CELLULITIS**

Recurrent cellulitis implies that factors facilitate the recurrent entry of organisms into the dermis. Effective management of recurrent cellulitis involves identifying these factors and, if possible, remedying them. Recurrent cellulitis may cause local persistent lymphedema, resulting in permanent hypertrophic fibrosis.

With respect to location, most often it is the lower limbs that are involved in recurrent cellulitis. The site may be the arm if, for example, the patient has received radiotherapy to the axillary area as part of breast cancer treatment. Other sites, such as the vulva and perianal region (sometimes in association with *Enterobius vermicularis*) can also be problematic.

To make matters more complex, cellulitis of the lower extremities is more likely to be complicated by thrombophlebitis in elderly patients, which in turn can encourage recurrence of cellulitis.

A number of clinical scenarios and risk activities render patients particularly vulnerable to recurrent episodes of cellulitis. These include:

- tinea pedis or onychomycosis;
- fissures between toes;
- diabetes mellitus – there may be a family history;
- peripheral vascular (arterial) disease – there may be a history of smoking, angina pectoris or hypertension;
- ischemic or venous ulceration of the skin (including sickle cell disease);
- post-deep venous thrombosis;
- eczema and dermatitis;
- immunodeficiency states, for example patients with HIV infection (who may be more prone to recurrent staphylococcal skin sepsis), neutropenia (granulocytopenia), Job’s syndrome (hyper IgE syndrome with recurrent staphylococcal cellulitis) or use of immunosuppressive or corticosteroid drugs – always establish the medication history.*

*Unusual organisms such as *Campylobacter jejuni* may cause an erysipelas-like cellulitis in patients with hypogammaglobulinaemia, probably as a result of a lack of serum bactericidal activity. Reference should be made to patients with agammaglobulinemia who develop *Campylobacter jejuni* cellulitis because of a lack of serum bactericidal effect (see Kerstens et al. in Further reading). *C. fetus* gives a similar picture in patients with deficient cell-mediated immunity.
lymphatic obstruction, for example post-radiotherapy (e.g. post-mastectomy), post-block dissection of lymph nodes for cancer (Fig. PP4.2), elephantiasis (e.g. due to infections by Wuchereria bancroftii, Brugia malayi, Onchocerca volvulus) or Milroy’s disease;

scar cellulitis (e.g. previous burn or skin graft sites and in areas from which veins were harvested for coronary artery bypass grafting);

trauma related, for example cosmetic piercings (studs, rings), intravenous drug users, recurrent localized trauma, self-harm or Munchausen’s syndrome;

nasal carriage of staphylococci;

lepromatous leprosy;

underlying occult osteomyelitis;

very poor personal hygiene (e.g. associated with alcoholism); and

morbid obesity – largely associated with recurrent lower limb cellulitis (see Fig. PP4.1).

MICROBIOLOGY

In immunocompetent individuals, cellulitis is usually the result of gram-positive aerobic cocci, particularly Staphylococcus aureus and Streptococcus pyogenes, or sometimes a combination of both. It can be clinically difficult to decide which of them is causing the problem.

A minority of Staph. aureus strains may produce the Panton–Valentine leukocidin toxin (PVL), a cytotoxin that causes leukocyte destruction and tissue necrosis. Outbreaks of recurrent cellulitis, boils and abscesses have been reported within families by this strain. Awareness of the high transmissibility and virulence of the PVL-producing strain is crucial in avoiding recurrence, eradicating reservoirs and preventing severe complications such as necrotizing pneumonia.

Non-group A streptococci, particularly groups B, C and G, are sometimes implicated in cellulitis, occurring in patients with lymphatic obstruction or post-vein harvesting for coronary artery bypass grafting.

Recurrent cellulitis due to streptococci may be seen in association with chronic lymphedema (e.g. from lymph node dissection, post-irradiation, Milroy’s disease, elephantiasis).

Neutropenic patients may develop cellulitis due to other organisms, such as gram-negative bacilli (e.g. Proteus, Serratia, Enterobacter spp.) and fungi. Rarely, the infection can be mixed with fungal and algal species (e.g. Aspergillus and Prototheca spp., Fig. PP4.3). Campylobacter species may cause both septicemia and cellulitis in hypogammaglobulinemic patients. The organism is often isolated from tissue biopsies and blood cultures.

Other organisms may be involved as part of a mixed picture, depending upon the source of the organisms. Incontinent patients may contaminate their lower limbs with urine and feces while intravenous drug users can inoculate their own tissues (Fig. PP4.4) with a variety of organisms from contaminated needles. Patients whose cellulitis is the result of deliberate self-harm may also yield multiple organisms on culture. This is an extremely difficult diagnosis to make and requires the highest levels of clinical acumen. For example, self-inoculation with milk has been reported as the cause of recurrent cellulitis.

IS IT REALLY CELLULITIS?

Sometimes the apparent recurrent cellulitis problem may not in fact be cellulitis, and the following should be considered:

acute gout can resemble recurrent cellulitis and certain diuretics may predispose to gout;

recurrent deep venous thrombosis;

migratory necrotic erythema associated with underlying neoplasia, particularly glucagonoma of the pancreas;

inflammatory carcinoma of the breast, which produces a picture of localized cellulitis unresponsive to antibiotics;

herpes zoster, which can cause recurrent rash that may be complicated by superinfection;

erythema nodosum, especially if it recurs;
Managing the acute phase of recurrences

Tissue penetration sufficient to achieve adequate local antibiotic concentrations can be problematic. For acute exacerbations, intravenous therapy may therefore be necessary. Useful combinations include (flucl)oxacillin–benzylpenicillin, (flucl)oxacillin–amoxicillin and clindamycin–ciprofloxacin.

Other antibiotics may be indicated, depending upon the clinical scenario:

- where allergy to β-lactam drugs is an issue – macrolides, levofloxacin or moxifloxacin;
- where MRSA is an issue – doxycycline and rifampin (rifampicin) can be given orally; vancomycin remains the first choice for parental therapy although linezolid, quinupristin–dalfopristin and more recently daptomycin and tigecycline are alternative options;
- where anaerobes are an issue – metronidazole, clindamycin or quinupristin–dalfopristin; and
- where Campylobacter spp. are an issue – macrolides, quinolones or carbapenems, with treatment according to sensitivities; regarding Campylobacter, macrolides, quinolones and imipenem are dependent on susceptibility with plasma treatment.

Surgeal care includes debridement of devitalized tissue. Incision and drainage may be indicated if suppuration occurs. Treat local effects of cellulitis by elevating the affected limb.

Prevent recurrences

Adequate patient education and training are essential. Skin and foot care for tinea pedis and onychomycosis includes:

- patient training regarding proper skin hygiene and suitable footwear;
- treating affected toe webs or feet with topical antifungals;
- consideration of oral antifungals such as itraconazole or terbinafine for severe chronic tinea pedis or onychomycoses; and
- expert podiatry – cuts and fissures should be washed and kept clean while healing.

Managing the patient with recurring skin infections

Fig. PP4.4 Intravenous drug user with severe recurrent cellulitis of the left arm.

- palmoplantar pustulosis and pyoderma gangrenosum, such as that associated with inflammatory bowel disease, can be mistaken for cellulitis;
- scurvy and pellagra; and
- fixed drug eruptions.

ASSESSMENT AND DIAGNOSIS

Unless pus has formed or an open wound is present, it is often difficult to isolate the responsible organism from a case of cellulitis. Aspiration of material from the advancing edge of the lesion, skin biopsy and blood cultures yield potential pathogens in only about 25% of cases. The etiology of most cases of cellulitis will usually be *Staph. aureus* and/or *Strep. pyogenes*.

In unusual circumstances, such as patients who are immunocompromised or those not responding to empiric therapy, or indeed whenever the clinical history points toward other infective or noninfective diagnostic options, further investigations may be warranted. This may become particularly important where the patient is suffering recurrent attacks. For example, among those with peripheral vascular disease or diabetes mellitus, minor injuries or cracked skin in the feet or toes can serve as an entry point for recurrent infection.

Attention should accordingly be directed toward establishing the presence or absence of factors that might be supporting the development of recurrent cellulitis and might be amenable to correction. The following range of tests can be applied selectively according to circumstances:

- microbiologic – samples for microscopy. Gram staining, culture and sensitivity, swabs from areas of abscess or bullae formation, needle aspiration of the advancing edge of cellulitis, full skin biopsy, interdigital skin and/or nail scrapings (especially where tinea pedis is present), blood culture (positive in only a few patients), nasal swabs (especially for *Staph. aureus* carriage, including meticillin-resistant *Staph. aureus*, MRSA), perianal cellophane tape (for *Enterobius* ova), throat swab (for *Strep. pyogenes* in those with erythema nodosum) and bullous fluid (for immunofluorescence antibody test for varicella-zoster);
- imaging – tissue scanning (plain radiographs, ultrasound, CT, MRI and indium leukocyte scanning) may identify collections of pus meriting drainage, foreign bodies or underlying osteomyelitis (if gas is seen in the tissues, the differential diagnosis then includes gangrene and fasciitis, which are generally considered to be surgical emergencies), Doppler scans (which may assist in identifying deep venous thrombosis or peripheral arterial disease);
- hematologic and immunologic – blood films (macrocytosis associated with alcohol excess and microfilaria in suspected filariasis), differential white cell count (to identify neutropenia, eosinophilia, e.g. in filariasis), hemoglobin electrophoresis in sickle-cell disease, immunoglobulin levels and subsets, complement levels, T-cell subsets;
- serology – HIV-1 and HIV-2, antistreptolysin titer (may point toward erythema nodosum as the diagnosis), hepatitis C, hepatitis B (may point toward occult intravenous drug abuse), filariasis, onchocerciasis if the patient is at risk;
- biochemistry – blood glucose, urate levels, liver function tests; and
- skin biopsy – may help with rarer causes of cellulitis.

MANAGEMENT
For cases caused by edema, treat any underlying cause (e.g. cardiac failure) and relieve edema using support stockings, specialized bandaging and nocturnal elevation of the affected area. Diuretics may have a role.

Immunocompromised patients will remain vulnerable to recurrent infections and therefore may need prolonged antibiotics until their immune status improves.

There is no convincing evidence for the value of antibiotic prophylaxis and there is a risk of antibiotic resistance. Penicillin, erythromycin and clindamycin have all been advocated. Early institution of antibiotics may help in cellulitis of the lower extremities. The patient must be trained to spot the early signs of a recurrence, and given a supply of antibiotics (such as amoxicillin or flucloxacillin) to take. They should be advised to seek medical advice as soon as possible.

Nasal carriage of *Staph. aureus* can be treated with mupirocin if it is thought to be associated with recurrent disease.

**CONCLUSION**

Recurrent cellulitis is responsible for much morbidity. Diagnosis is not always straightforward and it presents a significant management challenge.

**FURTHER READING**


