Review

Cellulitis
A Review

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IMPORTANCE Cellulitis is an infection of the deep dermis and subcutaneous tissue, 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.

OBSERVATIONS In the United States, an estimated 14.5 million cases annually of cellulitis account for $3.7 billion in ambulatory care costs alone. The majority of cases of cellulitis are nonculturable and therefore the causative bacteria are unknown. In the 15% of cellulitis cases in which organisms are identified, most are due to β-hemolytic *Streptococcus* and *Staphylococcus aureus*. There are no effective diagnostic modalities, and many clinical conditions appear similar. Treatment of primary and recurrent cellulitis should initially cover *Streptococcus* and methicillin-sensitive *S aureus*, with expansion for methicillin-resistant *S aureus* (MRSA) in cases of cellulitis associated with specific risk factors, such as athletes, children, men who have sex with men, prisoners, military recruits, residents of long-term care facilities, those with prior MRSA exposure, and intravenous drug users. Five days of treatment is sufficient with extension if symptoms are not improved. Addressing predisposing factors can minimize risk of recurrence.

CONCLUSIONS AND RELEVANCE The diagnosis of cellulitis is based primarily on history and physical examination. Treatment of uncomplicated cellulitis should be directed against *Streptococcus* and methicillin-sensitive *S aureus*. Failure to improve with appropriate first-line antibiotics should prompt consideration for resistant organisms, secondary conditions that mimic cellulitis, or underlying complicating conditions such as immunosuppression, chronic liver disease, or chronic kidney disease.

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Cellulitis is a bacterial infection of the skin, presenting with poorly demarcated erythema, edema, warmth, and tenderness. Although common, it often can be a diagnostic and therapeutic challenge. In this review, the pathophysiology, microbiology, clinical presentation, and risk factors of cellulitis are discussed. The approach to diagnosis is reviewed and the importance of differentiating cellulitis from clinical mimics of cellulitis is highlighted. An approach to empirical treatment is presented, with recent recommendations from the literature.

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 *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,[1] with annual US ambulatory

visits (outpatient and emergency departments) increasing from 4.6 million in 1997 to 9.6 million in 2005.[2] Furthermore, a significant proportion of patients with cellulitis are hospitalized for management, and inpatient numbers are increasing, with the number of hospital stays for cellulitis or abscess in the United States increasing by 73%, from 12 per 10 000 in 1997 to 21 per 10 000 in 2011.[3] In addition, a Netherlands study demonstrated that the total number of erysipelas, cellulitis, or abscess hospitalizations per inhabitants per year increased markedly with age, with a 5-fold increase from patients aged 54 years to those aged 85 years or older (incidence >100 per 100 000).[4]

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 dilation, 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.[5,6] 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 systemic 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 dilated and 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 on 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.[47,48]

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

Box. Uncommon Causes of Cellulitis, by Comorbidity and Associated Pathogens[a]

Immunosuppression (eg, transplant, systemic steroids, HIV/AIDS, SLE)
- *Streptococcus pneumoniae*[9-11]
- *Mycobacterium tuberculosis*[12,13]
- *Escherichia coli*[14]
- *Campylobacter*[15]
- *Serratia marcescens*[16]
- *Haemophilus influenzae*[17,18]
- *Helicobacter cinaedi*[19]
- *Shewanella putrefaciens*[20]
- *Cryptococcus neoformans*[21-24]
- *Cryptococcus gattii*[25]

Chronic liver disease
- *Vibrio* spp (*V vulnificus* or *V cholerae*)[26-28]
- *E coli*[29,30]
- *Pseudomonas aeriginosa*[30]
- *Campylobacter*[15]
- *Acinetobacter*[30]
- *Neisseria gonorrhoeae*[31]
- *Burkholderia cepacia*[32]
- *S putrefaciens*[20]
- Enterobacteriaceae spp[33]

Chronic kidney disease
- *V vulnificus*
- *V alginolyticus*[34]
- *Neisseria meningitidis*[35]
- *E coli*[29]

Aquatic soft tissue injury
- *Vibrio* spp[36]
- *Aeromonas* spp[36]
- *Mycobacterium marinum*[36]
- *Shewanella* spp[36]
- *Streptococcus iniae*[36]
- *Erysipelothrix rhusiopathiae*[36]

Animal and human bites
- Dog and cat[37,38]
  - *Pasteurella*
  - *Streptococcus*
  - *Staphylococcus*
  - *Neisseria*
  - *Corynebacterium*
  - *Moraxella*
  - *Fusobacterium*
  - *Porphyromonas*
  - *Prevotella*
  - *Bacteroides*
  - *Propionibacterium*
- Human[39]
  - α- and β-hemolytic *Streptococcus*
  - *S aureus*
  - *S epidermidis*
  - *Corynebacterium* spp
  - *Eikenella corrodens*
  - *Bacteriodes fraglis*
  - *Prevotella*
  - *Porphyromonas*
  - *Peptostreptococcus*
  - *Fusobacterium*
  - *Veillonello*
  - *Clostridium* spp
- Exotic animals: reviewed by Abrahamian and Goldstein[37]

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

[a] 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.

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.

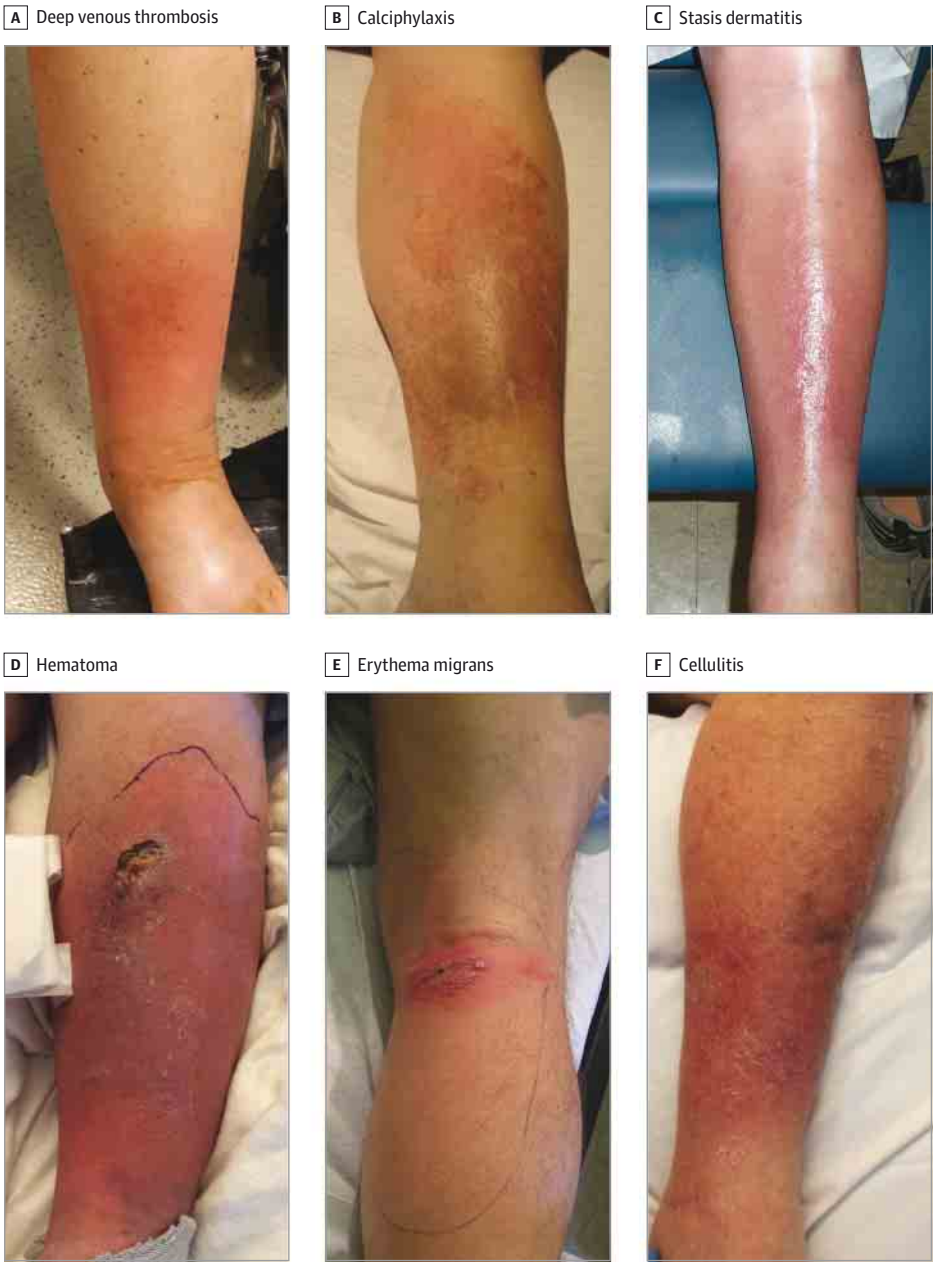
Risk Factors

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. Morris[63] 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

Figure 1. Clinical Presentation of Conditions That Mimic Cellulitis and True Cellulitis



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.

organism in cellulitis through traditional culture methods, whether blood, needle aspiration, or punch biopsy, is typically of low yield and not recommended.[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.[7]

Skin surface swab cultures, especially those of chronic wounds or ulcers, are commonly polymicrobial[68] or colonized with multidrug-resistant pathogens[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.[70] The Infectious Diseases Society of America does not recommend routine swab cultures in the management of infected ulcers.[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,[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.[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 µg/L).[74] Further studies are required before procalcitonin can be recommended broadly.

Table 1. Risk Factors Associated With the Development of Cellulitis or Erysipelas

Cellulitis	Associated Risk Factors
Primary	
Systemic	Age[51]; obesity[45,52-54]; homelessness[55]
Local	Barrier disruption (eg, wounds, ulcers, trauma)[45,52-54,56,57]; toe-web infection (eg, fungal, viral, and bacterial)[53,54,58]; edema (eg, lymphedema)[45,52,54,56,57]; history of cellulitis[53,54,56]; venous insufficiency[45,54]; xerosis[56]; dermatitis[56,57]; prior saphenous venectomy[53,56]; prior breast conservation surgery[59]
Recurrent	
Systemic	Obesity[5,52]; prior malignancy[60]; prior smoking[61]
Local	Edema (eg, lymphedema)[61,62]; tinea pedis[61]; venous insufficiency[61]; cellulitis tibial area involvement[60]; dermatitis[60]; prior ipsilateral surgical procedure[52,61]

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[75] found in a modeling study that a white blood cell count greater than 15 400 cells/mm^3 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[76] developed the Laboratory Risk Indicator for Necrotizing Fasciitis score according 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[77] 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.[78] 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.[79-81] 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.[82]

For the identification of drainable pus collections, the most widely used modalities are ultrasonography or magnetic resonance imaging.[78] 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%.[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,[84] 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).[85] 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.[85] 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.[7]

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 tetrad 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.[88] In the subgroup of hospitalized patients with cellulitis who required dermatology consultation, the misdiagnosis rate was 74%.[89]

Stasis dermatitis is the condition that most often mimics cellulitis.[90] It is distinguished by its bilateral nature because bilateral cellulitis in the absence of skin trauma is extremely rare,[45] 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 hematoma, 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 homogeneous erythema that self-resolves and leads to adverse sequelae if left

Table 2. Cellulitis Differential Diagnoses[a]

	Differential Diagnoses
Infectious	
Common	Erythema migrans, herpes simplex, herpes zoster, cutaneous abscess
Uncommon	Bacterial (eg, erysipeloid, necrotizing fasciitis); viral (eg, parvovirus B19, CMV); fungal (eg, *Cryptococcus neoformans*, *Sporothrix schenckii*, mucormycosis); mycobacterial; parasites (eg, *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 (eg, 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 (eg, 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.

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

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.[91] 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.[92] The treatment algorithms in **Figure 2** and **Figure 3** and dosing recommendations in **Table 3** incorporate Infectious Diseases Society of America 2014 guidelines,[7] Johns Hopkins antibiotic guidelines,[97] and results from randomized controlled trials.

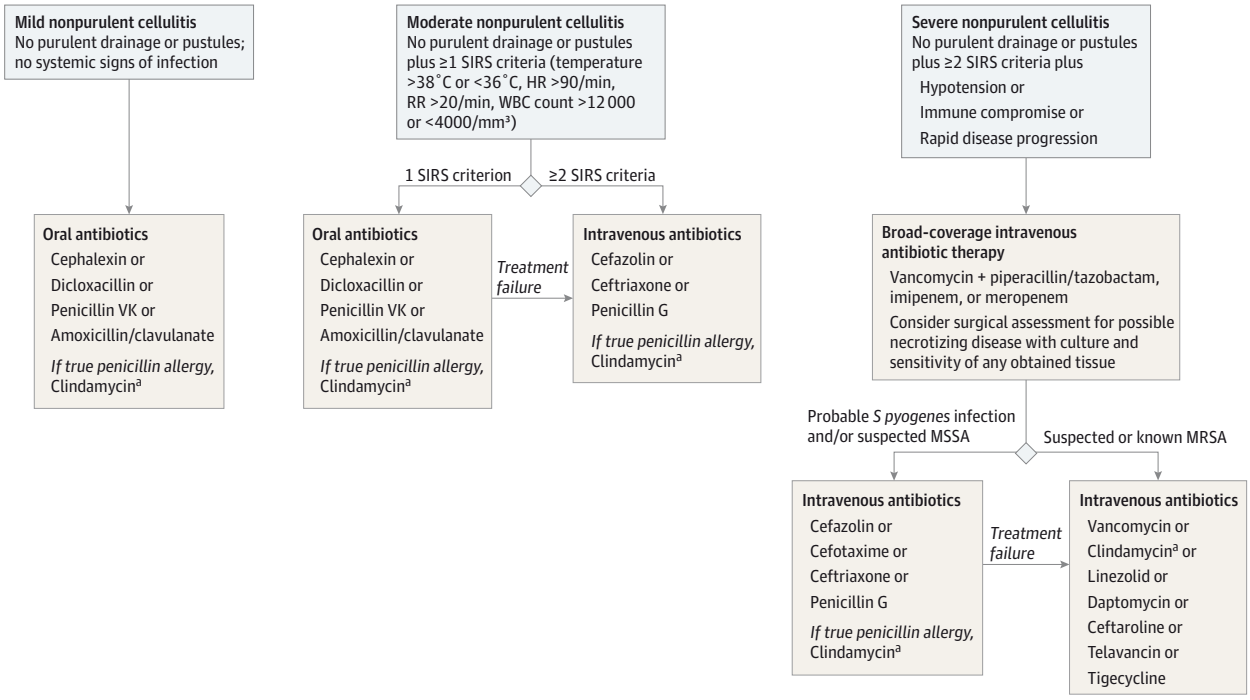
Typical cases of nonpurulent cellulitis without systemic signs of infection (mild cellulitis) should be treated with antistreptococcal antimicrobial agents such as cephalexin, dicloxacillin, penicillin VK, amoxicillin/clavulanate, or, in cases of penicillin allergy, clindamycin. A multicenter retrospective cohort study of outpatients treated for uncomplicated cellulitis found no statistically significant difference in failure rates when comparing oral β-lactams (eg, penicillin, cephalexin, dicloxacillin) with non-β-lactams (eg, clindamycin, trimethoprim-sulfamethoxazole, tetracyclines), with increased discontinuation in the non-β-lactam group because of adverse events (14.7% vs 17.0% failure rate, respectively; odds ratio, 0.85; 95% CI, 0.56-1.31).[99] A multicenter, double-blind, randomized controlled trial comparing the use of cephalexin to cephalexin and trimethoprim-sulfamethoxazole for cases of nonpurulent, uncomplicated cellulitis demonstrated no benefit to the addition of antibiotics against community-acquired MRSA (82% vs 85% cure rate, respectively; risk difference, 2.7%; 95% CI, −9.3% to 15%).[41]

Systemic signs of infection, such as fever, have been shown to predict failure of empirical outpatient antibiotic therapy.[100,101] Patients with nonpurulent cellulitis who meet any 1 criterion for systemic inflammatory response syndrome (SIRS),[102] such as temperature greater than 38°C or less than 36°C, heart rate greater than 90/min, respiratory rate greater than 20/min, or white blood cell count greater than 12 000 cells/mm^3 or less than 4000 cells/mm^3, are considered to have moderate cellulitis. Patients who meet only 1 SIRS criterion can initially receive the oral agents effective for mild disease. Patients who meet 2 or more SIRS criteria or who fail oral agents should be considered for an intravenous regimen of cefazolin, ceftriaxone, penicillin G, or, in cases of penicillin allergy, clindamycin.[7]

Vancomycin or other agents with activity against both streptococcal and MRSA infections should be used in severe cases of cellulitis, cases associated with penetrating trauma, evidence of MRSA infection or colonization elsewhere, or active injection drug use.[7] Oral linezolid is an alternative to vancomycin in patients who cannot receive or have a contraindication to intravenous vancomycin. Patients with severe immunocompromise should be treated with broad-spectrum antimicrobials.[7] For patients with nonpurulent cellulitis who demonstrate SIRS and hypotension, immunocompromise, or rapid progression (severe cellulitis), broader coverage should be initiated with empirical intravenous vancomycin with piperacillin/tazobactam, imipenem, or meropenem.[7] In cases of possible necrotizing cellulitis, surgical assessment should be considered with culture and sensitivity of any surgically obtained tissue. Patients with cellulitis and signs of shock should receive penicillin G and clindamycin for potential streptococcal toxic shock syndrome.[103,104]

In cases of purulent cellulitis, in which *S aureus* is more likely,[42] culture and sensitivity testing should always be performed to guide therapy, with empirical antibiotic selection based on patient risk factors for MRSA infections, as discussed previously.[44] For purulent cellulitis without systemic signs of infection (mild cellulitis) and no suspicion for MRSA infection, cephalexin, dicloxacillin, amoxicillin/clavulanate, or, in cases of penicillin allergy, clindamycin should be

Figure 2. Treatment Algorithm for Nonpurulent Cellulitis



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.[93] 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.

[a] True penicillin allergy as per published criteria.[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.

considered. If MRSA is suspected in mild purulent cases, trimethoprim-sulfamethoxazole, doxycycline, or minocycline should be used. These agents, however, do not offer adequate streptococcal coverage, and cephalexin or penicillin should be added if both organisms are involved.[97] Clindamycin or linezolid is an option for penicillin-allergic patients.

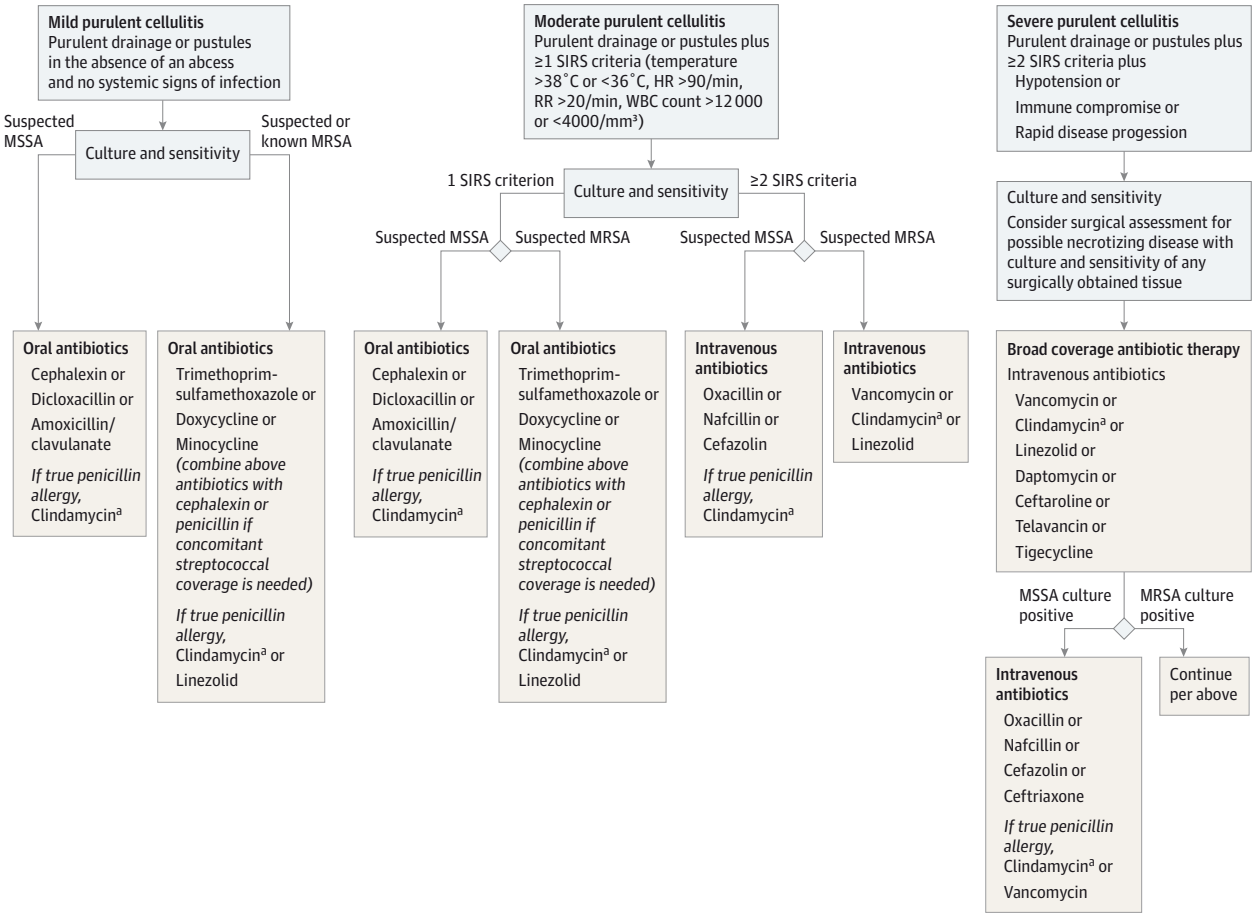
Patients with purulent cellulitis that meet 1 criterion for SIRS (moderate cellulitis) can be initially treated with the same oral agents effective for mild disease according to suspected methicillin-sensitive *S aureus* or MRSA. Patients who meet 2 or more criteria for SIRS should be considered for 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.[105] Clinicians should be aware of the increased cost, increased incidence of serotonin syndrome in patients concomitantly receiving a serotonergic agent (0.24%-4%),[106] and increased risk of thrombocytopenia with long-term use (RR, 13.06; 95% CI, 1.72-99.22).[105]

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 surgically 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.[7,107,108] Telavancin has been shown to be noninferior to vancomycin but with an increased risk of nephrotoxicity.[108] 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.[107,108] A single dose of oritavancin has been shown to be as effective as twice-daily intravenous vancomycin administered for 7 to 10 days.[109] Given the

Figure 3. Treatment Algorithm for Purulent Cellulitis



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.[93] 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.

[a] True penicillin allergy as per published criteria.[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.

limited use of these agents to date, they should be considered as needed on a case-by-case basis.

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.[110] The empirical use of vancomycin increased from 18% in 2000 to 69% in 2006, but low rates of bactericidal activity and penetration into tissues, as well as underdosing and prolonged courses, have led to the increase of vancomycin-resistant and -intermediate *S aureus*.[98,108] Because of high treatment failure rates associated with increased weight or body mass index, vancomycin dosing should be weight based (15-20 mg/kg per dose intravenously every 8-12 hours) rather than standardly dosed (1000 mg intravenously every 12 hours), with monitoring for the increased risk of nephrotoxicity.[108,111] Although MRSA is a significant and increasing problem in cellulitis, it has not yet been clearly demonstrated whether vancomycin-resistant and -intermediate *S aureus* plays a significant role.

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.[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,[112] some proposed this timeframe as a clinical guide for treatment failure.[98] We

Table 3. Standard Antimicrobial Dosing for Staphylococcal and Streptococcal Skin Infections[a]

Antibiotic	Adult Dosing	Comment
MSSA and *Streptococcus* Coverage		
Amoxicillin/ clavulanate	875 mg 2 times/d orally	Streptococcal and MSSA coverage
Cefazolin	1 g every 8 h intravenously	For true penicillin-allergic patients, less bone marrow suppression than nafcillin
Ceftaroline	600 mg every 12 h intravenously	Adjust for reduced creatinine clearance
Ceftriaxone	1-2 g/d intravenously	
Cephalexin	500 mg 4 times/d orally	Except in true penicillin-allergic patients with immediate hypersensitivity reactions[b]
Dicloxacillin	250-500 mg 4 times/d orally	Oral agent of choice for MSSA
Imipenem/cilastatin	500 mg every 6 h intravenously	Not to exceed 50 mg/kg or 4 g/d, whichever is lower
Meropenem	1 g every 8 h intravenously	
Nafcillin	1-2 g every 4 h intravenously	Parenteral drug of choice in MSSA
Oxacillin	1-2 g every 4 h intravenously	Parenteral drug of choice in MSSA
Penicillin G	2-4 million U every 4-6 h intravenously	
Penicillin VK	250-500 mg every 6 h orally	
Piperacillin/ tazobactam	3.375 g every 6 h intravenously	
MRSA Coverage		
Clindamycin	300-450 mg 4 times/d orally 600 mg every 8 h intravenously	Potential inducible resistance in MRSA Risk of *Clostridium difficile* infection
Daptomycin	4 mg/kg every 24 h intravenously	Costly (500 mg, $534.59[96]) Risk of myopathy
Doxycycline	100 mg 2 times/d orally	Possible photosensitivity Variable antistreptococcal activity
Linezolid	600 mg every 12 h orally 600 mg every 12 h intravenously	Costly (600-mg tablet, $184; 2 mg/mL [300 mL], $96[96]) Risk of serotonin syndrome and anemia, thrombocytopenia, leukopenia (long-term use) No cross-resistance with other antibiotic classes
Minocycline	100 mg 2 times/d orally	Variable antistreptococcal coverage
Telavancin	10 mg/kg every 24 h intravenously (infused during 1 h)	Costly (250 mg, $238.96[96]) Adjust for reduced creatinine clearance
Tigecycline	100 mg followed by 50 mg every 12 h intravenously	Adjust for severe liver impairment
Trimethoprim/ sulfamethoxazole	1-2 double-strength tablets 2 times/d orally	Increased risk of blistering skin reactions Poor streptococcal coverage
Vancomycin	15 mg/kg every 12 h intravenously	Parenteral agent of choice for MRSA infections

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S aureus*.

[a] Based on published guidelines.[7,97,98] Doses are standard based on normal adult weight and renal function.

[b] True penicillin allergy as per published criteria.[94,95]

recommend patient or clinician reassessment of the clinically affected area within 24-48 hours of treatment initiation for improvement in pain, redness, swelling, or warmth. If unimproved or worsened, then adjusting antibiotic selection should be considered for possible resistant pathogens such as MRSA or alternative diagnoses should be sought. One study assessing optimal treatment duration of uncomplicated cellulitis demonstrated that 5 days of antibiotic treatment, with course extension if inadequate response, is as effective as longer courses, without adverse sequelae, even if residual inflammation exists at the end of the 5-day course.[113] This is likely because cellulitis represents a paucibacillary infection that generates a strong inflammatory response that persists even after the organism is eliminated during the first few days of therapy.[113] In support of this hypothesis, a small study by Dall et al[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 apyrexia (<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 lymphaticolymphatic 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]

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.[8] 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.[52,61,121] 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 heterogenous, 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-blind, 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,[117,123] 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.

ARTICLE INFORMATION

Author Contributions: Drs Raff and Kroshinsky had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design; *acquisition, analysis, or interpretation of data*; *drafting of the manuscript*; *critical revision of the manuscript for important intellectual content*; *administrative, technical, or material support:* Both authors.
Study supervision: Kroshinsky.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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