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REVIEW

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Misdiagnosis of soft tissue infections: clinical pitfalls and management implications

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ABSTRACT

Introduction: Skin and soft tissue infections (SSTIs) are among the most frequent reasons for medical evaluation worldwide and are associated with significant clinical and healthcare implications. However, their diagnosis remains challenging, with frequent misdiagnosis, including both overdiagnosis of uncomplicated cellulitis and under-recognition of life-threatening necrotizing soft tissue infections.

Areas covered: We conducted a narrative review of the literature on diagnostic challenges in SSTIs. A search of PubMed/MEDLINE was performed for studies published up to March 2026, focusing on the misdiagnosis of cellulitis and necrotizing infections. We examined factors contributing to diagnostic errors, as well as the role of clinical assessment, laboratory tests, imaging, and multidisciplinary approaches in improving diagnostic accuracy and patient outcomes.

Expert opinion: Improving diagnostic accuracy in SSTIs requires structured clinical pathways based on careful assessment, early reassessment, and the selective use of imaging and specialist consultation. Future advances are more likely to derive from integrated diagnostic frameworks than from single diagnostic tests.

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KEYWORDS
Skin and soft tissue infections; cellulitis; necrotizing soft tissue infections; misdiagnosis; differential diagnosis

1. Introduction

Skin and soft tissue infections (SSTIs) represent one of the most frequent reasons for medical evaluation in both emergency departments (ED) and inpatient settings across different healthcare systems [1,2]. In the United States, population-based studies reported an overall SSTI incidence of 77.5 episodes per 1000 person-years between 2010 and 2020, with hospitalizations occurring at a rate of approximately 2.3 per 1000 person-years [1]. European data confirm a comparable burden, with hospital incidence of skin infections ranging from 1.8 to 2.4 per 1000 patient-days across several countries [2]. These infections therefore lead to considerable demand on healthcare services, including outpatient visits, antibiotic prescriptions, and hospitalizations, resulting in significant direct and indirect costs and highlighting the importance of accurate diagnosis and timely management [1–3].

Despite their apparent clinical familiarity, SSTIs are characterized by a remarkably high rate of diagnostic error. Various studies conducted in emergency and acute care settings have shown that up to 30–40% of patients initially diagnosed with cellulitis are ultimately found to have alternative, noninfectious diagnoses [4–7]. Conversely, time-critical infections such as necrotizing soft tissue infections (NSTIs) are frequently under-recognized in their early phases, when clinical signs may be subtle and nonspecific, and are often only identified at a later stage when more specific features, such as necrosis or bullae, become evident [8–10].

Together, these observations highlight the dual diagnostic challenge of SSTIs, which is prone both to the misclassification of noninfectious conditions as infection and to the failure to promptly recognize severe infections.

Several factors contribute to making SSTIs inherently 'diagnostically deceptive.' Clinical signs such as erythema, swelling, warmth, and pain are nonspecific and overlap with a wide range of vascular, inflammatory, and traumatic disorders, complicating early differentiation between infectious and noninfectious etiologies [4,6,7,10,11].

Beyond their high frequency, diagnostic errors in SSTIs have clinically relevant consequences. On the one hand, misclassification of noninfectious conditions as cellulitis leads to unnecessary antibiotic exposure, avoidable hospitalizations, and inappropriate use of healthcare resources, thereby increasing the risk of nosocomial infections, including *Clostridioides difficile* infection, as well as drug-related adverse events [3,7]. On the other hand, delayed recognition or missed diagnosis of NSTIs results in postponed surgical intervention, progression of tissue necrosis, and significantly increased mortality [10–12].

In this context, the present review aims to examine diagnostic errors in SSTIs, with a particular focus on community-acquired presentations, where diagnostic uncertainty is greatest due to nonspecific clinical features and a broad differential diagnosis. We discuss common diagnostic pitfalls, conditions most frequently mistaken for infection, and the consequences of delayed or inappropriate management, offering considerations for clinical and therapeutic management to improve diagnostic accuracy and patient outcomes.

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Article highlights

- Skin and soft tissue infections (SSTIs) are common and diagnostically challenging, with cellulitis frequently misdiagnosed and necrotizing infections often under-recognized.
- Misdiagnosis results in unnecessary antibiotics and hospitalizations; under-recognition delays surgery and increases morbidity and mortality.
- Current diagnostic tools, including scores, biomarkers, and imaging, are limited and insufficient as stand-alone tests.
- Structured clinical pathways, early reassessment, targeted use of imaging, and multidisciplinary collaboration represent key approaches to improve diagnostic accuracy and patient outcomes.

1.1. Literature search

This narrative review was based on a literature search conducted in PubMed/MEDLINE of studies published up to December 2025. The search strategy included combinations of the following keywords: 'skin and soft tissue infections,' 'cellulitis,' 'necrotizing soft tissue infections,' 'misdiagnosis,' 'diagnostic accuracy,' 'differential diagnosis,' and 'diagnostic tools.'

We included original studies, systematic reviews, and relevant clinical guidelines that focused on diagnostic challenges in SSTIs, particularly the misdiagnosis of cellulitis and the delayed recognition of necrotizing infections.

Studies were selected based on relevance to the topic and clinical applicability. Given the narrative nature of the review, no formal quality assessment or meta-analysis was performed.

2. Diagnostic pitfalls in skin and soft tissue infections: misdiagnosis in clinical practice

2.1. Diagnostic challenges in cellulitis

Cellulitis represents the most common form of skin and soft tissue infection and, at the same time, one of the conditions most frequently affected by diagnostic error [4–7]. Multiple studies across diverse healthcare settings have documented high rates of misdiagnosis. Prospective data from emergency departments in the United States suggest that cellulitis is misdiagnosed in approximately 19–35% of cases, with nearly 36% of initial cellulitis diagnoses in the ED not being confirmed after expert case review [6]. In a systematic review and meta-analysis of primary and unscheduled care settings (including outpatient clinics and inpatient wards in the U.S.A., UK, and Canada), the proportion of misdiagnosed uncomplicated cellulitis ranged widely, from 19% to 83%, with a pooled average misdiagnosis rate of 41% (95% CI 28–56%), reinforcing that diagnostic error is not confined to a single care environment [5]. Similar findings have been reported in other observational series, in which up to 30% of initial cellulitis diagnoses were ultimately judged incorrect when reassessed against expert review [7]. While misclassification of noninfectious conditions as cellulitis represents the most commonly reported error, failure to recognize true cellulitis may occur when it is mistaken for a noninfectious condition; however, untreated cellulitis typically progresses within 24–48 hours, often prompting clinical reassessment [13].

These diagnostic challenges have important clinical and healthcare implications. Misdiagnosis in the form of overdiagnosis frequently results in unnecessary antibiotic therapy, exposing patients to potential adverse drug effects and contributing to antimicrobial resistance [3,7]. In addition, misdiagnosed lower extremity cellulitis is associated with unnecessary hospital admissions, leading to excess inpatient costs of several thousand dollars per admission and significantly longer lengths of stay compared with accurately diagnosed patients [3]. These observations underscore the need for careful evaluation and ongoing clinical vigilance when assessing patients with suspected cellulitis.

The clinical presentation of cellulitis is characterized by erythema, edema, warmth, and tenderness [13]. This diagnostic uncertainty primarily applies to community-acquired presentations, whereas post-surgical cellulitis is generally more straightforward to recognize due to the presence of a surgical wound and a clear temporal association with the intervention [14].

Systemic signs such as fever may be absent, particularly in early or mild cases, and laboratory markers are often nonspecific, as demonstrated in a prospective cohort study of adult patients with cellulitis in the emergency department, where systemic signs of infection were present in only 34.7% of cases, including fever in 16.0%, tachycardia in 23.3%, tachypnea in 12.3%, and hypotension in 1.0% [15]. In the absence of a diagnostic gold standard, clinicians frequently diagnose cellulitis by exclusion rather than on the basis of positive objective criteria, which contributes substantially to diagnostic errors [13]. The clinical features of cellulitis may overlap with a broad range of infectious and noninfectious conditions, including venous stasis, lipodermatosclerosis, superficial thrombophlebitis, inflammatory dermatoses, drug reactions, and vasculitis. Supporting this, a recent study reported that among misdiagnosed cases, 54% were attributed to stasis dermatitis, eczematous dermatitis, or edema/lymphedema [5], while in another series, the most common alternative diagnoses were abscess (10%) for infectious conditions and stasis dermatitis (18%) for noninfectious conditions [7].

Beyond the nonspecific clinical signs, other factors contribute to diagnostic error, particularly overdiagnosis. Clinicians often face a heightened concern about missing a true infection, which can lower the threshold for initiating antibiotics [16]. The fast-paced environment of emergency departments, with high patient turnover and time pressures, frequently limits the opportunity for a thorough differential assessment or access to specialist input [6]. Together, these cognitive and contextual pressures can reinforce the default assumption of cellulitis and can lead to treatment initiation even when the diagnosis is uncertain.

Accurately diagnosing cellulitis requires a careful, methodical approach to distinguish true infection from alternative diagnoses. A combination of detailed patient history, thorough physical examination, and focused diagnostic assessment may help identify the underlying etiology [13]. Lymphangitic streaking may represent a useful clinical clue supporting the diagnosis of erysipelas and may help

differentiate infectious erythema from noninfectious conditions such as stasis dermatitis [13].

Although the diagnosis of lower-limb cellulitis remains largely clinical, some diagnostic scores and predictive models have been developed to support clinicians. The ALT-70 demonstrates high sensitivity (97.8%) but moderate specificity (47.6%) for distinguishing cellulitis from pseudocellulitis; notably, this score was developed and validated specifically for lower extremity presentations in the emergency department, and its applicability is limited to uncomplicated cases, as patients with recent surgery, penetrating wounds, underlying ulcers, or prior antibiotic use were excluded from the validation cohorts [17–19]. Moreover, a more recent validation study reported less favorable performance, with 40% of patients classified as 'likely cellulitis' ultimately receiving an alternative diagnosis, suggesting limited reliability in clinical practice [20]. The NEW-HavUN criteria, integrating clinical features and laboratory values across seven domains, showed high sensitivity (100%) and specificity (95%) in a retrospective derivation cohort, though prospective validation is still needed [18,21].

Biochemical markers have also been investigated. A delta neutrophil index of >17% has been proposed for distinguishing cellulitis from acute gout [22]. Procalcitonin has limited sensitivity for confirming cellulitis, but may be more useful for raising suspicion of necrotizing soft tissue infection versus uncomplicated cellulitis; however, available studies are small and results have not consistently reached statistical significance [23–25]. These tools remain limited and require further validation, emphasizing that careful clinical evaluation remains paramount [26].

Imaging can provide additional information in selected cases, particularly ultrasound to detect underlying abscesses or deeper tissue involvement, though it cannot replace clinical judgment [27–29].

Thermal imaging may help differentiate cellulitis from pseudocellulitis. One study demonstrated that a temperature difference ≥0.47°C between affected and unaffected limbs achieved 96.6% sensitivity [30], and a subsequent prospective validation confirmed a significant difference of 2.0°C (95% CI 1.3–2.7°C; $p < .001$) with 96.8% sensitivity [20]. This modality may also track clinical progress, though daily temperature changes may be small for individual-level monitoring [31,32].

Point-of-care ultrasound (POCUS) is a rapid bedside technique that has demonstrated good diagnostic performance for differentiating cellulitis from abscess. In a systematic review and meta-analysis of 14 studies (2,656 patients), POCUS was 94.6% sensitive and 85.4% specific, with specificity increasing to 89.1% in patients with high pretest suspicion for abscess or cellulitis; this permitted a correct change in management in 10.3% of cases [29].

Computed tomography (CT) and magnetic resonance imaging (MRI) are not routinely indicated for uncomplicated cellulitis but may help differentiate cellulitis from necrotizing fasciitis or pyomyositis when clinical suspicion is high [13].

Despite the availability of these imaging tools, specialist consultation, including dermatology and infectious disease evaluation, has been shown to improve diagnostic accuracy, optimize patient management, and reduce unnecessary antibiotic use and hospitalizations [33,34].

However, within this diagnostic framework, the routine use of ancillary tests in all patients presenting with erythema is of limited value, as investigations such as blood cultures or serial inflammatory markers rarely contribute to diagnostic clarification in uncomplicated superficial inflammatory conditions [35]. Similarly, microbiological cultures obtained from superficial soft tissue samples have limited diagnostic value in cellulitis, as they often reflect colonizing flora rather than true pathogens [13,35]. Therefore, routine microbiological testing should not be used to guide diagnosis or to broaden antimicrobial management in the absence of clinical or intraoperative evidence of invasive infection [13,35].

In selected mild to moderate cases, where diagnostic uncertainty persists, early clinical reassessment over time may provide additional diagnostic value, as disease evolution can help differentiate infectious from noninfectious conditions [13].

Awareness of clinical red flags can guide reconsideration of the diagnosis. Features suggesting alternative or more complex conditions include bilaterality, absence of fever or leukocytosis, chronic or recurrent course, lack of response to antibiotics, and hyperpigmented, indurated, or non-tender skin [13].

In routine practice, this translates into prioritizing clinical evaluation and early reassessment, reserving adjunctive tests and imaging for selected cases where diagnostic uncertainty persists or deeper infection is suspected.

2.2. Diagnostic challenges in necrotizing soft tissue infections

Necrotizing soft tissue infections represent one of the most severe and life-threatening forms of skin and soft tissue infection and, at the same time, one of the conditions most frequently affected by diagnostic error, predominantly in the form of initial misdiagnosis and subsequent delay of treatment [10,11,36,37].

Although NSTIs may also occur in healthcare-associated or post-surgical settings, the majority of diagnostic uncertainty arises in community or emergency department presentations, where early clinical findings are often nonspecific and may closely mimic uncomplicated cellulitis or other benign soft tissue infections [10,11].

Although relatively uncommon, NSTIs have a disproportionate clinical impact, as delayed recognition and treatment remain key determinants of poor outcomes [11,36,37]. Early manifestations (localized pain, erythema, and swelling) are often subtle and nonspecific, and initial presentations may closely resemble uncomplicated or non-necrotizing SSTIs, contributing to early diagnostic misclassification [38–41].

NSTIs encompass a spectrum of entities including necrotizing fasciitis, necrotizing myositis, and necrotizing cellulitis, often characterized by rapid extension along fascial planes with variable involvement of subcutaneous fat and muscle [10,11,36,37]. They are traditionally classified as polymicrobial type I infections, typically occurring in older patients or those with significant comorbidities and involving synergistic

aerobic and anaerobic flora; monomicrobial type II infections, most commonly caused by *Streptococcus pyogenes* or *Staphylococcus aureus* and their toxins; type III infections related to marine bacteria, such as *Vibrio vulnificus* or *Aeromonas hydrophila* following marine or freshwater trauma; and type IV infections caused by fungi (Table 1) [10,11,36,37,42,43]. While these microbiologic and epidemiologic distinctions may help orient suspicion, the heterogeneity of presentations can also contribute to diagnostic uncertainty, particularly in patients lacking classic risk factors or exposure histories [9–11,44].

The estimated incidence of necrotizing fasciitis ranges from 0.3 to 15 cases per 100,000 population, but reported mortality rates remain high, at around 20%, especially in polymicrobial infections, Fournier gangrene, cervical infections, and neonatal cases [11,37,42,45,46]. Excess mortality has consistently been associated with delays in diagnosis and surgical intervention rather than specific microbiologic characteristics alone [9,11,40]. Known risk factors include diabetes mellitus, peripheral vascular disease, obesity, alcoholism, malignancy, cirrhosis, immunosuppression, minor trauma, surgical wounds, and breaches of the skin or mucosa [11,36,37,41,42,45–47]. However, exclusive reliance on traditional risk profiles may be misleading, as NSTIs can also occur in previously healthy individuals, increasing the risk of underdiagnosis during early disease stages [9–11,44].

Clinically, NSTIs are classically associated with severe pain disproportionate to cutaneous findings, rapidly progressive edema extending beyond visible erythema, and systemic signs such as fever, tachycardia, or hemodynamic instability [11,36,37,42,45,46]. However, these hallmark features are often absent or underestimated during the initial phase of disease, when skin changes may be minimal and systemic signs are mild or nonspecific [38]. As a result, early NSTIs are frequently misdiagnosed as uncomplicated cellulitis or other benign soft tissue infections [39,41]. In observational studies, NSTIs are initially misdiagnosed in up to 96% of cases, most commonly as cellulitis, contributing significantly to delayed surgical referral and worsened outcomes [9,10].

Additional findings such as bullae, ecchymosis, necrosis, blue-gray discoloration, crepitus, or early hypoesthesia, reflecting microvascular thrombosis and nerve involvement, typically emerge later in the disease course, when extensive tissue necrosis has already developed [11,37,45].

Laboratory abnormalities, including leukocytosis, hyponatremia, metabolic acidosis, elevated inflammatory markers, acute kidney injury, and raised creatine kinase or AST, are common but nonspecific and may be absent early in the disease course [11,37]. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, which incorporates six routinely available laboratory parameters (C-reactive protein, white blood cell count, hemoglobin, sodium, creatinine, and glucose), is widely used to support the diagnosis of NSTI, with a score ≥6 traditionally considered suggestive and ≥8 as strongly predictive of disease. However, its sensitivity has shown considerable variability across different cohorts, and it should not be relied upon to exclude NSTI [11,37]. Reported performance varies across studies, with sensitivity ranging approximately from 36% to 77% and specificity from 72% to 93%, depending on the population and cutoff used [48]. When used as a rule-out tool, low or intermediate LRINEC scores may provide false reassurance in some cases and contribute to delayed surgical consultation [38,49,50].

Imaging may support clinical suspicion but cannot replace clinical judgment. Computed tomography is often preferred for its availability and ability to detect soft tissue gas and deep fascial involvement, while magnetic resonance imaging offers excellent tissue contrast but may overestimate disease extent and is frequently less practical in unstable patients [11,36,37,51]. Ultrasound may help identify fluid collections and differentiate cellulitis from abscess, but has a limited role in excluding NSTI. Its principal advantage is that it can be performed at the bedside [51]. Point-of-care ultrasound has shown promising diagnostic performance in small studies, with reported sensitivity of 85–100% and specificity of 44–98% for detecting necrotizing infections or deep soft tissue involvement, although data remain limited to a few small and heterogeneous studies [52]. Importantly, overreliance on imaging to rule out NSTI, particularly in early disease, may further delay definitive surgical evaluation.

The advantages and limitations of commonly used diagnostic tools for SSTIs are summarized in Table 2.

Ultimately, the diagnosis of NSTI is confirmed by prompt surgical exploration, which allows direct visualization of devitalized fascia, thin 'dishwater' fluid, and loss of normal tissue resistance on blunt dissection [11,36,37]. Multiple studies have demonstrated that delays exceeding 24 hours from presentation to surgical intervention are associated with significantly increased mortality, whereas early exploration, within a few hours, improves survival and limits tissue loss [11,36,37,42,45,46]. Notably, a systematic review showed that even surgical delays exceeding 6 hours after presentation are associated with a significant increase in mortality, underscoring the extreme time-sensitivity of NSTI management [53].

These findings underscore that failure to recognize NSTI early, rather than limitations of surgical or antimicrobial therapy, remains a principal driver of poor outcomes.

Taken together, NSTIs exemplify the opposite end of the SSTI misdiagnosis spectrum compared with cellulitis. While cellulitis is frequently overdiagnosed, NSTIs are often underestimated in their early stages, leading to delayed source control and excess mortality. Recognizing when an apparent

Table 1. Classification of necrotizing soft tissue infections [11].

Type	Main pathogens	Typical patients / risk factors
Type I (polymicrobial)	Streptococci, Staphylococci, anaerobes	Older adults, comorbidities (diabetes, vascular disease, immunosuppression)
Type II (monomicrobial)	*Streptococcus pyogenes*, *Staphylococcus aureus*	Young adults, otherwise healthy or mildly immunocompromised
Type III (environmental / aquatic)	*Vibrio vulnificus*, *Aeromonas hydrophila*	Marine or freshwater exposure, traumatic wounds
Type IV (fungal)	*Candida* spp., *Aspergillus* spp.	Immunocompromised, prior antifungal therapy

Table 2. Advantages and limitations of diagnostic tools for skin and soft tissue infections.

Tool / method	Advantages	Limitations
LRINEC score	Easy to calculate; supports NSTI suspicion	Variable sensitivity; cannot replace clinical evaluation
ALT-70 / NEW HavUN scores	Predictive models for cellulitis	Limited validation; inconsistent performance across settings
Biomarkers (e.g. delta neutrophil index)	May help differentiate from other inflammatory conditions	Not universally available; not diagnostic alone
Imaging: Ultrasound	Bedside, identifies superficial abscesses	Limited for deep fascial involvement or NSTIs
Imaging: CT / MRI	Good soft tissue definition; detects gas/necrosis	Costly; limited availability; may delay urgent surgery; for CT Ionizing radiation exposure
Specialist consultation (ID / Dermatology)	Improves diagnostic accuracy; reduces unnecessary treatment	Limited availability; time-consuming

Abbreviations: ALT-70, Assessment tool for lower limb cellulitis; CT, Computed tomography; ID, Infectious Diseases; LRINEC, Laboratory Risk Indicator for Necrotizing Fasciitis; MRI, Magnetic resonance imaging; NEW HavUN, New Haven University diagnostic criteria for cellulitis; NSTI, Necrotizing Soft Tissue Infection.

uncomplicated SSTI is not following the expected clinical course remains a critical clinical skill and a central lesson in avoiding diagnostic error in soft tissue infections.

3. Classification and differential diagnosis of skin and soft tissue infections

3.1. Purpose of classification in SSTIs

Skin and soft tissue infections (SSTIs) represent a heterogeneous group of clinical conditions involving varying depths of the epidermis, dermis, subcutaneous tissue, fascia, and muscle [51].

Appropriate classification is essential not only to guide therapeutic decisions and antimicrobial stewardship, but also to support diagnostic reasoning and reduce the risk of misdiagnosis, avoiding unnecessary use of antibiotics and delays in treatment [54].

Historically, SSTIs have been classified according to clinical complexity and depth of involvement. In 1998, the U.S. Food and Drug Administration (FDA) distinguished uncomplicated infections, such as cellulitis, simple abscesses, impetigo, and furuncles, from complicated infections, including necrotizing infections, infected ulcers, infected burns, and major abscesses [55]. Subsequently, in 2014, the Infectious Diseases Society of America (IDSA) proposed a more clinically oriented framework based on purulence, severity of disease (mild, moderate, and severe), and the presence or absence of tissue necrosis, allowing a more pragmatic approach to risk stratification and management [35].

Additional classification systems, such as the Eron classification, incorporate host factors and comorbidities (e.g. diabetes, obesity, vascular disease) to further guide clinical decision-making [56].

3.2. Differential diagnosis among infectious SSTIs

From a diagnostic perspective, an initial and essential distinction lies between superficial, deep, and necrotizing infections. Superficial SSTIs, including impetigo, folliculitis, erysipelas, and furuncles, are typically localized, mild, and confined to the epidermis or superficial dermis. These infections are more often monomicrobial and predominantly caused by *Staphylococcus aureus* or *Streptococcus pyogenes* [57]. In contrast, cellulitis extends into the deeper dermis and subcutaneous tissue, while deep infections, such as abscesses, fasciitis, myositis, and myonecrosis, may involve fascial planes or muscular compartments and are associated with greater morbidity and the potential for rapid clinical deterioration [14].

Necrotizing soft tissue infections represent the most severe end of the SSTI spectrum and constitute a true diagnostic and therapeutic emergency [9,11]. NSTIs can be classified according to microbiology (type I polymicrobial, type II monomicrobial, type III associated with *Vibrio vulnificus* or *Aeromonas hydrophila*, and type IV fungal infections), anatomical site (e.g., Fournier gangrene), or depth of tissue involvement [10,11,36,37,42,43]. Diagnosis is primarily clinical, and delays in recognition and surgical evaluation are strongly associated with increased mortality [9,11,40]. Imaging, particularly urgent computed tomography, may support assessment due to its high sensitivity and specificity for deep tissue involvement, but laboratory findings and scoring systems such as the LRINEC score should be considered adjunctive tools and must never delay surgical consultation when clinical suspicion is high [10,39].

Beyond the distinction among infectious SSTIs, clinicians are frequently challenged by conditions that require separate diagnostic consideration because of their unique pathophysiology and management [58,59]. Surgical site infections (SSIs), for instance, are classified as superficial incisional, deep incisional, or organ/space infections, with only the first two categories strictly involving soft tissues [60]. Burn wound infections and diabetic foot infections (DFIs) also represent distinct clinical entities [58,59]. Burn wounds often progress from colonization to invasive infection and are commonly associated with *Pseudomonas aeruginosa*, *Acinetobacter* spp., fungi, and multidrug-resistant organisms, necessitating a tailored diagnostic approach [58]. DFIs typically arise from neuropathic ulcers, are frequently polymicrobial, and require careful microbiological sampling, preferably through deep tissue or bone biopsy rather than surface cultures, to optimize targeted antimicrobial therapy and improve outcomes [57].

3.3. Differential diagnosis between infectious and noninfectious conditions

Finally, an accurate diagnostic approach to SSTIs must extend beyond infectious etiologies alone. Several noninfectious conditions can closely mimic SSTIs and contribute substantially to misdiagnosis [5,7]. This aspect of the differential diagnosis is particularly relevant in patients with underlying vascular

disease, autoimmune conditions, or chronic inflammatory disorders [61].

A symmetric or diffusely scattered pattern suggests a condition other than cellulitis. Venous stasis disease, stasis dermatitis, and lipodermatosclerosis are among the most common alternative diagnoses, typically presenting with chronic, often bilateral erythema, edema, hyperpigmentation, and limited tenderness. The inciting factor is chronic venous insufficiency, leading to interstitial edema, extravasation of red blood cells, hemosiderin deposition, and a chronic inflammatory process mediated by metalloproteinases [5,7]. Superficial thrombophlebitis may resemble cellulitis but is often characterized by localized tenderness along a palpable venous cord.

Lymphedema should be considered in the differential diagnosis and is characterized by progressive non-pitting edema of an affected extremity with induration and, in advanced stages, skin fibrosis, hyperkeratosis, and papillomatous changes. It can be primary, due to congenital abnormalities, or secondary to interruption of a previously functioning lymphatic system. These patients are at significantly increased risk of cellulitis, as lymphatic stasis provides an optimal environment for bacterial growth and impairs local immune responses [62].

Inflammatory dermatoses, drug reactions, panniculitis, and vasculitides can also present with erythema and swelling, often in the absence of systemic signs of infection; moreover, a long-standing, slowly progressive course and a history of unsuccessful treatment with antibiotics are strong indicators of a condition other than cellulitis [13].

Other noninfectious conditions that may mimic cellulitis include allergic and irritant contact dermatitis, which is a type IV delayed hypersensitivity reaction presenting with erythematous patches and plaques with well-defined borders, often in a geometric distribution corresponding to the area of contact with the offending agent [63,64]; eosinophilic cellulitis (Wells syndrome), a rare eosinophilic dermatosis characterized by infiltrated erythematous plaques that initially resemble erysipelas or cellulitis but do not respond to antibiotic treatment [65]; and papular urticaria, a hypersensitivity reaction to arthropod bites presenting with clustered pruritic papules [66].

Conversely, factors that favor a diagnosis of cellulitis include underlying immunosuppression, a more rapid progression, previous episodes, systemic symptoms such as fever or leukocytosis, new travel or outdoor exposure, and comorbidities such as diabetes and peripheral vascular disease [66].

Careful assessment of the medical history is essential to avoid misdiagnosis and unnecessary antimicrobial therapy [13].

To facilitate bedside clinical decision-making, a practical overview of common infectious and noninfectious conditions mimicking SSTIs, along with key diagnostic features, useful investigations, and major pitfalls, is summarized in Table 3.

4. Treatment approach of skin and soft tissue infections

The therapeutic approach to SSTIs should begin with a careful diagnostic assessment aimed at distinguishing infectious from noninfectious conditions. As highlighted in this review, the differential diagnosis between infectious SSTIs and inflammatory, vascular, or immune-mediated dermatoses can be challenging, and misclassification is common. Indeed, almost 40% of cases initially labeled as infectious SSTIs may ultimately be reclassified as noninfectious entities, underscoring the importance of diagnostic accuracy before initiating empiric antibiotic therapy [7]. Once an infectious etiology is suspected, management relies on the timely integration of clinical severity assessment, source control, and an appropriate antimicrobial backbone [35,61].

While a detailed discussion of therapeutic algorithms is beyond the scope of this review - readers are referred to current clinical guidelines for comprehensive recommendations [35,61] - this review highlights several key aspects, including the importance of a combined medical and surgical approach when indicated, the need for careful risk stratification to guide therapeutic decisions, and a brief overview of recent advances, including newer antimicrobial agents that may be considered in selected complex clinical settings.

When choosing the appropriate therapeutic management for SSTIs, a pivotal step is the evaluation of infection extent, distinguishing superficial from deep infections, as this stratification has major implications for both antimicrobial choice and the need for surgical intervention [35,61]. Superficial SSTIs can often be managed conservatively, whereas deep infections, including abscesses and necrotizing soft tissue infections, require a more aggressive and multidisciplinary approach [67]. Surgery represents a cornerstone of treatment across the SSTI spectrum, ranging from drainage of purulent collections to urgent, life-saving debridement in necrotizing infections. Recent position statements emphasize that early diagnosis combined with prompt medical and surgical treatment, within a multidisciplinary framework, is essential to improve patient outcomes [68].

Surgical intervention also plays a crucial role in microbiological diagnosis. Whenever feasible, microbiological sampling should be obtained to guide targeted therapy [69]. While empiric anti-staphylococcal coverage remains necessary in most SSTIs, particularly in the presence of risk factors or healthcare-associated infections [35,61], rapid diagnostic tools aimed at excluding methicillin-resistant *Staphylococcus aureus* (MRSA) may support antimicrobial stewardship. The increasing availability of rapid molecular tests has the potential to reduce unnecessary broad-spectrum exposure and allow earlier optimization of therapy [70].

Initial antibiotic selection should be guided by infection depth, host characteristics, clinical severity, and the most likely causative pathogens [35,61]. Overall, therapeutic strategies for SSTIs may vary across different clinical scenarios and heterogeneous patient populations, with variable quality and strength of the supporting evidence, making careful risk stratification essential. β-hemolytic streptococci and methicillin-susceptible *Staphylococcus aureus* remain the primary therapeutic targets in community-acquired SSTIs, and should be covered empirically with narrow-spectrum antibiotics, including penicillin and cephalosporins [35,61]. Empiric coverage for MRSA is indicated in specific settings, including severe systemic presentation, purulent manifestations, healthcare-associated infections, and immunocompromised states. It may also be considered in the presence of MRSA colonization, with

Table 3. Practical differential diagnosis of skin and soft tissue infections, including infectious and noninfectious alternative diagnosis, with key clinical features, diagnostic tools, and major pitfalls.

Diagnosis	Etiology	Clinical presentation and key features	Useful investigations	Red flags / pitfalls
Bacterial cellulitis	Infectious (bacterial)	Unilateral erythema, warmth, tenderness, poorly demarcated margins, possible fever, 'orange peel'	CBC, CRP, ultrasound (to exclude abscess), cultures in selected cases	Bilateral involvement, chronic course, lack of response to antibiotics
Erysipelas	Infectious (bacterial, streptococcal)	Raised, sharply demarcated erythematous plaque, fever	Clinical diagnosis, ASO titer (supportive, delayed marker; limited role in acute management)	Confusion with cellulitis; typically more superficial and well-demarcated
Cutaneous abscess	Infectious (bacterial)	Fluctuant, tender nodule, possible purulent drainage, fever	Ultrasound, culture of drainage	Mistaken for cellulitis without drainage → requires source control
Viral exanthem	Infectious (viral, HSV, VZV)	Vesicular or maculopapular rash, mucosal involvement, dermatomal distribution (VZV)	Exposure history (positive contact), clinical, PCR/ serology in selected cases	Misdiagnosed as bacterial infection → unnecessary antibiotics
Necrotizing fasciitis	Infectious (bacterial, polymicrobial or monomicrobial)	Severe pain disproportionate to findings, rapidly progressive edema, systemic toxicity ± minimal early skin changes	Urgent surgical exploration, CT (adjunctive), labs (LRINEC not definitive)	Early signs subtle; do not delay surgery for imaging
Sporotrichosis	Infectious (fungal)	Subcutaneous nodules along lymphatic drainage	Fungal culture, exposure history (plants/soil)	Misdiagnosed as bacterial infection
Lyme disease	Infectious (*Borrelia burgdorferi*)	Erythema migrans, annular expanding lesion	Clinical, serology (later stages), exposure history	Early serology may be negative
Urticaria	Noninfectious (immune-mediated)	Transient, pruritic wheals, rapid resolution (<24 h)	Clinical	Often misinterpreted as infection due to erythema
Pyoderma gangrenosum	Noninfectious (immune-mediated)	Painful ulcers with violaceous borders, rapid progression	Clinical, exclusion, association with IBD	Worsens with surgical debridement (pathergy)
Vasculitis	Noninfectious (immune-mediated)	Palpable purpura, often lower limbs, possible systemic involvement	Skin biopsy, autoimmune workup	May mimic infection; systemic signs not always infectious
Systemic lupus erythematosus	Noninfectious (autoimmune)	Malar rash, photosensitivity, systemic involvement	ANA, immunological tests	Misdiagnosed as cellulitis in early inflammatory phases
Drug eruption	Noninfectious (hypersensitivity)	Symmetric maculopapular rash, pruritus, recent drug exposure	Clinical history	Temporal relationship with drugs is key
Erythema multiforme	Noninfectious (immune-mediated)	Target lesions, often post-HSV or drug exposure	Clinical	Distinctive morphology helps differentiation
Stasis dermatitis / lymphedema	Noninfectious (vascular)	Bilateral, chronic erythema and edema, hyperpigmentation (brownish skin), minimal tenderness	Venous Doppler ultrasound	Bilaterality strongly suggests noninfectious etiology
Erythema nodosum	Noninfectious (inflammatory)	Painful, erythematous nodules (pretibial), often with systemic symptoms	Clinical, evaluate underlying cause (e.g. infection, sarcoidosis)	Frequently mistaken for cellulitis
Gout	Noninfectious (crystal-induced)	Acute monoarticular inflammation, erythema, swelling, severe pain	Joint aspiration (urate crystals)	Can closely mimic cellulitis, especially in lower limbs

Abbreviations: ANA: antinuclear antibodies; ASO: Antistreptolysin O; CBC: Complete blood count; CRP: C-reactive protein; CT: Computed Tomography; IBD: inflammatory bowel disease; LRINEC: Laboratory Risk Indicator for Necrotizing Fasciitis; PCR: Polymerase Chain Reaction; TB: tuberculosis.

Table 4. Newer antibiotics for skin and soft tissue infections (adapted and extended from [85]).

Drug	Class	Typical ABSSSI dose / route	Spectrum (high-yield)	Key advantages	Main disadvantages / gaps	Notable adverse effects & monitoring
Linezolid	Oxazolidinone	600 mg q12h IV or PO	Gram-positives incl. MRSA, streptococci	Excellent oral bioavailability; PO switch	Bacteriostatic; DDIs; limited spectrum	Myelosuppression; neuropathy; serotonin syndrome risk
Tedizolid	Oxazolidinone	200 mg once daily IV or PO	Gram-positives incl. MRSA, streptococci	Once daily; fewer DDIs; better tolerability than linezolid	Bacteriostatic	Reversible cytopenias; rare neuropathy
Daptomycin	Lipopeptide	8–10 mg/kg q24h IV	Gram-positives incl. MRSA	Rapid bactericidal activity	Limited spectrum	CPK elevation; eosinophilic pneumonia (rare)
Dalbavancin	Lipoglycopeptide	1500 mg IV OR 1000 mg +500 mg after 1 week	Gram-positives incl. MRSA	Single/twice weekly dosing; outpatient strategy	IV only	GI symptoms; infusion reactions
Oritavancin	Glycopeptide	1200 mg IV single dose	Gram-positives incl. MRSA, some VRE	Single-dose outpatient strategy	IV only; lab test interference	Headache; GI upset; infusion reactions
Delafloxacin	Fluoroquinolone	300 mg q12h IV or 450 mg q12h PO	Gram+ incl. MRSA; Gram− incl. *Pseudomonas*	Oral MRSA option; antibiofilm activity	FQ class warnings	Tendinopathy; neuropathy; CNS effects
Omadacycline	Aminomethylcycline	IV loading then PO	Gram+ incl. MRSA; some Gram−	IV/PO flexibility	GI intolerance	Nausea; class tetracycline warnings
Ceftaroline	5th-gen cephalosporin	600 mg q12h IV	MRSA; streptococci	Bactericidal beta-lactam for MRSA	IV only	Beta-lactam AEs; neutropenia
Ceftobiprole	Anti-MRSA cephalosporin	500 mg q8h IV	MRSA; streptococci; some Gram−	Broad single-agent potential	IV only	Beta-lactam AEs

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AEs, adverse events; CNS, central nervous system; CPK, creatine phosphokinase; DDIs, drug–drug interactions; FQ, fluoroquinolone; GI, gastrointestinal; GP, Gram-positive; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, oral administration; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; VRE, vancomycin-resistant *Enterococcus*.

a predictive value that depends on local epidemiology and prevalence [35,61]. Polymicrobial infections and Gram-negative pathogens become increasingly relevant in healthcare-associated infections, necrotizing presentations, and immunocompromised hosts [71,72]. In the presence of these risk factors, a patient-tailored assessment of the potential pathogens is necessary, and broad-spectrum empiric therapy may be indicated. This should be initiated promptly in severe infections, together with surgical evaluation, and subsequently refined based on clinical response and microbiological results. Interpretation of microbiological findings should be guided by clinical relevance to reduce unnecessary broad-spectrum antibiotics exposure, in line with antimicrobial stewardship principles [67].

Complementing guideline-recommended algorithms [35,61], several novel therapeutic options have expanded the treatment landscape for SSTIs in recent years, as summarized in Table 4 [71,73,74]. These agents may be considered in challenging clinical settings, including the presence of resistance and specific risk factors, when standard therapeutic options are limited. These agents primarily target Gram-positive pathogens, particularly MRSA, and have been developed to overcome limitations of older therapies related to resistance, safety, and logistical complexity. Fifth-generation cephalosporins such as ceftaroline and ceftobiprole combine potent bactericidal activity against MRSA with favorable pharmacokinetic profiles and good tissue penetration. Randomized clinical trials in acute bacterial skin and skin structure infections have demonstrated their non-inferiority to standard comparators [75,76]. These results could allow simplified single-agent regimens in selected patients [73,77].

Long-acting lipoglycopeptides, including dalbavancin and oritavancin, represent a paradigm shift in SSTI management by enabling single-dose or once-weekly intravenous regimens [71]. Clinical studies have shown high efficacy and safety in both uncomplicated and selected complicated SSTIs, supporting early discharge and outpatient parenteral antimicrobial therapy without compromising clinical outcomes [78–81]. Additionally, newer oral agents such as delafloxacin [82,83] and the next-generation oxazolidinone tedizolid [84] provide reliable anti-MRSA coverage with high oral bioavailability, facilitating early intravenous-to-oral switch strategies. Finally, investigational agents such as lefamulin, brilacidin, and emerging oxazolidinones further highlight an evolving treatment paradigm aimed at optimizing outpatient care pathways [73,74].

Indeed, although intravenous therapy remains recommended in severe infections, oral therapies may also represent first-line treatment in uncomplicated cases, and an early switch to oral treatment is a key stewardship objective. Transition to oral agents should be considered once clinical stability is achieved, effective source control has been performed, and drugs with adequate bioavailability are available [85]. These therapeutic advances may be particularly relevant in patients with correctly identified SSTIs, allowing effective treatment while avoiding unnecessary hospitalization and prolonged intravenous therapy.

5. Conclusion

Skin and soft tissue infections remain a frequent and clinically relevant cause of medical evaluation, and their diagnosis may be challenging in routine clinical practice. As highlighted in this review, SSTIs lie along a diagnostic continuum of misdiagnosis, with frequent overdiagnosis of uncomplicated cellulitis and under-recognition of necrotizing infections in their early stages. These opposing but interconnected errors are driven

by nonspecific clinical presentations, overlapping differential diagnoses, contextual pressures, and limitations of available diagnostic tools.

Improving diagnostic accuracy in SSTIs does not rely on a single test or score, but rather on careful clinical assessment, early reassessment, and awareness of red flags that suggest alternative diagnoses or disease progression.

6. Expert opinion

The evidence discussed in this review carries substantial implications for real-world clinical practice. Diagnostic inaccuracies in SSTIs extend beyond individual patient outcomes, exerting an impact on healthcare systems, including antibiotic prescriptions, hospital admissions, surgical decision-making, and overall utilization of healthcare resources. Misdiagnosis, most commonly manifesting as overdiagnosis of uncomplicated cellulitis, remains a major contributor to unnecessary antibiotic exposure and avoidable hospital admissions. Conversely, delayed or missed recognition of NSTIs continues to result in preventable morbidity and excess mortality. Addressing these dual and opposing diagnostic failures therefore represents a critical and high-impact opportunity to improve both patient safety and resource allocation.

From an implementation standpoint, enhancing diagnostic accuracy in SSTIs is unlikely to depend on novel diagnostic technologies, but rather on the structured and consistent application of existing clinical tools. A thorough medical history and clinical assessment remain the cornerstone of diagnosis, particularly when combined with heightened awareness of diagnostic 'red flags' such as rapid progression, disproportionate pain, and systemic toxicity.

In parallel, the selective use of imaging, particularly bedside ultrasound, and timely specialist consultation can provide clinically meaningful information such as the presence of abscess or alternative diagnoses, refining initial diagnostic impressions.

It is very important to timely involve other specialists when necessary, such as surgeons, dermatologists, immunologists, among others.

In this context, microbiological confirmation is often unavailable at the time of initial decision-making, and clinical management frequently relies on structured clinical reasoning rather than pathogen-specific evidence.

Within this framework, early and iterative reassessment emerges as a pivotal component for diagnostic refinement and for evaluating treatment response, particularly in cases initially managed with empiric therapy. Lack of clinical improvement should prompt reconsideration of the initial diagnosis and therapeutic strategy rather than continuation of an ineffective predefined antibiotic course. A lack of expected clinical improvement should not automatically prompt escalation or prolongation of antimicrobial therapy; instead, it should trigger a critical reappraisal of the working diagnosis and consideration of alternative etiologies, including noninfectious mimickers or deeper infectious processes.

However, adoption of routine reassessment is often limited by contextual factors such as time pressure in emergency settings, concerns about missing severe infections, variability in access to specialist expertise, and the absence of standardized diagnostic frameworks that explicitly incorporate reassessment as part of the diagnostic process. Additionally, the perceived risk of missing severe infections may drive defensive prescribing behaviors, contributing to antibiotic overuse. Variability in access to specialist consultation and imaging resources further exacerbates these challenges.

Overall, translating current evidence into practice appears feasible but requires a shift from a static, one-time diagnostic approach toward a dynamic and iterative model of clinical evaluation. Such a model emphasizes diagnostic flexibility, continuous data integration, and responsiveness to evolving clinical information.

A major unmet need in the field of SSTIs lies in the development of validated, widely applicable diagnostic frameworks that integrate clinical assessment, temporal evolution, and reassessment into a single decision-making process. Existing diagnostic scores and biomarkers have demonstrated variable performance across settings, restricting their utility as stand-alone tools [26,39]. Moreover, much of the available evidence derives from retrospective studies, single-center cohorts, or studies relying on expert adjudication, which limits generalizability and complicates the definition of robust diagnostic endpoints.

Future advances in the diagnosis of SSTIs are more likely to derive from the optimization of clinical pathways than from the introduction of a single transformative diagnostic test. Unlike other areas of infectious diseases in which molecular or rapid diagnostics have reshaped clinical workflows, SSTIs remain predominantly defined by clinical presentation, disease evolution, and response to initial management.

In this regard, research efforts should focus on integrating structured clinical assessment tools with early reassessment strategies, targeted use of imaging, and selective incorporation of biomarkers when appropriate. Although the heterogeneity of SSTIs limits the development of universal diagnostic criteria, even targeted improvements in diagnostic pathways may translate into meaningful gains in patient safety, antimicrobial stewardship, and healthcare resource utilization.

Moreover, fostering closer interdisciplinary collaboration among emergency medicine, infectious diseases, dermatology, radiology, and other specialties represents a key opportunity for advancing the field. Multidisciplinary input is particularly valuable in complex or atypical cases, where diagnostic ambiguity is highest and consequences of errors are most significant.

In this scenario, five years from now, the field may no longer rely solely on individual clinician judgment, but on structured, validated pathways that combine clinical expertise with selective adjunctive tools, translating into faster, safer, and more cost-effective management of SSTIs in routine clinical practice.

Finally, although emerging artificial intelligence-based algorithms may increasingly support diagnostic decision-making and risk stratification in SSTIs, accurate diagnosis will continue to rely on careful clinical evaluation, with a particular emphasis on a thorough patient history.

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Visualization, Writing – original draft, Writing – review & editing; **Federica Portunato:** Conceptualization, Data curation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Matteo Cerchiaro:** Data curation, Visualization, Writing – original draft, Writing – review & editing; **Laura Mezzogori:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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