Risk Stratification for Cellulitis Versus Noncellulitic Conditions of the Lower Extremity: A Retrospective Review of the NEW HAvUN Criteria

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PRACTICE **POINTS**

- Distinguishing cellulitis from noncellulitic conditions of the lower extremity is paramount to effective patient management in the emergent setting, given that misdiagnosis consumes hospital resources and can lead to inappropriate or excessive use of antibiotics.
- We evaluated the specificity and sensitivity of the following 7 clinical criteria: acute onset, erythema, pyrexia, history of associated trauma, tenderness, unilaterality, and leukocytosis.

Scholarly consensus is lacking for the risk stratification of patients who present with acute or subacute dermatologic conditions of the lower extremity, particularly cellulitis and its mimickers. This lack of consensus leads to overconsumption of hospital resources and may result in delayed recognition and treatment, adversely affecting patient outcomes. In this retrospective chart review, our aim was to test a set of clinical criteria—acute onset, erythema, pyrexia, history of associated trauma, tenderness, unilaterality (presence on 1 limb only), and leukocytosis—in patients with a known diagnosis of cellulitis or noncellulitis, as determined by dermatology consultation. We hope that these criteria can help clinicians better quantify risk based on history, physical examination, and risk factors, and thus help differentiate emergent and nonemergent dermatologic conditions of the lower extremity.

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Cellulitis is defined as an acute or subacute, bacterial-induced inflammation of subcutaneous tissue that can extend superficially. The inciting incident often is assumed to be invasion of bacteria through loose connective tissue.[1] Although cellulitis is bacterial in origin, it often is difficult to culture the offending microorganism from biopsy sites, swabs, or blood. Erythema, fever, induration, and tenderness are largely seen as clinical manifestations. Moderate and severe cases may be accompanied by fever, malaise, and leukocytosis. The lower extremity is the most common location of involvement (Figure 1), and usually a wound, ulcer, or interdigital superficial infection can be identified and implicated as the source of entry.

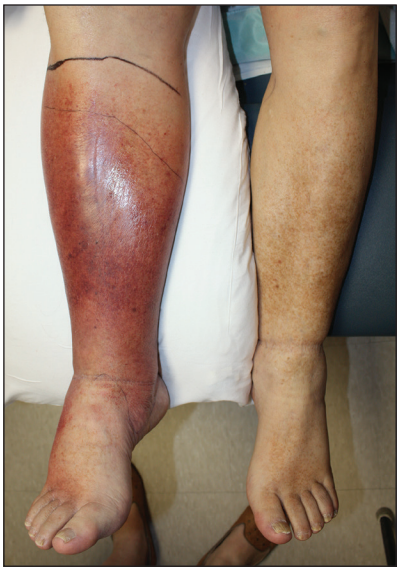

FIGURE 1. Cellulitis presenting as an extensive soft-tissue infection of the right leg, with a unilateral, well-demarcated, red, warm plaque.

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Effective treatment of cellulitis is necessary because complications such as abscesses, underlying fascia or muscle involvement, and septicemia can develop, leading to poor outcomes. Antibiotics should be administered intravenously in patients with suspected fascial involvement, septicemia, or dermal necrosis, or in those with an immunological comorbidity.[2]

The differential diagnosis of lower extremity cellulitis is wide due to the existence of several mimicking dermatologic conditions. These so-called pseudocellulitis conditions include stasis dermatitis, venous ulceration, acute lipodermatosclerosis, pigmented purpura, vasculopathy, contact dermatitis, adverse medication reaction, and arthropod bite. Stasis dermatitis and lipodermatosclerosis, both arising from venous insufficiency, are by far 2 of the most common skin conditions that imitate cellulitis.

Stasis dermatitis is a common condition in the United States and Europe, usually manifesting as a pigmented purpuric dermatosis on anterior tibial surfaces, around the ankle, or overlying dependent varicosities. Skin changes can include hyperpigmentation, edema, mild scaling, eczematous patches, and even ulceration.[3]

Lipodermatosclerosis is a disorder of progressive fibrosis of subcutaneous fat. It is more common in middle-aged women who have a high body mass index and a venous abnormality.[4] This form of panniculitis typically affects the lower extremities bilaterally, manifesting as erythematous and indurated skin changes, sometimes described as inverted champagne bottles (Figure 2). At times, there can be accompanying painful ulceration on the erythematous areas, features that closely resemble cellulitis.[5,6] Lipodermatosclerosis is commonly misdiagnosed as cellulitis, leading to inappropriate prescription of antibiotics.[7]

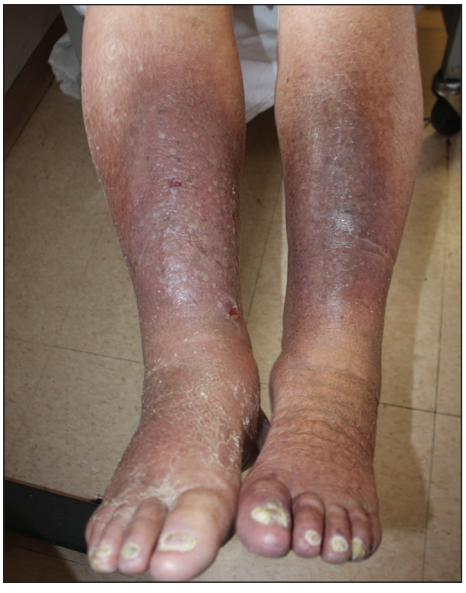

FIGURE 2. Lipodermatosclerosis with bilaterally thickened, cobblestoned plaques with venous ulcers on the medial malleolus.

Distinguishing cellulitis from noncellulitic conditions of the lower extremity is paramount to effective patient management in the emergent setting. With a reported incidence of 24.6 per 100 person-years, cellulitis constitutes 1% to 14% of emergency department visits and 4% to 7% of hospital admissions. Therefore, prompt appropriate diagnosis and treatment can avoid life-threatening complications associated with infection such as sepsis, abscess, lymphangitis, and necrotizing fasciitis.[8-11]

It is estimated that 10% to 20% of patients who have been given a diagnosis of cellulitis do not actually have the disease.[2,12] This discrepancy consumes a remarkable amount of hospital resources and can lead to inappropriate or excessive use of antibiotics.[13] Although the true incidence of adverse antibiotic reactions is unknown, it is estimated that they are the cause of 3% to 6% of acute hospital admissions and occur in 10% to 15% of inpatients admitted for other primary reasons.[14] These findings illustrate the potential for an increased risk for morbidity and increased length of stay for patients beginning an antibiotic regimen, especially when the agents are administered unnecessarily. In addition, inappropriate antibiotic use contributes to antibiotic resistance, which continues to be a major problem, especially in hospitalized patients.

There is a lack of consensus in the literature about methods to risk stratify patients who present with acute dermatologic conditions that include and resemble cellulitis. We sought to identify clinical features based on available clinical literature-derived variables. We tested our scheme in a series of patients with a known diagnosis of cellulitis or other dermatologic pathology of the lower extremity to assess the validity of the following 7 clinical criteria: acute onset, erythema, pyrexia, history of associated trauma, tenderness, unilaterality, and leukocytosis.

Materials and Methods

This retrospective chart review was approved by the Yale University (New Haven, Connecticut) institutional review board (HIC#1409014533). Final diagnosis, demographic data, clinical manifestations, and relevant diagnostic laboratory values of 57 patients were obtained from a database in the dermatology department's consultation log and electronic medical record database (December 2011 to December 2014). The presence of each clinical symptom—acute onset, erythema, pyrexia, history of associated trauma, tenderness, unilaterality, and leukocytosis—was assigned a score equal to 1; values were tallied to achieve a final score for each patient (Table 1). Patients who were seen initially as a consultation for possible cellulitis but given a final diagnosis of stasis dermatitis or lipodermatosclerosis were included (Table 2).

Clinical Criteria—The clinical criteria were developed based largely on clinical experience and relevant secondary literature.[15-17] At the patient encounter, presence of

TABLE 1. Clinical Criteria for Effective Cellulitis Diagnosis

Clinical Parameter	Description	Point Value
Acute onset	≤3 d	1
Erythema	Pink to light red erythema resulting from microvascular dilation[a]	1
Pyrexia	>100.4°F	1
History of associated trauma	Mechanical, surgical, insect bite, or burn; associated with time course of infection	1
Tenderness	Tenderness to light touch	1
Unilaterality	Lesion of concern appears on a single lower extremity; generally asymmetric anatomic involvement	1
Leukocytosis	Defined as a white blood cell count >10.0×10^9/L	1
Total		7

[a]More difficult to see in a darkly pigmented patient.

TABLE 2. Demographic Data of Evaluated Patients (N=57)

Characteristic	Patients
Gender, n (%)	
Male	32 (56)
Female	25 (44)
Final diagnosis, n (%)	
Cellulitis	20 (35)
Noncellulitis	37 (65)
Mean age, y	
Male	63
Female	61

each of the variables (Table 1) was assessed according to the following definitions:

- acute onset: within the prior 72 hours and more indicative of an acute infective process than a gradual and chronic consequence of venous stasis
- erythema: a subjective clinical marker for inflammation that can be associated with cellulitis, though darker, erythematous-appearing discolorations also can be seen in patients with chronic venous hypertension or valvular incompetence[4,15]
- pyrexia: body temperature greater than 100.4°F
- history of associated trauma: encompassing mechanical wounds, surgical incisions, burns, and insect bites that correlate closely to the time course of symptomatic development
- tenderness: tenderness to light touch, which may be more common in patients afflicted with cellulitis than in those with venous insufficiency
- unilaterality: a helpful distinguishing feature that points the diagnosis away from a dermatitislike clinical picture, especially because bilateral cellulitis is rare and regarded as a diagnostic pitfall[18]
- leukocytosis: white blood cell count greater than 10.0×10^9/L and is reasonably considered a cardinal metric of inflammatory processes, though it can be confounded by immunocompromise (low count) or steroid use (high count)

Statistical Analysis—Odds ratios (ORs) were calculated and χ^2 analysis was performed for each presenting symptom using JMP 10.0 analytical software (SAS Institute Inc). Each patient was rated separately by means of the clinical feature–based scoring system for the calculation of a total score. After application of the score to the patient population, receiver operating characteristic curves were constructed to identify the optimal score threshold for discriminating cellulitis from dermatitis in this group. For each clinical feature, $P<.05$ was considered significant.

Results

Our cohort included 32 male and 25 female patients with a mean age of 63 and 61 years, respectively. The final clinical diagnosis of cellulitis was made in 20 patients (35%). An established diagnosis of cellulitis was assigned based on a dermatology evaluation located within our electronic medical record database (Table 2).

Each clinical parameter was evaluated separately for each patient; combined results are summarized in Table 3. Acute onset (≤3 days) was a clinical characteristic seen in 80% (16/20) of cellulitis cases and 22% (8/37) of noncellulitis cases (OR, 14.5; $P<.001$). Erythema had similar significance (OR, 10.3; prevalence, 95% [19/20] vs 65% [24/37]; $P=.012$). Pyrexia possessed an OR of 99.2 for cellulitis and was seen in 85% (17/20) of cellulitis cases and only 5% (2/37) of noncellulitis cases ($P<.001$).

A history of associated trauma had an OR of 36.0 for cellulitis, with 50% (10/20) and 3% (1/37) prevalence in cellulitis cases and noncellulitis cases, respectively ($P<.001$). Tenderness, documented in 90% (18/20) of cellulitis cases and 43% (16/37) of noncellulitis cases, had an OR of 11.8 ($P<.001$).

Unilaterality had 100% (20/20) prevalence in our cellulitis cohort and was the only characteristic within the algorithm that yielded an incalculable OR. Noncellulitis or stasis dermatitis of the lower extremity exhibited a unilateral lesion in 11 cases (30%), of which 1 case resulted

from a unilateral tibial fracture. Leukocytosis was seen in 65% (13/20) of cellulitis cases and 8% (3/37) of noncellulitis cases, with an OR for cellulitis of 21.0 ($P<.001$).

All parameters were significant by χ^2 analysis (Table 3).

Comment

We found that testing positive for 4 of 7 clinical criteria for assessing cellulitis was highly specific (95%) and sensitive (100%) for a diagnosis of cellulitis among its range of mimics (Figure 3). These cellulitis criteria can be remembered, with some modification, using NEW HAvUN as a mnemonic device (**N**ew onset, **E**rythema, **W**armth, **H**istory of associated trauma, **A**che, **U**nilaterality, and **N**umber of white blood cells). This aid to memory could prove a valuable tool in the efficient evaluation of a patient in an emergency, inpatient, or outpatient medical setting.

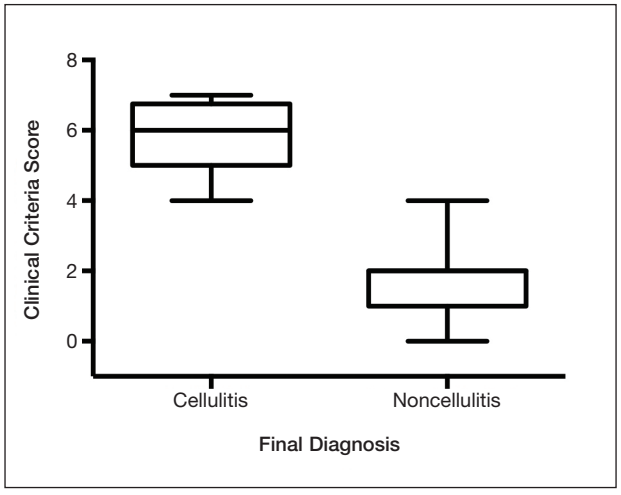

FIGURE 3. Clinical criteria score (1 point each for 7 clinical criteria) stratified by final diagnosis of cellulitis or noncellulitis. A score of 4 was a distinct inflection point for either clinical outcome.

Consistent with the literature, pyrexia, history of associated trauma, and unilaterality also were predictors of cellulitis diagnosis. Unilaterality often is used as a diagnostic tool by dermatologist consultants when a patient lacks other criteria for cellulitis, so these findings are intuitive and consistent with our institutional experience. Interestingly, leukocytosis was seen in only 65% of cellulitis cases and 8% of noncellulitis cases and therefore might not serve as a sensitive independent predictor of a diagnosis of cellulitis, emphasizing the importance of the multifactorial scoring system we have put forward. Additionally, acuity of onset, erythema, and tenderness are not independently associated with cellulitis when assessing a patient because several of those findings are present in other dermatologic conditions of the lower extremity; when combined with the other criteria, however, these 3 findings can play a role in diagnosis.

Effective cellulitis diagnosis provides well-recognized challenges in the acute medical setting because many clinical mimics exist. The estimated rate of misdiagnosed cellulitis is certainly well-established: 30% to 75% in independent and multi-institutional studies. These studies also revealed that patients admitted for bilateral "cellulitis" overwhelmingly tended to be stasis clinical pictures.[13,19]

Cost implications from inappropriate diagnosis largely regard inappropriate antibiotic use and the potential for microbial resistance, with associated costs estimated to be more than $50 billion (2004 dollars).[20,21] The true cost burden is extremely difficult to model or predict due to remarkable variations in the institutional misdiagnosis rate, prescribing pattern, and antibiotic cost and could represent avenues of further study. Misappropriation of antibiotics includes not only a monetary cost that

TABLE 3. Summary of Clinical Criteria Results

Clinical Criteria	Odds Ratio[a]	No. of Patients With Cellulitis (%) (n=20)	No. of Patients With Noncellulitis (%) (n=37)	*P* Value[b]
Acute onset	14.5	16 (80)	8 (22)	<.001
Erythema	10.3	19 (95)	24 (65)	.012
Pyrexia	99.2	17 (85)	2 (5)	<.001
History of associated trauma	36.0	10 (50)	1 (3)	<.001
Tenderness	11.8	18 (90)	16 (43)	<.001
Unilaterality	Incalculable[c]	20 (100)	11 (30)	
Leukocytosis	21.0	13 (65)	3 (8)	<.001

[a]For cellulitis.
[b]$P<.05$ is considered significant.
[c]Due to 100% prevalence in the cases of cellulitis among the study population.

encompasses all aspects of acute treatment and hospitalization but also an unquantifiable cost: human lives associated with the consequences of antibiotic resistance.

Conclusion

There is a lack of consensus or criteria for differentiating cellulitis from its most common clinical counterparts. Here, we propose a convenient clinical correlation system that we hope will lead to more efficient allocation of clinical resources, including antibiotics and hospital admissions, while lowering the incidence of adverse events and leading to better patient outcomes. We recognize that the small sample size of our study may limit broad application of these criteria, though we anticipate that further prospective studies can improve the diagnostic relevance and risk-assessment power of the NEW HAvUN criteria put forth here for assessing cellulitis in the acute medical setting.

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