



Cellulitis:

skin deep and spreading
across New Zealand

Adults and children with uncomplicated cellulitis can usually be managed in the community if they are clinically stable. Oral flucloxacillin is the first-line treatment for the majority of patients with mild to moderate cellulitis; broader spectrum oral antibiotics should only be considered if flucloxacillin is not tolerated, has not been effective or there is reason to believe the infection is caused by bacteria that are not normally commensal on the skin. Intravenous (IV) cefazolin with probenecid is the recommended community-based treatment for patients with cellulitis who have not responded to oral flucloxacillin or for patients with more developed cellulitis. Generally, patients with severe cellulitis should be referred to hospital for rest, elevation and IV antibiotic treatment.

Identifying cellulitis in primary care

Cellulitis is an acute, spreading bacterial infection of the lower dermis and subcutaneous tissue.¹ It most often affects lower limbs but may affect other areas depending on the cause, e.g. upper limb, periorbital, perianal, abdominal wall in patients who are obese, or any part of the body where surgery has recently been performed.^{1,2}

Cellulitis is characterised by localised pain, swelling, erythema and heat and patients may also present with fever, malaise and in severe cases oedema, blisters, ulcers and lymphangitis (infection within the lymph vessels).¹ Erysipelas is a superficial form of cellulitis affecting the upper dermis, that may coexist with cellulitis and is treated in the same way.³ Erysipelas is often fiery red and can be identified by its elevation above the level of the surrounding skin and a clear demarcation between involved and uninvolved tissue.³

Co-morbidities recognised as risk factors for cellulitis include: eczema, obesity, tinea pedis, diabetes, pregnancy, venous insufficiency, peripheral artery disease, ulcers and lymphoedema.¹ People who have previously had cellulitis are more likely to have a repeat episode and reported recurrence rates for cellulitis and erysipelas range from 12% over six months to 34% over 3.3 years.⁴

Causes of cellulitis

Cellulitis generally begins with a breach in the protective layer of the skin allowing bacterial entry, although the breach may be minor and hard to locate. Many conditions, events or procedures can cause this, including cracked skin due to dryness, eczema or tinea pedis, cuts or penetrating wounds, burns, insect bites or stings, surgery and IV cannulation.

Streptococcus pyogenes and other related streptococci (especially Group C and Group G streptococci) are reported to cause approximately two-thirds of cases of cellulitis or erysipelas and *Staphylococcus aureus* the majority of the remaining cases.⁵ However, a wide variety of causative organisms can be responsible if the bacteria that has breached the skin originated from a source that was external to the patient, e.g. a mammalian bite, or the infection occurs in the pelvic or perianal regions.^{1,2}

Cellulitis in New Zealand

In New Zealand there was a significant increase in *S. aureus* skin and soft tissue infections (SSTIs) reported for the 12 years until 2011: the incidence increased from 81 to 140 people per 100 000 or approximately a 5% increase per year during this time.⁶ The rates of *S. aureus* SSTIs in northern and central regions of New Zealand were approximately three times the rates in the south.⁶ Although not specifically reported, cellulitis infections are expected to account for a substantial portion of these figures.

Māori and Pacific peoples and people from low socioeconomic areas are known to be at increased risk of serious skin infections, which is likely to be due to a range of factors, including overcrowding and reduced access to primary healthcare; children are often affected.⁷

The diagnosis of cellulitis

Cellulitis can usually be diagnosed clinically by the presence of localised pain, swelling, erythema and heat. Table 1 includes a number of differential diagnoses that may be appropriate to consider in some patients.

Furuncles (boils) or carbuncles (multiple headed lesions) are easily misdiagnosed as cellulitis due to a rim of about 1 to 2 cm of tender erythema surrounding the central focus of the staphylococcal infection. This erythema, however, represents inflammatory change and not extension of infection into the tissues; patients with focal staphylococcal infections should not be treated as if they have cellulitis. The use of systemic antibiotics in patients with furuncles or carbuncles is usually unnecessary unless there is extensive surrounding cellulitis or the patient develops a fever.³

Investigations for cellulitis

Investigations are not normally required in patients with suspected cellulitis, but testing may be useful in some situations, e.g. differentiating infection from gout, or in patients who are systemically unwell, e.g. heart rate > 100 beats/min or systolic blood pressure < 90 mmHg or 20 mmHg below the patient's normal level.³


The white blood cell count can be expected to be elevated in almost half of patients with cellulitis, and approximately two-thirds of patients can be expected to have an elevated CRP.⁸ Neither marker is sensitive or specific enough to be used

diagnostically for cellulitis, although an elevated CRP is a more reliable indicator of bacterial infection than an elevated white blood cell count.⁸ Blood cultures may be considered in patients who are systemically unwell, but these are negative in most patients with cellulitis.¹ If the patient is at risk of acute kidney injury through dehydration, e.g. an older patient with chronic kidney disease, then a serum creatinine measurement may be useful in order to monitor renal function and to potentially guide dosing of antibiotics.

Taking a swab for microscopy and culture is not routinely recommended, unless:

- There is a lesion present that is deteriorating, increasing in size or failing to heal⁹
- There is reason to suspect the cellulitis is caused by organisms that are not normally commensal on the skin, e.g. the patient has recently had surgery or is living in an area or a residential care facility where there is an increased prevalence of methicillin-resistant *S. aureus* (MRSA)
- Empiric antibiotic treatment has failed

Table 1: Alternative diagnoses to cellulitis with differential characteristics¹

Condition	Major characteristics
Varicose eczema (stasis dermatitis)	Generally a long-term condition. Absence of pain or fever, usually bilateral with inflammation going right around the leg.
Gout	Joint pain often associated with the metatarsal-phalangeal joint
Deep vein thrombosis	May be associated with a period of inactivity or major surgery. Tenderness and erythema may be localised to an affected vein. With extensive thrombosis the limb may be purplish in colouration.
Hypersensitivity reaction	Pruritus and an absence of pain or fever, history may uncover a recent exposure, e.g. an allergen or medicine
Necrotising fasciitis	Severe pain, swelling and fever progressing rapidly, severe systemic toxicity, skin crepitus, ecchymosis (bleeding into the skin).  See: "Necrotising fasciitis: a rare but important differential diagnosis"
Arthritis	Joint pain often occurring with movement and a lack of erythema unless there is septic joint involvement
Pyoderma gangrenosum	Ulcerations of the leg and a history of inflammatory bowel disease (IBD)

Managing patients with cellulitis in the community

Assess the patient for signs of systemic toxicity, e.g. unresolved or worsening fever, hypotension, tachycardia and vomiting. Patients with red flags should be referred to hospital.

Red flags for hospital admission

It is recommended that patients with cellulitis and any of the following features should be referred to hospital; a lower threshold for referral is appropriate for young children, e.g. aged less than one year, and frail older people.¹³

- Signs of systemic involvement or haemodynamic instability, e.g. tachycardia, hypotension, severe dehydration
- A progressing infection despite prior antibiotic treatment, e.g. spreading margins or worsening lymphangitis
- Pain suggestive of necrotising fasciitis, e.g. the patient appears in severe pain or describes their pain as rapidly and dramatically worsening
- Unstable co-morbidities that may complicate the patient's condition, e.g. diabetes, vascular disease or heart failure
- Immunosuppression, e.g. a history of immunodeficiency illness, currently undergoing chemotherapy or taking immunosuppressant medicines such as prednisone, methotrexate, ciclosporin
- An animal or human bite wound requiring surgical debridement
- A large abscess formation requiring general surgical drainage
- Orbital involvement unless cellulitis is very mild

All patients with cellulitis should rest and elevate any affected limb. Antibiotics and elevation will generally reduce any discomfort the patient is experiencing. If analgesia is required, paracetamol is preferred over non-steroidal anti-inflammatory drugs (NSAIDs) (see: "Necrotising fasciitis").¹⁰ A line drawn around the leading edge of the erythematous area allows the progress of the cellulitis to be easily monitored.

Antibiotics with an appropriate spectrum of antimicrobial activity are the mainstay of treatment; these need to penetrate soft tissue and be prescribed in doses that are sufficient and frequent enough to achieve a sustained therapeutic concentration at the site of infection. Intravenous antibiotic treatment may be required initially to achieve a response, and may be available via a DHB community-based programme.

Necrotising fasciitis: a rare but important differential diagnosis

Necrotising fasciitis is a rapidly progressing soft tissue infection with a high mortality rate; it is often referred to as a "flesh eating" disease in the media. Necrotising fasciitis is characterised by extensive and progressive necrosis of the subcutaneous tissue and fascia.¹⁰ As in patients with cellulitis, infection may be present in the absence of visible trauma. When patients with necrotising fasciitis are examined erythema and oedema may be noticed. However, extreme tenderness of the infected area and severity of the patient's illness with the presence of hypotension, tachycardia and high fever helps to differentiate necrotising fasciitis from cellulitis.¹¹ If the patient is not treated their skin develops blue-gray patches after 36 hours and cutaneous bullae and necrosis after three to five days.¹¹

From 1990 – 2006 there were 247 people hospitalised in New Zealand with confirmed necrotising fasciitis.¹⁰ Approximately 33% of cases were precipitated by accidental trauma, with skin ulcers (16%) and surgery (11%) being the next most common causes.¹⁰ Diabetes, NSAID use in the previous seven days and obesity are predisposing characteristics for necrotising fasciitis.¹⁰ It is not known why NSAIDs increase the risk of necrotising fasciitis; an impaired immune response or delayed diagnosis due to symptoms being masked are possibilities.¹² Māori and Pacific peoples in New Zealand are more likely to be affected by necrotising fasciitis compared with the general population.¹⁰

Patients who are suspected of having necrotising fasciitis should be referred to hospital immediately and will often be admitted to an intensive care unit. Surgical excision of the affected tissues and intravenous antibiotic treatment are the mainstays of treatment.

If a cut, bite or abrasion is suspected to be the cause of the cellulitis the patient's tetanus status should be checked and a booster given if necessary. If a patient presents to general practice with cellulitis that is secondary to an injury then it may be appropriate for an Accident Compensation Corporation (ACC) claim to be lodged.

Trial oral antibiotics first in patients with mild to moderate cellulitis

Flucloxacillin has traditionally been the first-line oral antibiotic for patients with cellulitis because all *S. pyogenes* and other related streptococci are susceptible to treatment with flucloxacillin, as are approximately 90% of strains of *S. aureus* (i.e. all *S. aureus* except for MRSA), and because it is a narrow spectrum antibiotic that penetrates skin and soft tissue well.^{1,4} The importance of treatment adherence should be discussed, and patients advised to take oral flucloxacillin at least 30 minutes before eating.¹⁴ Microbiological swabbing of patients with cellulitis is not generally required before beginning treatment unless there are risk factors for MRSA. Due to a lack of trials there is uncertainty as to the optimal duration of antibiotic treatment for cellulitis;¹⁵ treatment recommendations provided may range from five to ten days.

It is recommended not to prescribe oral amoxicillin clavulanate in primary care for patients with cellulitis. Patients with cellulitis in the facial or periorbital region should be referred to secondary care due to the risk of vision loss.

Antibiotic treatment regimens for children with cellulitis

A child with early and mild cellulitis can be trialed on oral antibiotics for five days with review by a general practitioner after 24–48 hours.¹⁶

Flucloxacillin is recommended first-line. The Starship Children's Health recommended regimen for oral flucloxacillin for children with cellulitis is:¹⁶

- Flucloxacillin 10–25 mg/kg/dose, orally, three times daily, for five days (maximum 500 mg/dose) (some regimens recommended dosing four times daily)

Flucloxacillin syrup may be unpalatable to some children therefore capsules are recommended in preference to syrup for children who are able to swallow them.

Erythromycin can be prescribed as an alternative for children with a confirmed significant allergy to flucloxacillin. The Starship recommended regimen is:¹⁶

- Erythromycin 20 mg/kg/dose, orally, twice daily, or

10 mg/kg/dose, orally, four times daily for five days
(maximum 500 mg/dose)

If neither flucloxacillin syrup nor erythromycin are tolerated then cefalexin oral liquid, a broader spectrum antibiotic, is an alternative for children. The Starship recommended regimen is:¹⁶

- Cefalexin 20 mg/kg/dose, orally, twice daily, for five days (maximum 500 mg/dose)

N.B. An alternative regimen is cefalexin 12.5 mg/kg/dose, four times daily.¹⁷

Antibiotic treatment regimens for adults with cellulitis

Flucloxacillin is also the first-line recommended oral antibiotic treatment for cellulitis in adults. The recommended regimen from the Auckland DHB Adult Empirical Antibiotic Treatment Guidelines is:¹⁸

- Flucloxacillin 500 mg, orally, four times daily, for five days

Several protocols suggest that flucloxacillin up to 1 g, orally, four times daily, for five days may be more appropriate for some adult patients, e.g. those with moderate to severe cellulitis, patients who may not respond to lower doses of antibiotics due to vascular co-morbidities, e.g. diabetes or peripheral vascular disease, or patients in whom the complications of infection may be severe, e.g. those who are immunosuppressed.¹⁹ In some patients, e.g. an older patient with low body weight and reduced renal function, it may be appropriate to initiate treatment at a reduced dose, e.g. flucloxacillin 250 mg, four times, daily.

Erythromycin can be prescribed as an alternative for adults with a confirmed significant allergy to flucloxacillin:¹⁷

- Erythromycin 800 mg, orally, twice daily, or 400 mg, orally, four times daily, for five days

Managing patients who have not responded to treatment

The natural history of cellulitis means that patients may experience an increase in erythema and swelling within the first 48 hours of treatment. In most patients a reduction in pain in the affected skin and an improvement in appetite and level of energy are clear signs that the infection is being brought under control despite the area of erythema remaining unchanged or enlarging.

Treatment adherence, including the need to rest and elevate affected limbs, should be assessed in all patients who are not responding as well as expected; the four times daily dosing of flucloxacillin can be hard for some patients to remember or patients who have been instructed to take the antibiotic

before eating may skip doses if they miss a meal. It may be appropriate to reconsider the diagnosis in a patient who is adhering with treatment, but is not responding. If their overall condition deteriorates, e.g. fever or tachycardia increases, referral to hospital or a change in antibiotic treatment may be appropriate. Patients should be discussed with a paediatrician or infectious diseases physician.

Patients with mild cellulitis who are adhering to antibiotic treatment but not responding sufficiently after 48 hours may be candidates for community-based IV treatment (see below) or an adjustment of the dosing regimen may be an alternative option. For example, a higher oral dose taken less often may be effective, e.g. flucloxacillin 1 g, three times daily may maintain therapeutic levels of antibiotic.

The possibility that infection is due to MRSA or another organism resistant to standard treatment should also be considered if the patient's condition is not improving; microbiological swab and culture may be beneficial in this situation; if performed, details of current antibiotic treatment should be provided to the laboratory. If MRSA is isolated from swabs co-trimoxazole is the preferred antibiotic, unless susceptibility results suggest otherwise, at the following doses:^{16, 17, 18}

- Children aged over six weeks: co-trimoxazole 0.5 mL/kg oral liquid (40+200 mg/5 mL), twice daily, for five to seven days (maximum 20 mL/dose)
- Adults and children aged over 12 years: co-trimoxazole 160+800 mg (two tablets), twice daily, for five to seven days

N.B. Co-trimoxazole should be avoided in infants aged under six weeks due to the risk of hyperbilirubinaemia.¹⁷

If a patient has moderate cellulitis that is not responding to oral antibiotic treatment, referral to hospital should be considered. In some situations hospital staff may decide the community-based IV antibiotic treatment is appropriate for the patient.

When to consider community-based intravenous treatment

If a patient presents with severe cellulitis or has not responded satisfactorily to oral antibiotics then community-based IV antibiotic treatment may be appropriate, if red flags are absent. This involves a cannula being inserted and left *in situ* until the patient has completed the IV course of antibiotics. DHB protocols vary as to who is responsible for the day-to-day care of patients with cellulitis receiving IV treatment, which includes: prescribing, administering the IV antibiotic (and probenecid if indicated), IV line and cannula care, monitoring

Probenecid is not routinely recommended in combination with oral antibiotics

Probenecid is indicated as an adjunct to beta-lactam antibiotics, e.g. cephalosporins and penicillin derivatives, because it reduces the renal excretion of these antibiotics and lengthens the time that they maintain a therapeutic level.¹⁴ Probenecid tablets are recommended as an adjunctive treatment in patients treated with once daily IV cefazolin to prolong the duration of effective cefazolin tissue levels.

At present there is only a theoretical benefit in the combination of oral flucloxacillin with probenecid as there is no published evidence that treatment with this combination is more effective than treatment with flucloxacillin alone.


Probenecid is prohibited at all times by the World Anti-Doping Agency and should not be prescribed to elite athletes as it may be used as a masking agent.²⁰



Local protocols may differ for cellulitis treatment

Currently a national framework for funding community-based administration of IV antibiotics does not exist. Therefore individual DHBs have established their own arrangements in order for patients to qualify for funded treatment with IV cefazolin in their homes. For example, in the Auckland, Counties Manukau and Waitemata DHBs Primary Options for Acute Care (POAC) provide general practitioners with funds to manage patients in the community who may otherwise be admitted to hospital. In the Waikato DHB the first IV dose of cefazolin is given in general practice and subsequent doses are given by a district nurse. In the Southern DHB patients who are referred to hospital with cellulitis may have an IV cannula inserted and a first dose of treatment given in the Emergency Department and then treatment continued in their home by a district nurse.

It is suggested that primary care staff contact their local DHB to see what local protocols are in place. In some situations it may be helpful to discuss cellulitis management with local pharmacies as they may be able to stock IV cellulitis kits.

 For further information see: "Community-based IV administration: primary care reducing hospital admissions", BPJ 38 (Sep, 2011).

response to treatment (see: "Local protocols may differ"). In some DHBs practices are supplied with "cellulitis kits" and the primary care team has responsibility for care, in other areas IV antibiotic treatment is initiated in primary care and then continued by a district nurse, while in other DHBs a district nurse may be responsible for care following a hospital referral from general practice. Regardless of local protocols, the patient's individual circumstances are always important when considering if community-based IV antibiotic treatment is appropriate:

- Is the patient mentally and socially able to receive community-based treatment?
- Are there contraindications to providing the patient with readily accessible intravenous access – is the patient at risk of using the IV line for recreational drug use?
- Does the patient have family members at home to assist them?
- Can the patient be monitored at least daily?
- Can the patient return to the practice if their condition deteriorates, e.g. do they have ready access to a car?
- Can the patient easily contact medical services, e.g. do they have a phone?

Cefazolin, 2 g IV, once daily, with probenecid, 500 mg orally, twice daily, is recommended by many DHBs as the most appropriate community-based IV treatment for adult patients with cellulitis.^{13, 19} This regimen is preferred as it is the most studied and it is a once daily injection whereas intravenous flucloxacillin requires either four times daily IV administration or the use of a central line and a pump or infusor device to enable continuous infusion. Cefazolin is subsidised for the treatment of cellulitis, but only when it is prescribed in accordance with an approved DHB protocol and is endorsed by a general practitioner or secondary care prescriber for this purpose.

The dose of cefazolin may need to be reduced in patients with renal impairment, e.g. a creatinine clearance < 55 mL/min.²¹

Probenecid is given as a 500 mg tablet, twice daily, as an adjunctive treatment in the management of cellulitis with IV antibiotics.¹³ Probenecid is contraindicated in patients with a history of blood disorders, eGFR < 30 mL/min/1.73m², nephrolithiasis and during an acute attack of gout.¹⁴ Because of its mechanism of action, probenecid has a number of significant drug interactions:

- Any patients taking methotrexate should be monitored closely for symptoms of toxicity; methotrexate dose reductions may required

- Low dose aspirin for cardiovascular indications is not likely to be affected by probenecid, but patients should not use aspirin in analgesic doses
- Carbapenem antibiotics, that may be used in hospital, may require dose adjustment

Probenecid should be avoided in patients with an eGFR < 30 mL/min/1.73m².¹⁴ Patients taking probenecid should be advised to ensure they are drinking 2 – 3 L of fluid daily to prevent the formation of urinary stones.¹⁴

Patients receiving IV antibiotics for cellulitis can be expected to show significant clinical improvement after two to three days;²² at which time they can be switched to oral antibiotics, e.g. flucloxacillin. If the patient has not shown any clinical improvement after this time then it is recommended that they be referred to hospital for further assessment or discussed with an infectious disease consultant.

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