

## CLINICAL PRACTICE

## Cellulitis

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**An otherwise healthy 40-year-old man felt feverish and noted pain and redness over the dorsum of his foot. Tender edema and erythema extended up the pretibial area. Fissures were present between the toes. What diagnostic procedures and treatment are indicated?**

## THE CLINICAL PROBLEM

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**Cellulitis** is an acute, spreading **pyogenic** inflammation of the **dermis** and **subcutaneous tissue**, usually complicating a wound, ulcer, or dermatosis. The area, usually on the leg, is tender, warm, erythematous, and **swollen**. It **lacks sharp demarcation** from uninvolved skin. **Erysipelas** is a **superficial cellulitis** with prominent lymphatic involvement, presenting with an indurated, **"peau d'orange"** appearance with a **raised** border that is **demarcated** from normal skin. The distinctive features, including the anatomical location of cellulitis and the patient's medical and exposure history, should guide appropriate antibiotic therapy (Table 1).

## ANATOMICAL FEATURES

Periorbital cellulitis involves the eyelid and periocular tissues anterior to the orbital septum. Periorbital cellulitis should be distinguished from orbital cellulitis because of the potential complications of the latter: decreased ocular motility, decreased visual acuity, and cavernous-sinus thrombosis.

Before young children began to be immunized with conjugated *Haemophilus influenzae* type b vaccine, buccal cellulitis due to *H. influenzae* type b was responsible for up to 25 percent of cases of facial cellulitis in children 3 to 24 months of age; now such cellulitis is rare. Infection originates in the upper respiratory tract.

Perianal cellulitis occurs mainly in young children and is generally caused by group A streptococci.<sup>1</sup> Manifestations include perianal pruritus and erythema, anal fissures, purulent secretions, and rectal bleeding.

## TYPES OF EXPOSURE THAT PREDISPOSE PATIENTS TO CELLULITIS

Severe bacterial cellulitis has been known to occur as a complication of **liposuction**. The subcutaneous injection of illicit drugs ("skin popping") can result in cellulitis due to unusual bacterial species.<sup>2,3</sup>

A distinctive form of cellulitis, sometimes recurrent, may occur weeks to months **after breast surgery for cancer**. Cellulitis in the ipsilateral arm has been well described after radical mastectomy,<sup>4</sup> where it occurs **because** of associated **lymphedema**; cellulitis in the ipsilateral **breast** is **more common** now, occurring after breast-**conservation** therapy.<sup>5,6</sup> **Local lymphedema** from the combination of partial mastectomy, axillary lymph-node dissection, and breast irradiation is a predisposing factor.

Cellulitis also occurs in the legs of patients whose saphenous veins have been harvested for coronary-artery bypass.<sup>7</sup> Lymphatic disruption and edema occur on the removal of the vein.

#### UNUSUAL MANIFESTATIONS OF CELLULITIS

**Crepitant** cellulitis is produced by either **clostridia** or non-spore-forming anaerobes (**bacteroides** species, peptostreptococci, and peptococci) — either alone or **mixed** with facultative bacteria, particularly *Escherichia coli*, klebsiella, and aeromonas.

**Gangrenous cellulitis** produces necrosis of the subcutaneous tissues and overlying skin. **Skin necrosis may complicate conventional cellulitis** or may occur with distinctive clinical features (including necrotizing cutaneous **mucormycosis** in immunocompromised patients).

#### INITIATING SOURCES OF INFECTION

Identifying the **source** of cellulitis — whether it is **cutaneous**, **subjacent**, or **bacteremic** — can provide clues as to the causative microorganism and the identity of a process that requires additional intervention. Most commonly, the source is skin trauma or an underlying lesion (an ulcer or fissured toe webs, for example). Animal or human **bites** can cause cellulitis due to the skin flora of the recipient

of the bite or the oral flora of the biter (Fig. 1). Specific pathogens are suggested when infection follows exposure to **seawater** (*Vibrio vulnificus*), **fresh water** (*Aeromonas hydrophila*), or **aquacultured fish** (*Streptococcus iniae*).

**Edema predisposes** patients to cellulitis (Fig. 2). Some **lymphedema** persists after recovery from cellulitis or erysipelas and predisposes patients to recurrences,<sup>8</sup> which may be of longer duration than the initial inflammation.<sup>9</sup>

Occasionally, cellulitis may be caused by the spread of subjacent osteomyelitis. Rarely, infection may emerge as apparent cellulitis, sometimes distant from the initial site. Crepitant cellulitis on the left thigh, for instance, might be a manifestation of a colonic diverticular abscess.

Cellulitis infrequently occurs as a result of bacteremia. Uncommonly, **pneumococcal cellulitis** occurs on the face or limbs in patients with **diabetes mellitus**, **alcohol** abuse, **systemic lupus erythematosus**, the **nephrotic** syndrome, or a **hematologic cancer**.<sup>10</sup> Meningococcal cellulitis occurs rarely, although it can affect both children (periorbital cellulitis) and adults (cellulitis on an extremity).<sup>11</sup> Bacteremic cellulitis due to *V. vulnificus* with prominent hemorrhagic bullae may follow the ingestion of raw oysters by patients with cirrhosis, hemochromato-

**Table 1. Specific Anatomical Variants of Cellulitis and Causes of Predisposition to the Condition.**

Anatomical Variant or Cause of Predisposition	Location	Likely Bacterial Cause
Periorbital cellulitis	Periorbital	<i>Staphylococcus aureus</i> , pneumococcus, group A streptococcus
Buccal cellulitis	Cheek	<i>Haemophilus influenzae</i>
Cellulitis complicating body piercing	Ear, nose, umbilicus	<i>S. aureus</i> , group A streptococcus
Mastectomy (with axillary-node dissection) for breast cancer	Ipsilateral arm	Non-group A hemolytic streptococcus
Lumpectomy (with limited axillary-node dissection, breast radiotherapy)	Ipsilateral breast	Non-group A hemolytic streptococcus
Harvest of saphenous vein for coronary-artery bypass	Ipsilateral leg	Group A or non-group A hemolytic streptococcus
Liposuction	Thigh, abdominal wall	Group A streptococcus, peptostreptococcus
Postoperative (very early) wound infection	Abdomen, chest, hip	Group A streptococcus
Injection-drug use (“skin popping”)	Extremities, neck	<i>S. aureus</i> ; streptococci (groups A, C, F, G)*
Perianal cellulitis	Perineum	Group A streptococcus
Crepitant cellulitis	Trunk, extremities	See text
Gangrenous cellulitis	Trunk, extremities	See text
Erythema migrans (bright red, circular lesion at initial sites; secondary annular lesions may develop elsewhere several days later because of hematogenous spread)	Extremities, trunk	<i>Borrelia burgdorferi</i> (agent of Lyme disease)

\* Other bacteria to consider on the basis of isolation from skin or abscesses in this setting include *Enterococcus faecalis*, viridans-group streptococci, coagulase-negative staphylococci, anaerobes (including bacteroides and clostridium species), and Enterobacteriaceae.

sis, or thalassemia.<sup>12,13</sup> Cellulitis caused by other gram-negative organisms (e.g., *E. coli*) usually occurs through a cutaneous source in an immunocompromised patient but can also develop through bacteremia<sup>14</sup>; it sometimes follows *Pseudomonas aeruginosa* bacteremia in patients with neutropenia. In immunocompromised persons, less common opportunistic pathogens (e.g., *Helicobacter cinaedi* in patients with human immunodeficiency virus infection; *Cryptococcus neoformans*; and fusarium, proteus, and pseudomonas species) have also been associated with bloodborne cellulitis.<sup>15-17</sup>

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cellulitis is summarized in Table 2. Soft-tissue infections that resemble cellulitis must be distinguished from it, since the management of necrotizing fasciitis or gas gangrene requires extensive débridement. The diagnosis of necrotizing fasciitis can be established definitively only by direct examination on surgery or by biopsy with frozen section.<sup>23,24</sup>

### STRATEGIES AND EVIDENCE

#### DIAGNOSTIC STUDIES

##### Cultures of Aspirates and Lesions

The diagnosis of cellulitis is generally based on the morphologic features of the lesion and the clinical setting. Culture of needle aspirates is not indicated in routine care. However, data from five series using needle aspiration have elucidated common pathogens. Among 284 patients, a likely pathogen was identified in 29 percent.<sup>25-30</sup> Of 86 isolates, only

3 represented mixed cultures. Gram-positive microorganisms (mainly *Staphylococcus aureus*, group A or B streptococci, viridans streptococci, and *Enterococcus faecalis*) accounted for 79 percent of cases; the remainder were caused by gram-negative bacilli (Enterobacteriaceae, *H. influenzae*, *Pasteurella multocida*, *P. aeruginosa*, and acinetobacter species). A small study in children demonstrated higher yields when needle aspirates were obtained from the point of maximal inflammation than when they were obtained from the leading edge.<sup>30</sup>

In two small studies, the yield of punch biopsies was slightly better than that of needle aspirates,<sup>27,29</sup> and the biopsies revealed the presence of gram-positive bacteria in all but one case (*S. aureus* alone in 50 percent of cases, and either group A streptococci alone or *S. aureus* with other gram-positive organisms in most of the remainder). Cultures of ulcers and abrasions in areas contiguous to those with cellulitis have similarly revealed the presence of *S. aureus*, group A streptococci, or both in the majority of cases.<sup>28</sup> These data indicate that antimicrobial therapy for cellulitis in immunocompetent hosts should be focused primarily on gram-positive cocci.

Broader coverage is warranted in patients with diabetes. Among 96 leg-threatening foot infections (including cellulitis) in patients with diabetes, the main potential pathogens recovered from deep wounds or débrided tissue were gram-positive aerobes including *S. aureus*, enterococci, and streptococci (in 56 percent of cases); gram-negative aerobes including proteus, *E. coli*, klebsiella, entero-



**Figure 1. Cellulitis Due to *Pasteurella multocida* after a Cat Bite.**

Bite marks are evident, as are adjacent swelling and edema.



**Figure 2. Cellulitis Due to Group A Beta-Hemolytic Streptococci in Leg (Previously Mildly Edematous) of a Patient with Paraplegia.**

Some of the superficial skin is eroded. The initiating event was an abrasion on the lower leg.

bacter, acinetobacter, and *P. aeruginosa* (in 22 percent); and anaerobes including bacteroides and peptococcus (in 22 percent).<sup>31</sup> This broad range of microorganisms should also be considered as potential pathogens in cellulitis that occurs as a complication of decubitus ulcers.

**Blood Cultures**

Bacteremia is uncommon in cellulitis: among 272 patients, initial blood cultures were positive in 4 percent.<sup>25,26,28-30</sup> Two thirds of the isolates were either group A streptococci or *S. aureus*, and the remain-

der were either *H. influenzae* or *P. multocida*. A retrospective study of blood cultures in 553 patients with community-acquired cellulitis found a relevant isolate, mainly group A or group G streptococci (but also *S. aureus* and *V. vulnificus*), in only 2 percent,<sup>32</sup> indicating that blood cultures were not likely to be cost effective for most patients with cellulitis.

In contrast, blood cultures are indicated in patients who have cellulitis superimposed on lymphedema. In a study involving 10 such patients, 3 had positive blood cultures (all non-group A streptococci).<sup>9</sup> This high prevalence of bacteremia may be

**Table 2. Important Processes to Be Distinguished from Cellulitis.**

Process	Clinical Clues to Diagnosis
<b>Infectious</b>	
<b>Necrotizing fasciitis</b>	
Type I (mixed infection of anaerobes plus facultative species such as streptococci or Enterobacteriaceae)	Acute, rapidly developing infection of deep fascia; marked pain, tenderness, swelling, and often crepitus; bullae and necrosis of underlying skin
Type II (infection with group A streptococci)	Acute infection, often accompanied by toxic shock syndrome; rapid progression of marked edema to violaceous bullae and necrosis of subcutaneous tissue; absence of crepitus
Anaerobic myonecrosis (gas gangrene, due to <i>Clostridium perfringens</i> )	Rapidly progressive toxemic infection of previously injured muscle, producing marked edema, crepitus, and brown bullae (showing large, gram-positive bacilli with scant polymorphonuclear cells); on radiography, extensive gaseous dissection of muscle and fascial planes; bacteremic spread of <i>C. septicum</i> from occult colonic cancer can produce myonecrosis without penetrating trauma
Cutaneous anthrax	Gelatinous edema surrounding eschar of anthrax lesion may be mistaken for cellulitis; anthrax lesion is painless or pruritic; epidemiologic factors are of paramount importance
Vaccinia vaccination	Erythema and induration around vaccination site reaches peak at 10–12 days (more slowly than cellulitis); little toxicity; represents cellular response to vaccinia
<b>Inflammatory and neoplastic</b>	
Insect bite (hypersensitivity response)	History of insect bite, local pruritus; absence of fever, toxicity, or leukocytosis
Acute gout	Involvement of foot (podagra); joint pain; repeated attacks; increase in serum uric acid level
Deep venous thrombophlebitis	Involvement of leg; sentinel venous cord and linear extent
Familial Mediterranean fever–associated cellulitis-like erythema <sup>18</sup>	Occurs in Sephardic Jews and persons from the Middle East who have had previous episodes of recurrent fevers with or without episodes of acute abdominal pain
Fixed drug reaction	Skin erythema does not spread as rapidly as cellulitis; fever low, if present; history of medication use
Pyoderma gangrenosa (particularly lesions starting in subcutaneous fat as acute panniculitis)	Lesions become nodular or bullous and ulcerate; occurs particularly in patients with inflammatory bowel disease or collagen vascular syndromes
Sweet's syndrome (acute febrile neutrophilic dermatosis) <sup>19</sup>	Acute, tender erythematous pseudovesiculated plaques, fever, and neutrophilic leukocytosis; often associated with cancer (commonly hematologic); on face, may resemble erysipelas or periorbital cellulitis; corticosteroid-responsive
Kawasaki's disease <sup>20</sup>	Fever, conjunctivitis, acute cervical lymphadenopathy, oropharyngeal erythema; dermatitis of palms and soles; facial appearance may suggest periorbital cellulitis; occurs mainly in infancy and childhood
Wells' syndrome	Urticaria-like lesions with central clearing; lesions progress slowly and persist for weeks or months; histologically, infiltration with eosinophils; peripheral eosinophilia
Carcinoma erysipeloides <sup>21,22</sup>	A form of metastatic carcinoma with lymphatic involvement; occurs most often on anterior chest wall with cancer of the breast but may also occur at sites of distant metastases; absence of fever; slower progression than cellulitis

attributable to the preexisting lymphedema and the infecting bacterial species. Blood cultures are also warranted in patients with buccal or periorbital cellulitis, in patients in whom a salt-water or fresh-water source of infection is likely (Table 3), and in patients with chills and high fever, which suggest bacteremia.

**Radiology**

Radiologic examination is unnecessary in most cases of cellulitis. Plain-film radiography and computed tomography (CT) are of value, however, when the clinical setting suggests a subjacent osteomyelitis. When it is difficult to differentiate cellulitis from necrotizing fasciitis, magnetic resonance imaging (MRI) may be helpful, although surgical exploration for a definitive diagnosis should not be delayed when the latter condition is suspected.<sup>24</sup> In a

study involving 17 patients with suspected necrotizing fasciitis, 11 cases were ultimately confirmed to be necrotizing fasciitis (at surgery or, in 1 case, on autopsy), and 6 were confirmed to be cellulitis on the basis of the clinical course<sup>33</sup>; on MRI, all 11 cases of necrotizing fasciitis were identified (100 percent sensitivity), but 1 of the 6 cases of cellulitis was misdiagnosed (for a specificity of 86 percent). The criteria for identifying necrotizing fasciitis on MRI include the involvement of deep fasciae, as evidenced by fluid collection, thickening, and enhancement with contrast material.

Ultrasonography and CT are of less value in distinguishing necrotizing fasciitis from cellulitis, but ultrasonography can be helpful in detecting the subcutaneous accumulation of pus as a complication of cellulitis and can aid in guiding aspiration.<sup>34</sup> Gallium-67 scintigraphy may aid in the

**Table 3. Initial Treatment for Cellulitis at Specific Sites or with Particular Exposures.**

Variable	Bacterial Species to Consider*	Standard Antimicrobial Therapy†	Alternative Antimicrobial Agents
Buccal cellulitis	<i>H. influenzae</i>	Ceftriaxone (1–2 g/day intravenously)	Meropenem or imipenem–cilastatin
Limb-threatening diabetic foot ulcer	Aerobic gram-negative bacilli (Enterobacteriaceae, <i>P. aeruginosa</i> , acinetobacter); anaerobes (bacteroides, peptococcus)	Ampicillin–sulbactam (3 g intravenously every 6 hr)	Meropenem or imipenem–cilastatin; clindamycin plus a broad-spectrum fluoroquinolone (ciprofloxacin or levofloxacin); metronidazole plus a fluoroquinolone or ceftriaxone
Human bites	Oral anaerobes (bacteroides species, peptostreptococci); <i>Eikenella corrodens</i> ; viridans streptococci; <i>S. aureus</i>	Amoxicillin–clavulanate (500 mg orally every 8 hr)	Penicillin plus a cephalosporin
Dog and cat bites	<i>P. multocida</i> and other pasteurella species; <i>S. aureus</i> , <i>S. intermedius</i> , <i>Neisseria canis</i> , <i>Haemophilus felix</i> , <i>Capnocytophaga canimorsus</i> ; anaerobes	Amoxicillin–clavulanate (500 mg orally every 8 hr)	Moxifloxacin plus clindamycin
Exposure to salt water at site of abrasion or laceration	<i>Vibrio vulnificus</i>	Doxycycline (200 mg intravenously initially, followed by 100–200 mg intravenously per day in 2 divided doses)‡	Cefotaxime; ciprofloxacin
Exposure to fresh water at site of abrasion or laceration or after the therapeutic use of leeches	Aeromonas species	Ciprofloxacin (400 mg intravenously every 12 hr) or ceftazidime plus gentamicin‡	Meropenem or imipenem–cilastatin
Working as a butcher, fish or clam handler, veterinarian	<i>Erysipelothrix rhusiopathiae</i>	Amoxicillin (500 mg orally every 8 hr) for mild skin infections; penicillin G (12 million–20 million units intravenously daily) for bacteremic infections or endocarditis	Ciprofloxacin or cefotaxime or imipenem–cilastatin

\* These bacterial species should be considered in addition to the common pathogens.

† Doses given are for adults with normal renal function; the duration of treatment should be 7 to 15 days or longer, depending on the clinical response.

‡ Treatment is to be given along with antimicrobial agents targeted to the common pathogens.

detection of cellulitis superimposed on recently increasing, chronic lymphedema of a limb.<sup>35</sup>

#### ANTIMICROBIAL TREATMENT

Because most cases of cellulitis are caused by streptococci and *S. aureus*, beta-lactam antibiotics with activity against penicillinase-producing *S. aureus* are the usual drugs of choice. Initial treatment should be given by the intravenous route in the hospital if the lesion is spreading rapidly, if the systemic response is prominent (e.g., chills and a fever, with temperatures of 100.5°F [37.8°C] or higher), or if there are clinically significant coexisting conditions (such as immunocompromise, neutropenia, asplenia, preexisting edema, cirrhosis, cardiac failure, or renal insufficiency) (Table 4). Specially tailored treatment for other bacterial causes is warranted when cellulitis occurs after an unusual exposure (a human or animal bite or exposure to salt or fresh water), in patients with certain underlying conditions (neutropenia, splenectomy, or im-

munocompromise), or in the presence of bullae (Table 3). Diabetic foot infections involve multiple potential pathogens, and broad antimicrobial coverage is required.<sup>31</sup> Ampicillin-sulbactam and imipenem-cilastatin were shown in a randomized, double-blind trial to have similar cure rates in this setting (81 percent vs. 85 percent), but the former combination was more cost effective.<sup>38</sup>

Several trials have evaluated newer antibiotics. In a multicenter, double-blind trial involving 461 patients, oral ciprofloxacin (750 mg every 12 hours) was as safe and effective as parenteral cefotaxime (overall failure rate, 2 percent vs. 8 percent;  $P=0.008$ ) in the treatment of various skin and skin-structure infections.<sup>39</sup> The evaluation of these results must be tempered by the facts that most of the skin infections studied were infected ulcers and abscesses rather than cellulitis and that, since the time of the study, the fluoroquinolone resistance of *S. aureus*, the predominant pathogen isolated, has increased. More recently, oral moxifloxacin (400

**Table 4. Antimicrobial Treatment for a Usual Case of Cellulitis.\***

Initial Treatment	Subsequent Treatment
Cefazolin, 1.0 g intravenously every 6–8 hr	Dicloxacillin, 0.5 g orally every 6 hr or Cephadrine, 0.5 g orally every 6 hr or Cephalexin, 0.5 g orally every 6 hr or Cefadroxil, 0.5–1.0 g orally every 12–24 hr
or	
Nafcillin, 1.0 or 1.5 g intravenously every 4–6 hr	Same as above
or	
Ceftriaxone, 1.0 g intravenously every 24 hr†	Same as above
or	
Cefazolin, 2.0 g intravenously once daily, plus probenecid (1.0 g orally once daily)‡	Same as above
If methicillin-resistant <i>S. aureus</i> is suspected or patient is highly allergic to penicillin	
Vancomycin, 1.0–2.0 g intravenously daily	Linezolid, 0.6 g orally every 12 hr
or	
Linezolid, 0.6 g intravenously every 12 hr	Same as above

\* Doses given are for adults; patients should be switched to oral therapy when they are afebrile and skin findings begin to resolve (after approximately three to five days). The total duration of treatment should be 7 to 14 days or longer, depending on the rate of response. Treatment should last longer in cases with associated abscesses, tissue necrosis, or underlying skin process (e.g., infected ulcer).

† Ceftriaxone has the advantage of allowing early discharge home with intravenous doses of 1.0 g daily.<sup>36</sup>

‡ Cefazolin-probenecid is given as a substitute for a once-daily parenteral third-generation cephalosporin. It has been shown to be similar in efficacy to ceftriaxone (1.0 g intravenously once daily) in home-based therapy for moderate-to-severe cellulitis in adults.<sup>37</sup>

mg once daily) has been shown to be as effective (84 percent) as oral cephalexin (500 mg three times a day) in the treatment of uncomplicated skin and soft-tissue infections.<sup>40</sup>

In a randomized, open-label trial of treatment of “complicated” skin and skin-structure infections in which high-dose levofloxacin (750 mg intravenously once daily) was compared with ticarcillin–clavulanate (3.1 g intravenously every four to six hours), therapeutic equivalence was demonstrated (success rates of 84 percent and 80 percent, respectively).<sup>41</sup> However, cellulitis (as a complication of preexisting skin lesions, immunosuppression, or vascular insufficiency) accounted for only 7 percent of the 399 skin infections. Linezolid (600 mg intravenously every 12 hours) has been compared with oxacillin (2 g intravenously every 6 hours) in a randomized, double-blind trial of treatment of complicated skin and soft-tissue infections in 819 hospitalized adults,<sup>42</sup> 44 percent of whom had cellulitis. The cure rates were 89 percent for linezolid and 86 percent for oxacillin. Clinically relevant pathogens isolated from contiguous sites included *S. aureus* (in 35 percent), group A streptococci (in 11 percent), and group B streptococci (in 27 percent), but infections due to methicillin-resistant *S. aureus* were excluded. A trial comparing linezolid and vancomycin in the treatment of adults with methicillin-resistant *S. aureus* infections, including 175 skin and soft-tissue infections,<sup>43</sup> found similar cure rates (79 percent with linezolid and 73 percent with vancomycin), but cellulitis accounted for only 13 percent of these infections.

#### ANCILLARY MEASURES

The local care of cellulitis involves the elevation and immobilization of the involved limb to reduce swelling and cool sterile saline dressings to remove purulence from any open lesion. Interdigital dermatophytic infections should be treated with a topical antifungal agent until they have been cleared. Such lesions may provide ingress for infecting bacteria. Several classes of topical antifungal agents are effective in clearing up fungal infection when applied one to two times daily; these include imidazoles (clotrimazole and miconazole), allylamines (terbinafine), and substituted pyridones (ciclopirox olamine).<sup>44</sup> Observational data suggest that after the successful treatment of such dermatophytic infections, the subsequent prompt use of topical antifungal agents at the earliest evidence of recurrence (or prophylactic application once or twice

per week) will reduce the risk of recurrences of cellulitis.

Patients with peripheral edema are predisposed to recurrent cellulitis. Support stockings, good skin hygiene, and prompt treatment of tinea pedis can prevent recurrences. In patients who, despite these measures, continue to have frequent episodes of cellulitis or erysipelas, the prophylactic use of penicillin G (250 to 500 mg orally twice daily) may prevent additional episodes; if the patient is allergic to penicillin, erythromycin (250 mg orally once or twice daily) may be used.

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#### AREAS OF UNCERTAINTY

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A variety of antimicrobial agents have been used to treat cellulitis because of their spectrum of action against likely causative organisms and have been approved by the Food and Drug Administration for use in skin and soft-tissue infections. However, such approval is often based on clinical studies of heterogeneous collections of cutaneous infections (including infected ulcers, abscesses, and wound infections); in some studies, cellulitis accounts for a minority of the infections.<sup>39,43</sup>

Most studies of cellulitis have involved patients with serious infections. Studies are needed to determine specific criteria that define the types of mild cases that are highly likely to respond to oral antibiotics administered at home. Penicillinase-resistant penicillins and cephalosporins have been used because most community-acquired pathogens causing cellulitis (streptococci and *S. aureus*) are susceptible to methicillin. However, the rate of community-acquired methicillin-resistant *S. aureus* infections in patients without identified risk factors appears to be increasing. In a rural Native American community, 55 percent of 112 isolates of *S. aureus* were methicillin-resistant, and 74 percent of these cases were community-acquired; the risk factors did not differ from those in patients with community-acquired methicillin-susceptible strains.<sup>45</sup> It remains uncertain how this change in resistance patterns will affect the management of cellulitis.<sup>46</sup>

Although there is a rationale for the empirical prophylactic use of penicillin to prevent recurrences of cellulitis in patients with multiple previous episodes, the results of efficacy studies have been conflicting. In a study of prophylaxis with monthly intramuscular doses of penicillin G benzathine (1.2 million units) after treatment for an acute episode of streptococcal cellulitis in the lower leg, such

prophylaxis reduced the rate of recurrence from 17 percent to 0 (0 of 11) among patients who did not have predisposing factors, but it failed to prevent recurrence in those who had such predisposing factors as lymphedema (4 of 20 cases).<sup>47</sup> Whether it would be more effective to shorten the interval between doses to two or three weeks or to increase the dose is not known. Long-term erythromycin therapy (250 mg orally twice daily for 18 months) has been used to prevent recurrences in patients with a history of two or more episodes of cellulitis or erysipelas.<sup>48</sup> Episodes did not occur in 16 treated patients, whereas 8 of 16 controls had one or more recurrences.

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#### GUIDELINES

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Guidelines for the treatment of skin and soft-tissue infections (including cellulitis) are being prepared by the Infectious Diseases Society of America.

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#### SUMMARY AND RECOMMENDATIONS

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Cellulitis is a clinical diagnosis based on the spreading involvement of skin and subcutaneous tissues with erythema, swelling, and local tenderness, accompanied by fever and malaise. The approach to

therapy involves the identification of the likely source as either local (secondary to abrasion or ulcer or due to another exposure, such as an animal bite or seawater, which implicates particular bacterial species — *P. multocida* and *V. vulnificus*, respectively) or an uncommon bacteremic spread of infection. Distinctive features of the patient (such as the presence of diabetes or immunocompromise) or anatomical sites should also be considered in treatment decisions. Streptococci (groups A, G, and B) and *S. aureus* are the most frequently isolated bacterial species.

Initial empirical antimicrobial treatment for moderate or severe cellulitis in a patient such as the one described in the vignette would thus consist of an intravenous cephalosporin (cefazolin or ceftriaxone) or nafcillin (vancomycin in patients with an allergy to penicillin), followed by dicloxacillin or an oral cephalosporin, generally for a course of 7 to 14 days. In patients with recurrent cellulitis of the leg, any fissures in the interdigital spaces caused by epidermophytosis should be treated with topical antifungal agents in order to prevent recurrences. Daily prophylaxis with oral penicillin G (or amoxicillin) should be considered for patients who have had more than two episodes of cellulitis at the same site.

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