CELLULITIS: A BACTERIAL SKIN INFECTION, THEIR CAUSES, DIAGNOSIS AND TREATMENT

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ABSTRACT
Family physicians frequently treat bacterial skin infections in the office and in the hospital. Common skin infections include cellulitis, erysipelas, impetigo, folliculitis, and furuncles and carbuncles. Cellulitis is an infection of the dermis and subcutaneous tissue that has poorly demarcated borders and is usually caused by Streptococcus or Staphylococcus species. And that is characterized by warmth, edema, and advancing borders. Cellulitis commonly occurs near breaks in the skin, such as surgical wounds, trauma, tinea infections, or ulcerations. Patients may have a fever and an elevated white blood cell count. The most common sites of cellulitis were the legs and digits, followed by the face, feet, hands, torso, neck, and buttocks. For infection in patients without diabetes, empiric treatment with a penicillinase-resistant penicillin, first-genera- tion cephalosporin, amoxicillin-clavulanate (Augmentin), macrolide, or fluoroquinolone (adults only) is appropriate. Limited disease can be treated orally, but more extensive disease requires parenteral therapy. Antibiotics should be maintained for at least three days after the resolution of acute inflammation. Adjunctive therapy includes the following: cool com- presses; appropriate analgesics for pain; tetanus immunization; and immobilization and elevation of the affected extremity. The patient may also require a plain radiograph of the area or surgical debridement to evaluate for gas gangrene, osteomyelitis, or necrotizing fasciitis. Recurrent episodes of cellulitis or undergoing surgery, such as mastectomy with lymph node dissection. Herbal medicines are also used for cellulitis.

Keywords: Cellulitis, Bacterial skin infection, Dermis, Edema, Antibiotics.
INTRODUCTION
Cellulitis is an acute inflammatory condition of the dermis and subcutaneous tissue usually found complicating a wound, ulcer or dermatosis. Spreading and pyogenic in nature, it is characterized by localized pain, erythema, swelling and heat. The involved area, most commonly on the leg, lacks sharp demarcation from uninvolved skin. Erysipelas, a superficial cellulitis with prominent lymphatic involvement, does have an indurated, raised border that demarcates it from normal skin. These distinctive features create what is known as a “peaud’orange” appearance.[1]

THE SKIN
The skin is the largest organ of the human body. It is made up of three main layers:

- **the epidermis** – the outer surface of skin and an underlying section of cells, which the body uses to create new skin cells
- **dermis** – the middle layer of skin that contains blood vessels, sweat glands and hair follicles
- **subcutis** – the bottom layer of skin that consists of a layer of fat and collagen (a tough, spongy protein), which helps protect the body and regulate temperature.[2]

ETIOLOGY

**common causes**

- Group A β-hemolytic streptococci (*Streptococcus pyogenes*)
- *Staphylococcus aureus*
- Haemophilus influenzae (decreasing in frequency)
- Group B, C, D, or G β-hemolytic streptococci

Cellulitis may be caused by indigenous flora colonizing the skin and appendages, like *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes* (*S. pyogenes*), or by a wide variety of exogenous bacteria. Bacteria gain entry into the body in many ways: breaks in the skin, burns, insect bites, surgical incisions and intravenous (IV) catheters are all potential pathways. *S. aureus* cellulitis starts from a central localized infection and spreads from there. An abscess, folliculitis or infected foreign body, such as a splinter, prosthetic device or IV catheter, may serve as a possible focus for this condition.

Cellulitis due to *S. pyogenes* follows a different pattern. It spreads rapidly and diffusely and is frequently associated with lymphangitis and fever. Recurrent streptococcal cellulitis of the
lower extremities, seen in conjunction with chronic venous stasis or with saphenous vein harvest for coronary artery bypass surgery, often comes from organisms of group A, C or G. Cellulitis is also seen in patients with chronic lymphedema resulting from elephantiasis, Milroy’s disease or lymph node dissection such as that associated with mastectomy. Staphylococcal and streptococcal species are also the most common pathogens in bacterial infections among drug-users \(^3\), and infections that implicate an unusual organism are often related to a specific drug or drug-use behavior.

Many other bacteria cause cellulitis. Haemophilus influenzae was once a major pathogen in facial cellulitis in young children, but these infections are now rare due to the type B vaccine. Pasteurella multocida is the pathogen in cellulitis associated with animal bites, mostly those of cats. Aeromonas hydrophila can cause an aggressive form of cellulitis in a laceration sustained in fresh water. Pseudomonas aeruginosa is the source of three types of soft tissue infection: ecthyma gangrenosum in neutropenic patients, hot tub folliculitis and cellulitis following a penetrating wound, like that sustained from stepping on a nail. Gram-negative bacillary (rod) cellulitis, like P. aeruginosa, is common among hospitalized, immunocompromised patients and may have multidrug resistance. Culture and sensitivity tests are very important in this setting. \(^4, 5\)

“Fig. 1”: Patient with cellulitis of the left ankle. This cellulitis was caused by community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA).

**contributory or predisposing factors**

- Break in the skin due to trauma, puncture, laceration, animal bite, or sting
- Burns
• Skin lesions caused by furuncle, ulcer, or fungal infection (e.g., tineapedis)
• Surgical procedure or incision, including lymphadenectomy, saphenous vein stripping, and mastectomy
• Previous cellulitis
• Diabetes mellitus (type 1 and type 2)
• Lymphatic stasis
• Peripheral vascular disease
• Chronic steroid use
• Intravenous drug addiction
• AIDS or other immunodeficiency disorder
• Liver disease
• Renal failure
* Occupational exposure: farm workers; gardeners; handlers of fish, shellfish, and aquariums[^6]

**EPIDEMIOLOGY**

Incidence and prevalence

**frequency**

Common in the U.S., but because it is a non-reportable infection, exact incidence is not known.

**Demographics**

**Age**

• Facial cellulitis usually occurs in adults aged 50 years or above, or children aged 6 months to 3 years
• Perianal cellulitis usually affects children

**Gender**

• Perianal cellulitis is more common in male patients than in female patients
• No gender difference for other types of cellulitis

**Geography**

Cellulitis caused by halophilic *Vibrio* species occurs in coastal areas (shellfish handlers).
Socioeconomic status

- Immigrant populations who may not have been vaccinated against *Haemophilus influenzae* type b and tetanus are at increased risk of infection.
- Overcrowded conditions may also exacerbate infection.
- Farm, garden, fish, and shellfish workers are at increased risk of infection by rare agents causing cellulitis.[6,7]

**GRADES OF CELLULITIS**[8, 9]

- **Class I**- Patients have no signs of systemic toxicity, have no comorbidities and can usually be managed with oral antimicrobials as outpatients.
- **Class II**- Patients are either systemically ill or systemically well but with a comorbidity such as peripheral vascular disease, chronic venous insufficiency or morbid obesity which may complicate or delay resolution of their infection.
- **Class III**- Patients may have a significant systemic upset such as acute confusion, tachycardia, tachypnoea, or may have unstable comorbidities that may interfere with a response to therapy, or have a limb-threatening infection due to vascular compromise.
- **Class IV**- Patients have sepsis syndrome or severe life-threatening infection such as necrotising fasciitis.

“Fig. 2”: Mild cellulitis with a fine lace like pattern of erythema. This lesion was only slightly warm and caused minimal pain.

“Fig. 3”: Swelling seen in cellulitis involving the hand. In a situation with hand cellulitis, always rule out deep infection by imaging studies or by obtaining surgical consultation.
“Fig. 4”: Severe cellulitis of the leg. The cellulitis developed beneath a cast and was painful and warm to the touch. Significant erythema is evident.

**SYMPTOMS**

Symptoms of cellulitis include:

- **Fever**
- Pain or tenderness in the affected area
- **Skin redness or inflammation** that gets bigger as the infection spreads
- Skin sore or rash that starts suddenly, and grows quickly in the first 24 hours
- Tight, glossy, stretched appearance of the skin
- Warm skin in the area of redness

**Signs of infection:**

- Chills or shaking
- Fatigue
- General ill feeling
- **Muscle aches** and pains
- Warm skin
- Sweating

“Fig. 5”: Symptoms of cellulitis, redness.

Other symptoms that can occur with this disease

- Hair loss at the site of infection
- **Joint stiffness** caused by swelling of the tissue over the joint
- Nausea and vomiting

**COMPLICATION OF CELLULITIS**
Complications of cellulitis can include blood poisoning, abscesses, and meningitis.

**blood poisoning**
If the bacteria that infect your skin and tissue enter your bloodstream, they can cause blood poisoning (septicaemia). Symptoms of blood poisoning include:
- high temperature (fever) of 38°C (100.4°F) or above
- rapid heart beat
- rapid breathing
- low blood pressure, which will make you feel dizzy when you stand up
- changes in mental behaviour, such as confusion or disorientation
- diarrhoea
- reduced urine flow
- cold, clammy skin
- pale skin
- loss of consciousness

**Abscess**
Some cases of cellulitis can result in an abscess forming near the site of the infection.
An abscess is a swollen, pus-filled lump under the surface of the skin. It is caused by a build-up of bacteria and dead white blood cells.

In some cases, the antibiotics that are used to treat cellulitis may also help to remove the abscess. However, if this is not the case, the pus will have to be drained from the abscess through a small cut in your skin.

**Facial cellulitis and meningitis**
Facial cellulitis is an uncommon form of cellulitis that develops on the skin of the face. It accounts for an estimated 8.5% of all cases of cellulitis.

Facial cellulitis is most common in children under three year’s old and older adults above 50. If facial cellulitis is left untreated in children, the bacteria can potentially spread to the outer membranes of their brain (the meninges) and trigger a serious brain infection called meningitis.
Symptoms of meningitis can differ in adults, but symptoms in babies and children under three years old include:

- becoming floppy and unresponsive, or stiff with jerky movements
- becoming irritable and not wanting to be held
- unusual crying
- vomiting and refusing feeds
- pale and blotchy skin
- loss of appetite
- staring expression
- very sleepy and reluctant to wake up

Bacterial meningitis is very serious and should be treated as a medical emergency. If left untreated, a bacterial infection can cause severe brain damage and infect the blood.

**PREVENTING CELLULITIS** [2]

- Not all cases of cellulitis can be prevented. But you can take steps to reduce the risk of developing the condition.
- These involve steps to prevent skin wounds, and treating wounds properly when they occur.

**Treating skin wounds**

- Make sure that any cuts, grazes or bites are kept clean. Wash the damaged skin under running tap water and, if necessary, apply an antiseptic cream.
- Keep the wound covered with a plaster or dressing. Make sure you change the plaster or dressing if it becomes wet or dirty. Plasters and dressings will reduce the risk of the wound being damaged further, and they will help to create a barrier against bacteria entering the skin.

**Hand hygiene**

- Wash your hands regularly, particularly when treating or touching a wound or skin condition.
- If you have an itchy skin condition, such as atopic eczema or chickenpox, keep your fingernails clean and short at all times. If you scratch your skin and your fingernails are short and clean, the risk of skin damage and infection will be reduced.
Keep your skin moisturised

- If your skin is dry or prone to cracking, keep your skin well moisturised. Cracked skin can create an entry point for bacteria.

Preventing cellulitis in lymphedema

- People with lymphoedema (a condition that causes swelling of the arms and legs) have a much higher risk of developing cellulitis than others. This is because the swelling of the skin that is associated with lymphoedema makes it more vulnerable to bacterial infection.
- If you are diagnosed with lymphoedema, you may be given a two-week course of antibiotics to take in case you start having the initial symptoms of cellulitis.
- If you have two or more episodes of cellulitis in a year, it is usually recommended that you begin taking antibiotics on a long-term basis to protect against further infection.

DIAGNOSIS

Generally, no workup is required in uncomplicated cases of cellulitis that meet the following criteria:

- Limited area of involvement
- Minimal pain
- No systemic signs of illness (eg, fever, altered mental status, tachypnea, tachycardia, hypotension)
- No risk factors for serious illness (eg, extremes of age, general debility, immunocompromise)

The Infectious Disease Society of America (IDSA) recommends the following blood tests for patients with soft-tissue infection who have signs and symptoms of systemic toxicity:[11]

- Blood cultures
- CBC with differential
- Levels of creatinine, bicarbonate, creatine phosphokinase, and C-reactive protein (CRP)

Blood cultures should also be done in the following circumstances:[11]

- Moderate to severe disease[11] (eg, cellulitis complicating lymphedema[12])
- Cellulitis of specific anatomic sites (eg, facial and especially ocular areas)
- Patients with a history of contact with potentially contaminated water[13]

Other tests to consider are as follows:
• Mycologic investigations are advisable if recurrent episodes of cellulitis are suspected to be secondary to tineapedis or onychomycosis
• Creatinine levels help assess baseline renal function and guide antimicrobial dosing.

**Imaging studies**
• Ultrasonography may play a role in the detection of occult abscess and direction of care[^14]
• Ultrasonographic-guided aspiration of pus can shorten hospital stay and fever duration in children with cellulitis[^15]
• If necrotizing fasciitis is a concern, CT imaging is typically used in stable patients; MRI can be performed[^16], but MRI typically takes much longer than CT scanning
• Strong clinical suspicion of necrotizing fasciitis should prompt surgical consultation without delay for imaging.

**Aspiration, dissection, and biopsy**
• Needle aspiration should be performed only in selected patients or in unusual cases, such as in cases of cellulitis with bullae or in patients who have diabetes, are immunocompromised, are neutropenic, are not responding to empiric therapy, or have a history of animal bites or immersion injury[^17,18,19]
• Aspiration or punch biopsy of the inflamed area may have a culture yield of 2-40% and is of limited clinical value in most cases[^20]
• Gram stain of aspiration or biopsy specimens has a low yield and is unnecessary in most cases, unless purulent material is draining or bullae or abscess is present; however, Gram stain and culture following incision and drainage of an abscess yields positive results in more than 90% of cases[^11]
• Dissection of the underlying fascia to assess for necrotizing fasciitis may be determined by surgical consultation or indicated following initial evaluation and imaging studies[^21]
• Skin biopsy is not routine but may be performed in an attempt to rule out a noninfectious entity.

**Hospital admission**
The IDSA recommends considering inpatient admission in patients with hypotension and/or the following laboratory findings:[^11]
• Elevated creatinine level
• Elevated creatine phosphokinase level (2-3 times the upper limit of normal)
• CRP level >13 mg/L (123.8 mmol/L)
• Low serum bicarbonate level
• Marked left shift on the CBC with differential

DRUG THERAPY AND TREATMENT

• **Class I** patients can usually be managed with oral antimicrobials on an outpatient basis.
• **Class II** patients are suitable for short-term (up to 48 hours) hospitalisation and discharge on outpatient parenteral antimicrobial therapy (OPAT), where this service is available.
• **Class III and Class IV** patients require hospitalisation until the infected area is clinically improving, systemic signs of infection are resolving and any co-morbidities are stabilised. Patients with suspected necrotising infection require urgent surgical assessment and extensive debridement of the affected area.

Table 1: Suitable Drug Therapy for Typical Cellulitis

<table>
<thead>
<tr>
<th>Class</th>
<th>First line</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Flucloxacillin 500mg qds po</td>
<td>Penicillin allergy: Clarithromycin 500mg bd po</td>
</tr>
<tr>
<td>Class 2</td>
<td>Flucloxacillin 2g qds IV Or *Ceftriaxone 1g od IV</td>
<td>Penicillin allergy: Clarithromycin 500mg bd IV Or Clindamycin 600mg tds IV</td>
</tr>
<tr>
<td>Class 3</td>
<td>Flucloxacillin 2g qds IV</td>
<td>Penicillin allergy: Clarithromycin 500mg bd IV Or Clindamycin 900mg tds IV</td>
</tr>
<tr>
<td>Class 4</td>
<td>Benzylpenicillin 2.4g 2-4 hourly IV + Ciprofloxacin 400mg bd IV + Clindamycin 900mg tds IV (If allergic to penicillin use Ciprofloxacin and Clindamycin only) NB Discuss with local Medical Microbiology Service</td>
<td></td>
</tr>
</tbody>
</table>

* Must not be used in penicillin anaphylaxis

**Rationale**

The vast majority of cases of cellulitis are caused by beta-haemolytic streptococci or S.aureus. Empiric antimicrobial therapy should therefore provide adequate cover for these micro-organisms.

Flucloxacillin exerts a bactericidal effect on streptococci as well as staphylococci and for this reason has been suggested as monotherapy orally for Class I infections and initially
intravenously for Class II and Class III infections. Custom and practice has traditionally combined the use of benzylpenicillin and flucloxacillin in the management of hospitalised patients with cellulitis. The short half-life of benzylpenicillin necessitates administration at least four hourly and when combined with intravenous flucloxacillin results in ten doses of an antimicrobial agent over a twenty-four hour period. In most cases this is not seen as practical or necessary. If a recognised pathogen is isolated from blood cultures seek specific advice from a Medical Microbiologist.

Although co-amoxiclav also exerts a bactericidal effect on streptococci and staphylococci this antibiotic has a considerably broader spectrum of activity including Gram-negative organisms and anaerobes and is therefore unnecessary in this situation.

Penicillin allergy: It is essential to obtain a detailed history of a patient’s reaction to penicillin as this may allow a clinician to exclude allergy. The vast majority of patients with a history of penicillin rash tolerate cephalosporins without significant reaction.[22] If the patient has experienced an anaphylactic reaction or immediate urticarial rash to a penicillin, this class of drug must be avoided. Macrolide antibiotics or clindamycin are suitable alternatives.

Clindamycin suppresses toxin production by group A streptococci, C. prefringens and S. aureus. It is for this reason that it is used in the management of necrotizing fasciitis. It has been associated with cases of Clostridium difficile diarrhoea and in non-life threatening infection the development of diarrhoea should prompt discontinuation.

In the past, it has been standard practice to hospitalize Class II patients with serious soft tissue infections, such as cellulitis. However, those of Class II severity can be treated safely and effectively with OPAT followed by transition to oral agents as the infection resolves. Ceftriaxone has been listed for the management of Class II infections. This agent is administered once daily making it a suitable agent if OPAT is locally available and considered appropriate. Its safety and efficacy in this situation is well established.[23, 24, 25]

**Non-responders**

There may be an increase in erythema in the first 24-48 hours of treatment possibly related to toxin release. Further deterioration should prompt consultation with the local Medical Microbiology/Dermatology/Tissue Viability Service or Surgical Team as appropriate.
Oral Antimicrobial switch and hospital discharge
Although criteria for the switch from parenteral to oral antibiotics for patients with community acquired pneumonia have been studied,\[26, 27\] there is less information in relation to cellulitis. It has been suggested that patients can be switched safely to oral antibiotics within 3.5 days of therapy for uncomplicated cellulitis.\[28\]
Use of IV therapy for longer than 3-4 days does not correlate with better outcomes.\[29\]
Delay of discharge until complete resolution of fever and all signs of inflammation is usually unnecessary.\[30,31\]

Suggested criteria for oral switch and/or discharge
- Pyrexia settling
- Co-morbidities stable
- Less intense erythema
- Falling inflammatory markers

Suitable agents for oral switch therapy
- Flucloxacillin 500mg qds
  If penicillin allergy-
- Clarithromycin 500mg bd
- Clindamycin 300mg qds
  If an oral preparation of the parenteral drug is available this will, on most occasions, be the most appropriate oral switch agent.

Clarithromycin and clindamycin are suitable agents in the penicillin allergic patient.

Table 2: Suitable Drug Therapy for Atypical Cellulitis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>First line</th>
<th>Penicillin allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human bite</td>
<td>Co-amoxiclav 625mg tdspo</td>
<td>Clarithromycin 500mg bdpo or Doxycycline 100mg bdpo and Metronidazole 400mg tdspo</td>
</tr>
<tr>
<td>Cat/Dog bite</td>
<td>Co-amoxiclav 625mg tdspo</td>
<td>Doxycycline 100mg bdpo and Metronidazole 400mg tdspo</td>
</tr>
<tr>
<td>Exposure to fresh water at site of skin break</td>
<td>Ciprofloxacin 750mg bdpo and Flucloxacillin 500mg qdspo</td>
<td>Ciprofloxacin 750mg bdpo And Clarithromycin 500mg bdpo</td>
</tr>
</tbody>
</table>
Discontinuation of antibiotics
The duration of antimicrobial therapy for cellulitis has not been extensively studied. Most cases of uncomplicated cellulitis can be successfully treated with 1-2 weeks of therapy although complicated cases may require more prolonged therapy.

The bacterial aetiology of cellulitis associated with bites or non-chlorinated water is more diverse than “simple” cellulitis.

In the case of human bites cover for mouth anaerobes as well as staphylococci and streptococci is essential and provided with co-amoxiclav monotherapy. Combination therapy is recommended in cases of penicillin allergy. In animal bites co-amoxiclav also provides cover for other common Gram-negative pathogens such as Pasturellamultocida. In cases of penicillin allergy clarithromycin does not provide this Gram-negative cover and doxycycline is recommended.

LOCAL MANAGEMENT OF CELLULITIS
Management of the locally affected area should include the following:

- Adequate analgesia to ensure pain relief
- Monitoring and management of any pyrexia
- Consider hydration – intravenous/oral
- Recording of the site and/or limb affected
- Mark off the extent of erythema present on admission

If applicable:

- Measurement of the limb
- Elevation of the limb
- Use of a bed cradle

Blistering
In some instances cellulitis may lead to the skin blistering and subsequent breakdown of the skin.

Where there is potential for blisters to burst spontaneously, proactive management is advocated. This includes aseptic aspiration and/or deroofing of the blister. If in doubt, seek specialist advice.
Broken and Exudating Skin
The impact of the cellulitis on the skin is to cause tension and swelling which in some cases leads to ulceration and subsequent loss of large amounts of exudate. Products normally used for management of wound exudate should be considered and selection of these will depend on the site and size of area to be covered. Topical antibiotics should not be used in the management of cellulitis.

Compression Bandages
Once the critical stage of swelling and redness has subsided and the patient is reasonably pain free, the patient should be assessed for compression bandaging.

Lymphoedema
Patients with lymphoedema require referral to appropriate lymphoedema services.

RISK OF RECURRENCE OF CELLULITIS AND NEED FOR PROPHYLAXIS
Studies on recurrence rates for cellulitis show that 29% of patients who have previously been admitted to hospital with cellulitis develop a recurrence within a mean of 3 years. Other reported studies show 17% recurrences but no defined follow-up time and a 12% recurrence after a follow-up of only 6 months. Strobart 1985 demonstrated a recurrence rate of 34% in 103 patients who had 2 episodes of erysipelas followed for a mean of 3.3 years. Venous insufficiency has been reported to be the commonest predisposing factor. Other studies show that lymphoedema is the most important risk factor in the development of recurrent cellulitis. As lymphoedema and venous insufficiency are often associated, it would clearly be best to combine these two as the main risk factors for recurrent cellulitis. Each episode of cellulitis adds to the lymphatic damage. Therefore, prophylaxis should be considered for patients with recurrent episodes.

Long-term Prophylaxis
Cellulitis is presumed to be caused mainly by streptococci. However in more than 80% of cases a pathogen is not identified and the pathogenesis of recurrent episodes of cellulitis is poorly understood. Although there is weak and inconclusive evidence on whether long-term antibacterial prophylactic therapy prevents recurrent cellulitis, it may be worth trying for 1 – 2 years in patients with predisposing conditions who have had at least 2 episodes of cellulitis at the same site. Antibiotic prophylaxis for recurrent cellulitis is purely empirical and optimal treatment and prophylaxis in these patients remains to be determined. Prophylaxis
may be more effective in patients without predisposing factors. Early patient initiated treatment rather than long-term prophylaxis may be preferable. Small series have reported benefit from prophylaxis with low dose Penicillin V or Erythromycin (both typically 250mg bd) or with intermittent IM depot Penicillin. However it is not proven whether a prolonged course of antibiotics after a single acute episode will prevent future recurrences.

**Prophylaxis for Recurrent Cellulitis**
- 2 or more episodes at the same site
- Penicillin V 250mg bd or Erythromycin 250mg bd for up to 2 years.

**CONCLUSION**
The majority of bacterial skin infections are caused by the gram-positive bacteria Staphylococcus and Streptococcus species. Antibiotics are used empirically with consideration for resistance patterns. Current antibiotic recommendations include penicillinase-resistant penicillins, first-generation cephalosporins, azithromycin, clarithromycin, amoxicillin- clavulanic acid, or a second-generation fluoroquinolone in the skeletally mature patient. Gram-negative coverage with a second-, third, or fourth-generation cephalosporin is usually indicated in children under three years and in patients with diabetes or who are immunocompromised.

**REFERENCES**