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Clinical Review

TOP 10 MYTHS REGARDING THE DIAGNOSIS AND TREATMENT OF CELLULITIS

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☐ **Abstract—Background: Cellulitis is commonly treated in the emergency department (ED). Patients who present with cellulitis incur significant health care costs and may be overtreated with antibiotics. The accurate diagnosis and treatment of cellulitis plays an important role in cost-effective, high-quality medical care, as well as appropriate antibiotic utilization. Objective: We aim to describe common fallacies regarding cellulitis. We present 10 myths that result in misdiagnosis, overtreatment, or inappropriate empiric management of cellulitis. Clinical presentation, including swelling and redness, is explored in depth, along with incidence of community-acquired methicillin-resistance *Staphylococcus aureus*, management of tick bites, and effective antibiotic therapy for cellulitis. Discussion: Patients are often treated for cellulitis unnecessarily or inappropriately. Awareness of these myths will help guide providers in clinical decision making in order to effectively tailor treatment for these infections. Conclusions: Cellulitis is not as simple as it might seem, and is commonly misdiagnosed in the ED. Noninfectious causes of local symptoms, including lymphedema, venous stasis, and deep vein thrombosis need to be considered. Cellulitis should be treated with empiric antimicrobial therapy based on patient risk factors and regional susceptibility patterns. This review will assist providers in managing cellulitis and avoiding treatment errors that lead to high costs, unwanted side effects for patients, and overuse of antibiotics.** © **2017 Elsevier Inc. All rights reserved.**

☐ **Keywords—cellulitis; acute bacterial skin and skin structure infections; CA-MRSA; stewardship; antimicrobial; treatment; diagnosis**

INTRODUCTION

Acute bacterial skin and skin structure infections (ABSSSI) were the cause of more than 4 million emergency department (ED) visits in 2010, and are associated with a $1.4–$13.8 billion burden to society annually in the United States (1–4). According to the Healthcare Cost and Utilization Project National Inpatient Sample data, ABSSSI-related hospital admissions accounted for 1.8% of total admissions from 2005 through 2011 (5). Dramatically increasing rates of hospitalizations for these infections have resulted in a critical need to design best-practice models that minimize complications, costs, and inappropriate antibiotic use, while optimizing outpatient management of ABSSSI (1). Differential diagnoses for skin conditions include infection, acute gout, deep vein thrombophlebitis, and neoplastic disorders, making the clinical decision pathway difficult for providers (2,6). A recent study found that 30.5% of patients are misdiagnosed with cellulitis in the ED. Of those misdiagnosed, 84.6% had an unnecessary hospital

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admission and 92.3% received unnecessary antibiotics (7). A separate study discovered 15.5% of patients that present to the ED for an ABSSSI (surface area of infection at least 75 cm^2) are discharged with two or more antibiotics, demonstrating there is room for improvement in the management of cellulitis (1,4).

METHODS

The authors are experienced clinicians and pharmacists in emergency medicine or infectious diseases and antimicrobial stewardship. The 10 myths and lessons outlined here were chosen by consensus to address the common misperceptions associated with the diagnosis and treatment of cellulitis. They were derived from personal observations and historical teachings that are propagated annually to trainees at their practice site. A literature search was conducted via PubMed using key words including but not limited to: cellulitis, bilateral cellulitis, cellulitis mimics, ["cellulitis" and "methicillin-resistant staphylococcus aureus"], ["cellulitis" and "antibiotic"], ["cellulitis" and "clindamycin"], and skin and soft tissue infections. Bibliographies and author libraries were also reviewed to identify additional pertinent literature as they pertained to the individual myths. Studies were chosen to address each myth in the form of a lesson intended to aid the ED provider with cellulitis diagnosis, management, and antimicrobial stewardship principles.

Myth 1: Skin that is red and swollen is definitely cellulitis.

Lesson 1: Local presentation of edema, erythema, warmth, hyperemia, tenderness, "orange peel" appearance, vesicles, bullae, petechiae, and pain may lead to a diagnosis of ABSSSI (6,8–10).

1. Diagnoses of deep venous thrombosis (DVT), venous stasis dermatitis, venous insufficiency, lymphedema, contact dermatitis, gout, herpes zoster, acute lipodermatosclerosis, noninfectious phlebitis, insect bite hypersensitivity, Sweet's syndrome, and fixed drug reaction should also be considered (6,11).
2. Fever and leukocytosis may be present, but are not required, for the diagnosis of cellulitis. These may also be caused by noninfectious inflammatory conditions (7,12).
3. A simple physical examination skill that can help differentiate true cellulitis from other etiologies of erythema of the lower extremity is the passive leg raise. During this examination, the patient lies horizontally on the examination table/bed and the leg is manually elevated to a 45-degree angle or higher. The leg is held aloft for 1 to 2 minutes while observing whether the erythema abates. Cellulitis erythema will persist upon elevation, whereas erythema due to other etiologies, such as stasis dermatitis and lymphedema without superimposed cellulitis, usually disappears with elevation (11,13).

Myth 2: My patient has bilateral lower-extremity swelling and redness; my patient has bilateral cellulitis.

Lesson 2: Bilateral lower-extremity cellulitis is exceedingly rare. If bilateral swelling is present, noninfectious etiologies should be considered first, including but not limited to chronic stasis dermatitis, DVT, heart failure, venous stasis, and lymphedema (14–17).

1. Lower-extremity cellulitis is generally caused by direct inoculum to an affected limb through a breech in the skin. Bilateral cellulitis via this mechanism would require bacterial dispersion from one limb to the other. Simultaneous, independent inoculum of both legs is required for an acute bilateral cellulitis.
2. Treatment for noninfectious leg swelling should be considered before treatment of bilateral cellulitis and should generally consist of lower-extremity elevation. If the affected area improves rapidly via drainage of the edema, this may confirm the noninfectious etiology. Patients or providers can consider applying compression garments to assist with edema reduction (18).

Myth 3: All skin and soft-tissue infections need antibiotic treatment.

Lesson 3: Some skin and soft-tissue infections do not require antibiotic treatment.

1. For simple abscesses and boils ($\leq$5 cm in diameter of erythema), incision and drainage alone is likely adequate as sole treatment without the need for antibiotics (6,8,19).
2. Treatment with antibiotic therapy should be considered for patients with abscesses and large erythema (combined diameter > 5 cm), multiple lesions, signs of systemic infection, rapid progression of cellulitis, areas that are difficult to drain (e.g., face, hand, and genitalia), or risk factors for reduced ability to heal (e.g., diabetes, immunosuppression) (8,19).

Myth 4: With the increased prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community, all clinically stable, community-dwelling patients presenting to the ED with cellulitis should be treated with an antibiotic that has activity against MRSA.

Lesson 4: The antibiotic spectrum decision should be based on several factors, including presence or absence of purulence, severity of illness, patient-specific risk factors for MRSA, and local bacteria ecology.

1. Impetigo, erysipelas, and cellulitis that is diffuse, erythematous, nonpurulent with extensive lymphangitic spread, or unassociated with a defined portal is more commonly caused by Group A or other β-hemolytic streptococci rather than *Staphylococcus* spp., however, *S. aureus* may also be present (20,21). In nonpurulent cellulitis, the addition of MRSA coverage (with trimethoprim-sulfamethoxazole [TMP-SMX]) to cephalexin does not improve patient outcomes, including clinical cure or progression to abscess (22,23).
2. Infection with *Staphylococcus* spp. (both methicillin-susceptible *S. aureus* [MSSA] and MRSA) commonly results in a purulent lesion. For cellulitis with abscess that is purulent, fluctuant, has penetrating trauma, or is associated with shallow ulcer or blister with surrounding erythema, *Streptococcus* spp. and *Staphylococcus* spp. including MRSA should be targeted with antibiotic therapy (6,8–10).
3. Abscess material should be obtained for culture before antibiotic initiation whenever possible to guide definitive antibiotic therapy (8).
4. Studies report the rate of *S. aureus* colonization in noninfected patients to be 16.6–26.6% with only 1.5–5.3% of carriers colonized with MRSA (24–26). There is a notable discrepancy between rates of MRSA colonization and rates of MRSA from cultured ABSSSI material. In recent phase 3 trials for ABSSSI, rates of cultured MRSA were up to 53% (27). This paradox between colonization and infection rates can be explained by culture bias; only abscesses are amenable to microbiologic culturing and, therefore, *S. aureus* is likely over-represented in microbiologic outcomes. MRSA is further over-represented in microbiologic outcomes because hospitalized patients are more likely to be cultured than stable patients in the outpatient setting.
5. Risk factors for acquisition of MRSA skin infection in the community include (28):
   a. History of MRSA infection or colonization in patient or close contact
   b. Recurrent skin disease
   c. Crowded living conditions (e.g., homeless shelters, military barracks)
   d. History of incarceration
   e. Participation in contact sports
   f. Skin or soft-tissue infection with poor response to β-lactam antibiotics
   g. Recent or frequent antibiotic use
   h. Injection drug use
   i. Member of Native American, Pacific Island, Alaskan Native populations
   j. Male with history of having sex with men
   k. Shaving of body hair
6. If the patient has risk factors for MRSA and has a purulent lesion that is not amenable to drainage and culture, providers should be familiar with their local antibiogram to select the best empiric treatment. Specifically, providers should know the rates of resistance to oral MRSA treatment options at their practice sites (see Myths 6 and 7).

Myth 5: My patient requires hospitalization for cellulitis, therefore, my patient has a MRSA infection and requires MRSA targeted anti-infective therapy.

Lesson 5: Similar to lesson 4, the presence or absence of purulence, severity of illness, patient-specific risk factors for MRSA, and local bacteria ecology should guide the provider in determining the causative pathogen of an ABSSSI, irrespective of the location of the patient.

1. Infectious epidemiology increasingly demonstrates a shift from the paradigm of hospital-acquired and community-acquired MRSA isolates to an era where there is no distinction between MRSA strains. It is important for providers to recognize that all MRSA isolates can cause severe infection and patient location alone should not drive antibiotic decision making (29).
2. In patients who are sick enough to be hospitalized, it is reasonable to begin an antibiotic with activity against MRSA, such as vancomycin, and culture the lesion. If the lesion is not culturable, it is reasonable to obtain MRSA swabs of the nares and pooled axilla/groin to guide definitive antibiotic therapy (30–35).
3. The negative predictive value of the nasal swab MRSA polymerase chain reaction test ranges from 0.89 to 0.98, depending on institution prevalence of MRSA and is reliable to rule out MRSA disease. The positive predictive value is much lower, therefore, a negative swab should guide decisions on definitive antibiotic therapy, whereas a positive swab does not necessarily mean the patient is infected with MRSA (32,35).

Myth 6: Clindamycin is an effective empiric antibiotic for MRSA.

Lesson 6: Clindamycin should only be used for the treatment of cellulitis when other alternative agents are contraindicated.

1. Clindamycin may exhibit inducible resistance to MRSA, and caution should be used when prescribing this agent for MRSA (36,37). The majority of microbiology laboratories now routinely test for

inducible resistance and will report clindamycin as resistant if this gene is present.
2. Resistance rates to clindamycin of > 35% have been reported for MRSA. A recent study from 143 medical centers in the United States examined 8437 MRSA isolates collected from 2012–2014. Clindamycin susceptibility rates were 44.6% and 66.1% for hospital MRSA isolates and community MRSA isolates, respectively (38).
3. TMP-SMX and doxycycline resistance rates remain at < 10% in most communities (6,8–10,39,40). A 2015 study examining clindamycin vs. TMP-SMX for uncomplicated skin infections found 12.4% of MRSA isolates were clindamycin-resistant and only 0.5% TMP-SMX-resistant (41). Resistance of *S. aureus* to linezolid is identified as 0.05% (42)
4. Clindamycin has a high odds ratio for development of *Clostridium difficile* infection and should be avoided whenever possible (43). Penicillin and cephalosporin allergies should be substantiated before clindamycin is chosen.

Myth 7: Because one cannot tell whether cellulitis is caused by *Streptococcus* spp., MSSA, MRSA, Gram-negative or anaerobic pathogens, each patient needs to be treated with broad-spectrum antibiotic therapy.

Lesson 7: Antibiotic therapy should be selected based on the characteristics of the infection, severity of illness, and patient-specific risk factors for different organisms. Most cases of uncomplicated cellulitis without abscess or purulence will not need combination therapy with a β-lactam and anti-MRSA antibiotic (22,44). Gram-negative and anaerobic coverage is generally unnecessary (44–46).

1. Dicloxacillin and cephalexin exhibit excellent antimicrobial activity against MSSA and *Streptococcus* spp. and can be prescribed as monotherapy for most cases of nonpurulent cellulitis (see Myth 4) (6,8–10).
2. For patients who warrant MRSA coverage but do not need intravenous antibiotics, TMP-SMX, doxycycline, or linezolid can be initiated. Providers should note that while studies have demonstrated the activity of TMP-SMX against β-hemolytic streptococci, overall the activity of TMP-SMX and doxycycline against β-hemolytic streptococci is largely unknown (8,47).
   a. If TMP-SMX or doxycycline is initiated, it is reasonable to consider combination therapy with a β-lactam antibiotic for the treatment of possible mixed MRSA/streptococcal infection (8).
   b. Linezolid has excellent activity against *Streptococcus* spp. and does not warrant combination therapy.
   c. See discussion under Myth 4 and 5 for more about MRSA coverage.
3. Gram-negative and anaerobic coverage should generally be reserved for patients with:
   a. Intensive care unit (ICU) level of care
   b. Concern for bloodstream or necrotizing infection
   c. Peri-rectal involvement, peri-orbital involvement, human or animal bite, surgical wound infection, traumatic aquatic injury, or osteomyelitis
   d. Chronic diabetic foot wounds
   e. Intravenous illicit drug use
   f. Presence of neutropenia or severe cell-mediated immunodeficiency
4. The local antibiogram should be consulted when deciding on the most appropriate antibiotic for ABSSSIs with concern for Gram-negative pathogens.

Myth 8: If the redness extends beyond the drawn wound margin in a patient with cellulitis, the patient is getting worse.

Lesson 8: Because of the subacute spread of redness, edema, or induration in some patients at the time of presentation with cellulitis, the lesion may continue to spread for the first 48 h after administration of antibacterial drug therapy (48).

1. Erythema may extend beyond documented margins during the first 48 h without necessarily representing treatment failure. The intensity of the erythema is often a more important variable, with improving cases resulting in less intensely red inflammation (48,49).
2. If erythema and fever continue beyond 48 to 72 h, treatment failure should be considered and antibiotic therapy should be reassessed (48,49).
3. The Infectious Diseases Society of America recommends 5 days of treatment for erysipelas and cellulitis, with the option to extend treatment duration in the absence of clinical improvement within this time period (8).

Myth 9: Patients should never have another skin infection if they are taking antibiotic prophylaxis for recurrent skin infections.

Lesson 9: Antibiotic prophylaxis has been shown to be effective in suppressing infection and decreasing rates of recurrence, but recurrence may occur despite adherence to therapy. Treatment of causes of infection and

optimization of treatment of other disease states may decrease the risk of recurrence (50–52).

1. A study of 398 cases compared to 8005 controls discovered 40% of patients experienced cellulitis recurrence despite prophylactic treatment with benzathine penicillin. A multivariate analysis revealed psoriasis, chronic dermatoses, diabetes, increasing age, and increasing body mass were independently associated with recurrent cellulitis (53).
2. Causes of superimposed cellulitis, such as tinea pedis infection, should be treated to prevent recurrence (54,55).
3. The management of other disease states, such as diabetes mellitus and especially lymphedema, should be optimized in order to decrease the risk of recurrence (53).
4. Skin should be kept well hydrated with emollients to avoid dryness and cracking. Underlying edema should be reduced by elevating the affected extremity and by the use of compression stockings (55).
5. Reconfirmation of the diagnosis of cellulitis, appropriateness of antibiotic, dosing, timing, and adherence should also be assessed in patients with recurrence (56).

Myth 10: All patients with tick bites and surrounding redness have cellulitis.

Lesson 10: Local tick bite reactions are predictable and do not indicate that a patient has cellulitis (57). These reactions are usually no more than a few centimeters in size.

1. Erythema surrounding a tick bite can be differentiated from streptococcal and staphylococcal cellulitis based the characteristics of erythema. Erythema due to tick bites usually remains localized with limited spread to the site of the bite, with the exception of erythema migrans from *Borrelia burgdorferi*, which will continue to extend several centimeters beyond the bite site. Unlike cellulitis, however, this spread will be circular in nature, often presenting like a target, with evidence of a macular rash (58).

DISCUSSION

Cellulitis is a common condition that results in millions of ED visits annually. Despite the prevalence of cellulitis in American society, no well-defined treatment algorithms or classification systems exist for patients that present with warm, erythematic, edematous, or tender skin (59). We reviewed 10 common misperceptions associated with the diagnosis and treatment of cellulitis to enhance care of patients with cellulitis in the ED.

Studies have shown that up to 25% of patients fail antibiotic therapy for cellulitis in the ED (60,61). There are several independent risk factors associated with therapy failure, including lymphedema and previous cellulitis treatment. This demonstrates the need to delineate conditions mimicking cellulitis from infectious cellulitis and the importance of antimicrobial stewardship in improving long-term patient outcomes (7). Physical examination findings should be paired with anatomic knowledge, radiographic evidence, and culture data when able to establish a correct diagnosis in patients with presumed cellulitis (8).

The authors note that several fallacies have been perpetuated over time regarding the diagnosis and treatment of cellulitis in the ED and that these drive the majority of decision making around the differential diagnosis, empiric antibiotic selection, and need for hospitalization. It is crucial to review the lessons presented here in order to optimize treatment of these conditions. These lessons include: considering noninfectious causes of skin disease, treating modifiable risk factors of cellulitis with nonpharmacologic therapy when possible, and utilizing patient-specific factors in combination with institutional antibiograms when selecting empiric antibiotics.

CONCLUSIONS

Emergency medicine providers encounter cellulitis and conditions mimicking cellulitis frequently. Several misperceptions surrounding the diagnosis and treatment of cellulitis persist, leading to overuse of antibiotics and potential underuse of nonpharmacologic treatments. By recognizing these common misperceptions, emergency medicine providers will be better able to accurately diagnosis and treat these conditions. This is expected to result in increased patient safety, improved patient outcomes, and enhanced antimicrobial stewardship.

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ARTICLE SUMMARY

1. Why is this topic important?

Misdiagnosis of cellulitis in the emergency department (ED) leads to potential undertreatment of noninfectious skin disorders and overuse of antibiotic therapy. Studies have repeatedly shown the frequency of unnecessary hospital admissions for cellulitis and conditions mimicking cellulitis. Additionally, antimicrobial stewardship has been identified by the Centers for Disease Control, The Joint Commission, and the Centers for Medicare and Medicaid Services as a national priority.

2. What does this review attempt to show?

Common misperceptions regarding the diagnosis and treatment of cellulitis and noninfectious skin diseases are described. Evidence is presented to guide practitioners in the treatment of cellulitis and assist in optimizing patient outcomes.

3. What are the key findings?

A myriad of conditions can present like cellulitis, and it is crucial for providers to quickly and efficiently identify infectious versus non-infectious diseases. Data presented in this review demonstrate that significant improvements can be made in the ED to effectively treat these patients. Notably, nonpharmacologic treatments can be utilized in order to decrease hospitalizations and unnecessary antibiotic prescribing. The clinical status of the patient, appearance of infection, and patient-specific risk factors for certain pathogens should guide choice of antibiotic therapy.

4. How is patient care impacted?

Correction of these misperceptions in clinical practice will improve patient care through increased treatment response, improved utilization of health care resources, and adherence with antimicrobial stewardship principles.