Cellulitis
A Review

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Cellulitis is a bacterial infection of the skin, presenting with expanding erythema, warmth, tenderness, and swelling. Cellulitis is a common global health burden, with more than 650,000 admissions per year in the United States alone.

Methods

A literature search of the entire PubMed database was conducted with search terms and synonyms for cellulitis. The search was performed on October 9, 2014, and repeated on August 28, 2015. The initial search identified 10,154 articles and the updated search identified an additional 306. Studies published in non-English languages (unless translated), and studies involving exclusively children or animals were excluded. Meta-analyses, systematic reviews, references cited in published clinical practice guidelines, and antibiotic reference tools were also reviewed. Bibliographies of the retrieved studies and previous reviews were searched for other relevant studies. Initially, 595 articles were identified for full review, and of these, the most pertinent 125 were selected for inclusion. Articles were reviewed for the quality of evidence and contribution to current understanding of cellulitis, with priority given for clinical trials, large observational studies, and more recently published articles.

Results

Epidemiology

The majority of epidemiology studies on cellulitis rely on the International Classification of Diseases, Ninth Revision, codes (ie, 681.x and 682.x) that unfortunately link cellulitis and abscess, creating some limitations. However, these data remain valuable by providing a general scope of the problem and trends over time.

Cellulitis or abscess is a common diagnosis whose incidence is increasing and accounted for 10% of infectious disease-related US hospitalizations from 1998 to 2006, with annual US ambulatory...
Pathophysiology

Cellulitis is a deep dermal and subcutaneous infection that occurs when pathogens gain entry into the dermis through breaks in the skin. Cutaneous barrier disruption can be caused by toe web space bacteria, fungal foot infections (eg, tinea pedis, onychomycosis), pressure ulcers, and venous leg ulcers. Skin surface pathogenic organism colonization is reduced by the presence of a low surface pH, low temperature, and commensal microorganisms.

The histologic features of cellulitis are nonspecific and include dermal edema, lymphatic dilatation, and diffuse, heavy neutrophil infiltration around blood vessels. Later stages may also feature lymphocytes and histiocytes, along with granulation tissue.

Usually, cultures performed with needle aspiration or biopsy yield negative results, and when they are positive, the concentration of bacteria is low.6,7 This suggests that either a very small number of bacteria are responsible for the induction of the robust inflammatory response or the immune system reduces the number of viable bacteria to very low or nonexistent numbers by the time patients present for treatment. Bacterial toxins and other inflammatory mediators that trigger an escalating inflammatory response may better define the pathogenesis of cellulitis than the bacterial load itself.

Microbiology

Cellulitis in immunocompetent adults is usually thought to be caused by group A streptococci (Streptococcus pyogenes), with Staphylococcus aureus as a notable but less common cause.7 However, given the difficulty culturing cellulitis, the specific causative bacterium in most cases remains unknown, and several studies demonstrate conflicting evidence in regard to prevalence of causative organisms.6,8

A systematic review of 808 adult and pediatric cellulitis patients undergoing needle aspiration or punch biopsy found that only 16% of them had cultures that established a bacterial diagnosis.6 Among the positive culture results, 51% were for S aureus and 27% were for S pyogenes. Although abscess was excluded from the systematic review, purulent cellulitis was not, which may have skewed the microbiology toward S aureus.

Blood cultures identified bacteria in only 7.9% of 1578 patients assessed in a systematic review.8 Of these, 19% were S pyogenes, 38% were other β-hemolytic streptococci, 14% were S aureus, and 28% were gram-negative organisms.8 The authors postulated that the high proportion of gram-negative bacteria might be due to inclusion of immunocompromised patients and those with cirrhosis, exposure to aquatic injuries, or animal bites (discussed with other uncommon causes of cellulitis in the Box).8 In addition, patients included in these studies reviewed may have had a greater disease burden, resulting in a greater likelihood that they would have systemic signs of infection and undergo blood culture examination than the typical cellulitis patient. Because most cellulitis is treated empirically, bacterial pathogens are rarely identified in the disease, making it impossible to know the true frequency of bacterial etiologies.

There has been increasing concern about antibiotic-resistant bacteria, such as community-acquired methicillin-resistant S aureus (MRSA), which is reflected in the increased use of anti-MRSA antibiotics (eg, vancomycin, trimethoprim-sulfamethoxazole, doxycycline, clindamycin) and broad-spectrum gram-negative antibiotics (eg, β-lactam/β-lactamase inhibitors, levofloxacin, ceftriaxone) during the past decade.40 However, most cases of cellulitis do not involve gram-negative organisms, and in cases of nonpurulent and uncomplicated cellulitis, the addition of antibiotics against community-acquired MRSA did not improve outcomes.41 As such, narrow-spectrum antibiotics against Streptococcus and methicillin-sensitive S aureus remain appropriate. In purulent cellulitis (presence of a pustule, abscess, or purulent drainage), S aureus infection is more likely, as demonstrated by a study of 422 patients who presented with “purulent skin and soft tissue infections” to 11 emergency departments throughout the United States, in which skin surface swab cultures revealed MRSA in 59% of patients, methicillin-sensitive S aureus in 17%, and β-hemolytic streptococci in 2.6%.42 Because methicillin-sensitive S aureus and MRSA can be difficult to differentiate according to clinical features alone,43 MRSA should be considered for purulent infections in known high-risk populations, such as athletes, children, men who have sex with men, prisoners, military recruits, residents of long-term care facilities, individuals with previous MRSA exposure, and intravenous drug users.44

Clinical Presentation

Cellulitis usually presents as an acute, spreading, poorly demarcated area of erythema. The skin findings in cellulitis follow the classic signs of inflammation: dolor (pain), calor (heat), rubor (erythema), and tumor (swelling). Additional clinical features may include edematous skin lymphatics, leading to a peau d’orange (orange peel) appearance; bulla formation; or inflamed lymphatics proximal to the area of cellulitis, leading to linear erythematous streaks or lymphangitis (Figure 1). Inflammation in the lymphatics may also result in regional tender lymphadenopathy. Cellulitis is nearly always unilateral.45 It is typically found on the lower extremities, although it can appear on any area of the skin and is often found in the upper extremities in patients who are intravenous drug users.46 The presence of fever is variable, ranging from 22.5% to 77.3%, although these estimates may be high because the studies reporting fever examined emergency department or inpatient populations and not outpatient populations.47

Erysipelas is an infection of the superficial dermis and lymphatics presenting as a sharply demarcated, bright-red area of raised skin.8 Given similar etiologies,6 it may be argued that erysipelas is a type of cellulitis. This review will consider erysipelas within the context of cellulitis because risk factors, diagnosis, and management of erysipelas are similar to those for cellulitis.

Necrotizing fasciitis is a rare but serious skin and soft tissue infection of the subcutaneous tissue and fascia that is rapidly progressive and destructive, with a high mortality rate. It may resemble cellulitis, with spreading skin erythema; however, the skin may initially
be spared. It presents with pain out of proportion to clinical findings, edema, skin necrosis, bullae, cutaneous numbness, fever, or crepitus.49 It is important to recognize necrotizing fasciitis because prompt treatment with surgical management is required.

The distinction between an abscess—a collection of pus within the dermis or subcutaneous space—and cellulitis can be made on examination or using ultrasound and has important pathogenic and treatment implications. Abscesses are more likely to be due to S aureus and are primarily treated with incision and drainage.50 Abscesses and cellulitis may coexist within the same patient, leading to treatment failure and necessitating careful examination, imaging as needed, and patient-specific treatment.

**Risk Factors**

Systemic and local risk factors associated with the development of primary and recurrent cellulitis are listed in Table 1. The most commonly associated risk factor for cellulitis is edema, especially lymphedema because lymphatic fluid is thought to facilitate bacterial growth. Morris63 found that 77% of patients with cellulitis had a portal of entry for infection, 50% being a superficial fungal infection, usually tinea pedis, with or without concomitant onychomycosis. Immunosuppression, alcohol intake, diabetes, and smoking were not associated with increased risk of acute cellulitis.45,52,56,61

**Assessment and Diagnosis**

Because cultures are usually unrevealing, most cellulitis cases are diagnosed by history and physical examination alone. Routine or uncomplicated cellulitis in patients without comorbidities or complications (eg, fever, diabetes, other immunosuppressive disorders) does not usually require laboratory testing. Elevations in white blood cell counts, erythrocyte sedimentation rate, or C-reactive protein levels are observed in 34% to 50%,64-66 59% to 91%,64-66 and 77% to 97% of patients,64,65 respectively. However, these laboratory tests are not specific for cellulitis. The identification of a causative

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**Box. Uncommon Causes of Cellulitis, by Comorbidity and Associated Pathogens**

Immunosuppression (eg, transplant, systemic steroids, HIV/AIDS, SLE)

Streptococcus pneumoniae20-23

Mycobacterium tuberculosis22,23

Escherichia coli24

Campylobacter15

Serratia marcescens16

Haemophilus influenzae27,28

Helicobacter cinaedi29

Shewanella putrefaciens30

Cryptococcus neoformans31-34

Cryptococcus gattii35

Chronic liver disease

Vibrio spp (V vulnificus or V cholerae)26-28

E coli29,30

Pseudomonas aeruginosa30

Campylobacter15

Acinetobacter30

Neisseria gonorrhoeae31

Burkholderia cepacia32

S putrefaciens30

Enterobacteriaceae spp33

Chronic kidney disease

V vulnificus

V alginolyticus34

Neisseria meningitidis35

E coli35

Aquatic soft tissue injury

Vibrio spp36

Aeromonas spp36

Mycobacterium marinum36

Shewanella spp36

Streptococcus iniae36

Erysipelothrix rhustopathiae36

Animal and human bites

Dog and cat37,38

Pasteurella

Streptococcus

Staphylococcus

Neisseria

Corynebacterium

Morganella

Fusobacterium

Porphyromonas

Prevotella

Bacteroides

Propionibacterium

Human39

α- and β-hemolytic Streptococcus

S aureus

S epidermidis

Corynebacterium spp

Eikenella corrodens

Bacteroides fragilis

Prevotella

Porphyromonas

Peptostreptococcus

Fusobacterium

Veillonella

Clostridium spp

Exotic animals: reviewed by Abrahamian and Goldstein37

Abbreviations: HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

* Patients presenting with particular comorbidities or in certain clinical contexts should alert clinicians to consider uncommon organisms. Immunosuppression, cirrhosis, renal disease, aquatic injury, or bites carry increased risks for particular pathogenic organisms.
organism in cellulitis through traditional culture methods, whether blood, needle aspiration, or punch biopsy, is typically of low yield and not recommended.\textsuperscript{7,8,67} However, patients who are at increased risk for complicated cellulitis or have abnormal exposure history (Box) should be considered for possible needle aspiration or punch biopsy culture.\textsuperscript{7}

Skinsurface swab cultures, especially those of chronic wounds or ulcers, are commonly polymicrobial\textsuperscript{68} or colonized with multidrug-resistant pathogens\textsuperscript{69} that are not involved in the etiology of underlying cellulitis. Therefore, caution must be taken when interpreting or pursuing surface cultures because they can often lead to unnecessarily broad antibiotic therapy.\textsuperscript{70} The Infectious Diseases Society of America does not recommend routine swab cultures in the management of infected ulcers.\textsuperscript{7} Purulent infections, such as pustules or abscesses, however, should be drained and cultured.

Procalcitonin is a surrogate biomarker for the early detection or ruling out of bacterial infections. Since its first description in 1993,\textsuperscript{71} it has been used for a variety of bacterial diseases (eg, pneumonia, sepsis) to guide initiation and termination of antibiotics; however, studies exploring its utility in skin and soft tissue infections are limited.\textsuperscript{72-74} The only study to compare patients with cellulitis to a clinical mimic of cellulitis (deep vein thrombosis) demonstrated that procalcitonin had a sensitivity of 58.1%, specificity of 82.4%, positive likelihood ratio of 3.3, and negative likelihood ratio of 0.5 (cutoff $\geq 0.1 \mu g/L$).\textsuperscript{74} Further studies are required before procalcitonin can be recommended broadly.

The image in panel A provided courtesy of Daniel Sugai, MD, Massachusetts General Hospital Dermatology, Boston. The image in panel B provided courtesy of Anthony Cukras, MD, PhD, Beth Israel Deaconess Medical Center Dermatology, Boston.
In cases of suspected necrotizing fasciitis, early surgical assessment is recommended; however, laboratory testing may help differentiate cellulitis from early evolving necrotizing fasciitis. Wall et al. found in a modeling study that a white blood cell count greater than 15,400 cells/mm³ or serum sodium level less than 135 mEq/L could suggest a diagnosis of necrotizing fasciitis with a sensitivity of 90%, specificity of 76%, positive likelihood ratio of 3.75, and negative likelihood ratio of 0.13. Similarly, Wong et al. developed the Laboratory Risk Indicator for Necrotizing Fasciitis score accounting to white blood cell count and levels of C-reactive protein, hemoglobin, serum sodium, creatinine, and serum glucose, which had a sensitivity of 90%, specificity of 95%, positive likelihood ratio of 19.95, and negative likelihood ratio of 0.10. Finally, Murphy et al. identified that for necrotizing fasciitis among cases in their series, a serum lactate level of 2.0 mmol/L had a sensitivity of 100%, specificity of 76%, positive likelihood ratio of 4.17, and negative likelihood ratio of 0. All of these tests are offered as adjunctive tools, along with history, physical examination, and surgical exploration, to guide diagnosis of necrotizing fasciitis.

Imaging studies are not diagnostic of cellulitis but can help distinguish it from more severe forms of infection and can identify drainable fluid collections, such as abscesses. Osteomyelitis can sometimes complicate cellulitis and when suspected can be best ruled out with magnetic resonance imaging or radiography, if chronic. Furthermore, magnetic resonance imaging or computed tomography can help differentiate cellulitis from necrotizing fasciitis or pyomyositis. The appearance of gas on computed tomography scan in the absence of soft tissue trauma or a rim-enhancing fluid collection, as would be found with an abscess, is considered pathognomonic of, but not requisite for, a diagnosis of necrotizing fasciitis. A recent study evaluating the utility of modern-day computed tomography scanners demonstrated a positive predictive value of 76% and a negative predictive value of 100% and found that only 36% of cases of necrotizing fasciitis included gas.

For the identification of drainable pus collections, the most widely used modalities are ultrasonography or magnetic resonance imaging. Ultrasonography can detect occult abscesses, prevent unnecessary invasive procedures, and provide guidance for further imaging. In a systematic review on ultrasonography in detecting cutaneous abscesses, the sensitivity ranged from 89% to 98% and the specificity ranged from 64% to 88%. In comparison, the sensitivity of clinical assessment ranged from 75% to 90% and the specificity ranged from 55% to 83%. Therefore, ultrasonography could potentially aid abscess diagnosis, especially in cases of indeterminate clinical assessment.

Although the use of compression ultrasonography to rule out deep vein thrombosis in hospitalized patients with cellulitis is common practice, studies show that the risk of deep vein thrombosis in patients with cellulitis is low (incidence rate 3.1% for any deep vein thrombosis; n = 1054). The rate of acute ipsilateral deep vein thrombosis was 0.75% (1/133) and matched the rate of acute contralateral deep vein thrombosis. Furthermore, the majority of deep vein thromboses found (8/133) were previously diagnosed; therefore, overuse of compression ultrasonography rarely changed practice. Unless clinical suspicion is high or the patient is not responding to appropriate first-line therapy, the routine use of compression ultrasonography to rule out deep vein thrombosis in hospitalized patients with cellulitis is not recommended.

Ultimately, the 2014 Infectious Diseases Society of America guidelines recommend against performing routine blood, skin aspirate, swab, or biopsy cultures. Instead, blood cultures are strongly recommended and tissue cultures are recommended only for patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites.

### Differential Diagnosis

There are no gold standard diagnostic techniques to confirm a diagnosis of cellulitis, and therefore the clinical presentation and assessment are relied on. Unfortunately, the well-taught clinical tetrarc of dolor, calor, rubor, and tumor was actually first ascribed to inflammation rather than infection, and as such there are many conditions, known collectively as pseudocellulitis, that generate cutaneous inflammation and clinically mimic cellulitis (Figure 1, Table 2). These also can induce fever, malaise, or leukocytosis, further confusing the picture. Misdiagnosis rates have been estimated to be as high as 33%, with patients usually referred to the hospital because they are not improving with conventional therapy for cellulitis. In the subgroup of hospitalized patients with cellulitis who required dermatology consultation, the misdiagnosis rate was 74%. Stasis dermatitis is the condition that most often mimics cellulitis. It is distinguished by its bilateral nature because bilateral cellulitis in the absence of skin trauma is extremely rare, and alternate diagnoses should be evoked before a diagnosis of bilateral cellulitis is conferred. In addition, unilateral presentations of stasis dermatitis can occur, particularly with a history of unilateral leg injury or anatomical variation such as varicosities. Another common condition that can be mistaken for cellulitis is hematomata, often found in patients with a history of trauma or anticoagulation; it can be confirmed with ultrasonography. Gout is also frequently confused for cellulitis, especially because it can present with fever or leukocytosis and serum uric acid level may not be elevated, and it should be considered in cases in which the erythema overlies a joint. A trial of nonsteroidal anti-inflammatory drugs or joint aspiration can help distinguish gout from cellulitis.

Several infrequent conditions can easily be confused with cellulitis but must be recognized early to facilitate initiation of appropriate therapy. These include erythema migrans and calciphylaxis. Although an annular erythematous lesion is most characteristic of erythema migrans, the majority of cases present with homogenous erythema that self-resolves and leads to adverse sequelae if left...
### Cellulitis Differential Diagnoses

**Infectious**

**Common**
- Erythema migrans, herpes simplex, herpes zoster, cutaneous abscess

**Uncommon**
- Bacterial (e.g., erysipelas, necrotizing fasciitis); viral (e.g., parvovirus B19, CMV); fungal (e.g., Cryptococcus neoformans, Sporothrix schenckii, mucormycosis); mycobacterial; parasites (e.g., Trypanosoma cruzi, Dermatobia hominis [myiasis]); osteomyelitis; septic joint

**Inflammatory**

**Common**
- Drug reactions; contact dermatitis; angioedema; Sweet syndrome; gout; acute bursitis; erythema nodosum

**Uncommon**
- Fixed drug reaction; pyoderma gangrenosum; sarcoidosis; eosinophilic cellulitis (Well syndrome); relapsing polychondritis; familial Mediterranean fever; polyarteritis nodosa; panniculitis (e.g., lipodermatosclerosis, morphea, eosinophilic fasciitis, traumatic, pancreatic, lupus); cutaneous GVHD

**Vascular**

**Common**
- Venous stasis dermatitis; lymphedema; deep vein thrombosis; superficial thrombophlebitis; hematoma

**Uncommon**
- Erythromelalgia; calciphylaxis

**Neoplastic**

**Uncommon**
- Carcinoma erysipeloides; Paget disease of the breast; extramammary Paget disease; inflammatory breast carcinoma; lymphoma; leukemia

**Miscellaneous**

**Common**
- Insect bites/stings; reaction to foreign body implant (e.g., metal, mesh, silicone or paraffin injections); postcutaneous injection; intravenous line infiltration

**Uncommon**
- Compartment syndrome; radiation recall; pressure/coma bullae

Abbreviations: CMV, cytomegalovirus; GVHD, graft-vs-host disease.

*Common and uncommon conditions that present similarly to cellulitis. Based on data from Falagas and Vergidis* [86] and Kroshinsky et al. [87]

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untreated. These lesions, however, are well demarcated; in contrast, cellulitis is poorly demarcated. Although calciphylaxis is considered to present with retiform purpura or ulceration, early lesions can present analogously to cellulitis, although patients typically have severe pain out of proportion to physical examination findings and which is greater than that routinely observed with cellulitis. Calciphylaxis should be considered in these cases, particularly in at-risk populations such as patients with end-stage renal disease, diabetes, obesity, or liver disease, or those receiving warfarin.

In general, failure to respond to appropriate therapy, or multiple, symmetric, long-standing, or slowly progressive lesions warrant consideration of an alternate diagnosis (Table 2).

### Treatment

Despite published guidelines, little evidenced-based agreement exists on a preferred antibiotic approach to cellulitis. A Cochrane review of 25 randomized controlled clinical studies on the diagnosis and management of cellulitis could not provide treatment recommendations because no 2 studies used the same treatment regimen. A [review of cellulitis management in 5 urban Canadian emergency departments demonstrated substantial practice variation, with 25 different initial treatment regimens identified and 40 different antibiotic regimens prescribed when patients were discharged from the emergency department. The treatment algo-
Figure 2. Treatment Algorithm for Nonpurulent Cellulitis

<table>
<thead>
<tr>
<th>Mild nonpurulent cellulitis</th>
<th>Moderate nonpurulent cellulitis</th>
<th>Severe nonpurulent cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No purulent drainage or pustules; no systemic signs of infection</td>
<td>No purulent drainage or pustules plus ≥1 SIRS criteria (temperature &gt;38°C or &lt;36°C, HR &gt;90/min, RR &gt;20/min, WBC count &gt;12,000 or &lt;4000/mm³)</td>
<td>No purulent drainage or pustules plus ≥2 SIRS criteria plus hypotension or immune compromise or rapid disease progression</td>
</tr>
</tbody>
</table>

### Oral antibiotics
- Cephalexin or Doxycycline or Amoxicillin/VK or Penicillin VK or Amoxicillin/clavulanate
- If true penicillin allergy, Clindamycin<sup>a</sup>

### Intravenous antibiotics
- Ceftriaxone or Cefotaxime or Penicillin G
- If true penicillin allergy, Clindamycin<sup>a</sup>

### Intravenous antibiotic therapy
- Vancomycin or Daptomycin or Ceftaroline or Telavancin or Tigecycline

24-48 hours. If unresponsive after 24-48 hours, consider possible pseudocellulitis or resistant or atypical organisms.

<sup>a</sup> True penicillin allergy as per published criteria. For organisms not susceptible to clindamycin, azithromycin 500 mg orally once, then 250 mg/d for 4 days, or levofloxacin, 500 mg/d orally.

SIRS indicates systemic inflammatory response syndrome; HR, heart rate; RR, respiratory rate; WBC, white blood cells; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*. This algorithm is based on studies that used a prior definition for SIRS. SIRS is no longer included in the new definition of sepsis. Antibiotics are ordered by preference with first choice listed on top. Adjust antibiotic selection based on culture results, local resistance patterns, and clinical response after treatment failure.

Patients with purulent cellulitis that meet 1 criterion for SIRS (moderate cellulitis) can be initially treated with the same oral agents effective for mild disease according to suspected methicillin-sensitive *S aureus* or MRSA. Patients who meet 2 or more criteria for SIRS should be considered for intravenous antibiotics such as oxacillin, nafcillin, or cefazolin for suspected methicillin-sensitive *S aureus*, or vancomycin, clindamycin, or linezolid for suspected MRSA. A 2013 Cochrane review comparing oral linezolid with intravenous vancomycin for the treatment of skin and soft tissue infections demonstrated that linezolid had better clinical and microbiological cure rates overall (RR, 1.09 vs 1.08; 95% CI, 1.03-1.16 vs 1.01-1.16, respectively), as well as for MRSA infections (relative risk [RR], 1.09 vs 1.17; 95% CI, 1.03-1.17 vs 1.04-1.32, respectively), with a 3-day-shorter length of stay, leading to overall reduced costs despite linezolid use being more expensive. Clinicians should be aware of the increased cost, increased incidence of sepsis syndrome in patients concomitantly receiving a serotonergic agent (0.24%-4%), and increased risk of thrombocytopenia with long-term use (RR, 13.06; 95% CI, 1.72-99.22).

For patients with purulent cellulitis who meet SIRS criteria, as well as have hypotension, immunocompromise, or rapid progression (severe cellulitis), coverage for MRSA should be initiated with empirical intravenous vancomycin, clindamycin, linezolid, daptomycin, or ceftaroline. Patients should additionally be considered for surgical assessment for possible necrotizing disease with culture and sensitivity taken from any surgical obtained tissue. If culture sensitivities demonstrate methicillin-sensitive *S aureus*, coverage can be narrowed to oxacillin, nafcillin, cefazolin, or ceftriaxone.

In general, caution is required when clindamycin is administered to patients with known community-acquired MRSA because of inducible or constitutive clindamycin resistance. The use of clindamycin alone for MRSA should be based on local resistance patterns.

Novel antibiotics such as telavancin, tedizolid, dalbavancin, and oritavancin have recently been introduced as options to treat skin and soft tissue infections, including MRSA cellulitis. Telavancin has been shown to be noninferior to vancomycin but with an increased risk of nephrotoxicity. Tedizolid, a novel oxazolidinone with gram-positive activity including MRSA, is promising because it can be administered daily in oral or intravenous forms, and dalbavancin, a second-generation lipoglycopeptide that covers MRSA, can be administered as infrequently as once weekly. A single dose of oritavancin has been shown to be as effective as twice-daily intravenous vancomycin administered for 7 to 10 days. Given the...
increased risk of nephrotoxicity.\textsuperscript{108,111} Although MRSA is a significant problem, it has not yet been clearly demonstrated whether vancomycin-resistant and -intermediate \textit{S. aureus} plays a significant role.

The empirical use of antibiotics may be contributing to increasing rates of resistant organisms causing soft tissue infections. MRSA soft tissue infection rates increased from 26.2\% to 47.4\% between 1998 and 2004.\textsuperscript{110} The empirical use of vancomycin increased from 18\% in 2000 to 69\% in 2006, but low rates of bacterial activity and penetration into tissues, as well as underdosing and prolonged courses, have led to the increase of vancomycin-resistant and -intermediate \textit{S. aureus}.\textsuperscript{98,108} Antibiotics are ordered by preference with first choice listed on top. Adjust antibiotic selection based on culture results, local resistance patterns, and clinical response after 24-48 hours. If unresponsive after 24-48 hours, consider possible pseudocellulitis or resistant or atypical organisms.

For all cases of cellulitis, coverage should be narrowed according to culture results, response after 24-48 hours, and given risk factors. If symptoms are unresponsive after 24-48 hours, possible pseudocellulitis or resistant or atypical organisms should be considered. In immunocompromised patients, numerous organisms can cause cellulitis, and broader antimicrobial coverage should be considered for fungal, viral, and parasitic organisms in addition to bacteria. Early biopsy or aspiration for histologic and microbiological review should be conducted (Table 2).

### Duration of Therapy

The duration of treatment should be based on the clinical response. In general, treatment durations for outpatient cellulitis range from 5 to 10 days. Immunocompromised patients may require 7 to 14 days.\textsuperscript{7} Although the Food and Drug Administration mandates the pharmaceutical industry to evaluate for clinical response 48-72 hours after treatment initiation with novel antibiotics,\textsuperscript{112} some proposed this timeframe as a clinical guide for treatment failure.\textsuperscript{98} We recommend the following treatment regimens based on susceptible cultures and patient characteristics.

#### Figure 3. Treatment Algorithm for Purulent Cellulitis

<table>
<thead>
<tr>
<th>Suspected</th>
<th>MSSA</th>
<th>Culture and sensitivity</th>
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<tbody>
<tr>
<td>Oral antibiotics</td>
<td>Cephalexin or</td>
<td>Clavulanate</td>
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<td></td>
<td>Dicloxacillin or</td>
<td>Amoxicillin/</td>
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<td></td>
<td>Amoxicillin/</td>
<td>clavulanate</td>
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<td></td>
<td>Clindamycin\textsuperscript{a}</td>
<td></td>
</tr>
<tr>
<td>Suspected</td>
<td>MRSA</td>
<td>Culture and sensitivity</td>
</tr>
<tr>
<td>Intravenous antibiotics</td>
<td>Vancomycin or</td>
<td>Clindamycin\textsuperscript{a} or</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td>Suspected</td>
<td>MSSA</td>
<td>Culture and sensitivity</td>
</tr>
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\textsuperscript{a} True penicillin allergy as per published criteria.\textsuperscript{94,95} For organisms not susceptible to clindamycin, azithromycin 500 mg orally once, then 250 mg/d for 4 days, or levofloxacin, 500 mg/d orally.

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Dalletal.114 demonstrated that 100% (31/31) of patients receiving antibiotics plus ibuprofen had resolution of cellulitis in 4 to 5 days, whereas 24.2% (8/33) of patients receiving antibiotics alone required 6 to 7 days of treatment and 6.1% (2/33) required 7 or more days. There were no adverse sequelae to the addition of an anti-inflammatory. Intravenous antibiotics should be changed to oral administration after 48 hours of afebrile (<37.8°C) and regression of inflammation from skin markings.115

Preventive Measures

Regular foot examinations; dry skin care; treatment of tinea pedis, onychomycosis, or other chronic dermatoses; use of support hose and other tools for lymphedema control; and intensive wound care for ulceration can help prevent primary and recurrent cellulitis.116,117 In very specific patient populations with chronic recalcitrant lymphedema, lymphovenous anastomoses, lymphatic grafting, or lymphaticocutaneous bypass can be considered.117

Managing lymphedema was shown to reduce the incidence of cellulitis from 58% to 9%,118 with each pound (£) spent on lymphedema management saving £100 in hospital admission costs.119 The Red Legs Program in the United Kingdom saved £232 890 in 1 year by reducing 90% of admissions.120

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult Dosing</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td><strong>MSSA and Streptococcus Coverage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>875 mg 2 times/d orally</td>
<td>Streptococcal and MSSA coverage</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1 g every 8 h intravenously</td>
<td>For true penicillin-allergic patients, less bone marrow suppression than nafcillin</td>
</tr>
<tr>
<td>Ceftriaxime</td>
<td>600 mg every 12 h intravenously</td>
<td>Adjust for reduced creatinine clearance</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1-2 g/d intravenously</td>
<td></td>
</tr>
<tr>
<td>Cephalaxime</td>
<td>500 mg 4 times/d orally</td>
<td>Exceptions in true penicillin-allergic patients with immediate hypersensitivity reactionsb</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>250-500 mg 4 times/d orally</td>
<td>Oral agent of choice for MSSA</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td>500 mg every 6 h intravenously</td>
<td>Not to exceed 50 mg/kg or 4 g/d, whichever is lower</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g every 8 h intravenously</td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td>1-2 g every 4 h intravenously</td>
<td>Parenteral drug of choice in MSSA</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>1-2 g every 4 h intravenously</td>
<td>Parenteral drug of choice in MSSA</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>2-4 million U every 4-6 h intravenously</td>
<td></td>
</tr>
<tr>
<td>Penicillin VK</td>
<td>250-500 mg every 6 h orally</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/taxobactam</td>
<td>3.375 g every 6 h intravenously</td>
<td></td>
</tr>
<tr>
<td><strong>MRSA Coverage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>300-450 mg 4 times/d orally</td>
<td>Potential inducible resistance in MRSA</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>4 mg/kg every 24 h intravenously</td>
<td>Risk of Clostridium difficile infection</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg 2 times/d orally</td>
<td>Possible photosensitivity</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg every 12 h orally</td>
<td>Costly (600-mg tablet, $184; 2 mg/mL [300 mL]; $9696)</td>
</tr>
<tr>
<td>Minocycline</td>
<td>100 mg 2 times/d orally</td>
<td>Variable antistreptococcal activity</td>
</tr>
<tr>
<td>Telavancin</td>
<td>10 mg/kg every 24 h intravenously (infused during 1 h)</td>
<td>Costly (250 mg, $238.9696)</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100 mg followed by 50 mg every 12 h intravenously</td>
<td>Adjust for severe liver impairment</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>1-2 double-strength tablets 2 times/d orally</td>
<td>Increased risk of blistering skin reactions Poor streptococcal coverage</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg every 12 h intravenously</td>
<td>Parenteral agent of choice for MRSA infections</td>
</tr>
</tbody>
</table>

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Table 3. Standard Antimicrobial Dosing for Staphylococcal and Streptococcal Skin Infectionsa

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aBased on published guidelines.7,97,98 Doses are standard based on normal adult weight and renal function.

bTrue penicillin allergy as per published criteria.94,95

Abbreviations: MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive S. aureus.
Complications
Appropriate identification and prompt treatment of cellulitis are necessary. There is a low but real risk of subsequent bacteremia, more often arising in cases of streptococcal disease relative to staphylococcal or gram-negative infections. Endocarditis, glomerulonephritis, osteomyelitis, toxic shock, and elephantiasis verrucosa nostra can also develop. Cellulitis can damage lymphatics, and the subsequent lymphedema predisposes patients to recurrent episodes of cellulitis. The risk of mortality in uncomplicated, nonpurulent cellulitis is very low, even in hospitalized patients.40

Recurrent Cellulitis
Recurrent cellulitis is common, with 22% to 49% of patients who have cellulitis reporting at least 1 previous episode of the disease.45,52,56,61,62 Recurrences occur in approximately 14% of cellulitis cases within 1 year and in 45% of cases within 3 years. These tend to occur in the same location.52,63,121 When hospitalized, patients with recurrent cellulitis require longer hospitalizations relative to nonrelapsing cellulitis patients.61 When recurrent disease occurs, identification and treatment of predisposing conditions such as edema, obesity, eczema, venous insufficiency, and toe web space abnormalities should be pursued to help prevent repeated infections.7 Additional risk factors for recurrent cellulitis are listed in Table 1.

Prophylactic Therapy
Prophylactic antibiotics, although controversial, can be considered for patients with 3 to 4 episodes of cellulitis per year who have optimized control of risk factors. Proposed regimens include oral penicillin 250 mg or 1 g twice daily, erythromycin 250 mg twice daily, dicloxacillin 500 mg orally twice daily, clindamycin 150 mg orally every day, and intramuscular benzathine penicillin 1.2 million U/mo for durations as variable as 4 to 52 weeks.7,122 Although a meta-analysis of 5 studies conducted from 1991 to 2012 concluded that antibiotic prophylaxis may prevent cellulitis in patients with at least 1 episode of cellulitis (RR, 0.46; 95% CI, 0.26-0.79), the reduction was not statistically significant for the target group of patients with 2 or more episodes of cellulitis (RR, 0.35; 95% CI, 0.12-1.02).123 However, there were few analyzed studies and they were heterogeneous, varying not only in duration of therapy (6, 12, or 18 months or unspecified) but also in antibiotic type, dosage used, monitoring of adverse events, and duration of follow-up.123

A subsequent 2013 double-blinded, randomized controlled trial of 274 patients with 2 or more episodes of cellulitis who were randomized to penicillin 250 mg twice daily vs placebo for 12 months demonstrated that prophylaxis significantly reduced the risk of recurrent leg cellulitis; however, the effect diminished when penicillin was discontinued.124 In addition, several factors were predictive of prophylaxis failure, including body mass index greater than or equal to 33 (P = .01), 3 or more previous episodes of cellulitis (P = .001), and preexisting edema (P = .06).124 Long-term prophylaxis for staphylococcal cellulitis has not been studied.123

Although antibiotic prophylaxis may be cost-effective,17,22,23 cost-benefit analysis has to be taken into account, considering triggering of allergy, drug reaction, drug resistance, and Clostridium difficile infection. Because of these risks, along with conflicting study conclusions, further analysis is required before standard recommendations on prophylaxis can be imparted.

Despite antibiotic prophylaxis, cellulitis may recur with no identifiable cause in 22% of cases,124 underscoring the need to consider alternative diagnoses in cases of recurrence. In fact, the UK National Institute for Health and Care Excellence clinical knowledge summary recommends that patients experiencing more than 2 episodes of cellulitis at the same site within 1 year be referred to dermatology for assessment and evaluation for possible alternate diagnoses.123 Similarly, decolonization efforts have not proven to be beneficial. Despite modest difference in eradication rates between controls (education only) and the best-performing regimen for eradication (mupirocin/bleach baths) at 4 months (48% vs 71%; P = .02), the rates of skin and soft tissue infection between these groups were no different at 4-month (41% vs 35%; P = .51) or 6-month follow-up (54% vs 50%; P = .63).125

Treatment Failures
Of acute cellulitis cases, 16.6% were found to be unresponsive to initial treatment efforts.98 Inappropriate antimicrobial selection and dosing may adversely affect clinical outcomes, with obese patients at highest risk of treatment failure, suggesting they may benefit from weight-based rather than standardized antimicrobial dosing.111 In cases of cellulitis unresponsive to conventional therapy, antibiotic resistance, atypical cases, or pseudocellulitis should be considered.

Conclusions
Cellulitis is a common and expensive problem worldwide. It generally responds to relatively simple and inexpensive antibiotic regimens; however, recurrent disease is common and can be minimized by optimizing risk factors for cellulitis, such as lymphedema and skin damage. When cellulitis does not respond to treatment, other conditions that mimic it should be considered. Additional research on the diagnosis and management of cellulitis is needed.


37. CREST (Clinical Resource Efficiency Support Team). Guidelines on the Management of Cellulitis in


Diagnosis and Treatment of Cellulitis

Review Clinical Review & Education


