

## REVIEW ARTICLE

# Skin & Soft Tissue Infections: It's More Than Just MRSA

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**ABSTRACT:** Skin and soft tissue Infections (SSTIs) encompass a broad range of pathologies and represent a significant reason for outpatient visits. It is important to distinguish between complicated and uncomplicated SSTIs, which differ in terms of its presentation, severity, and treatment options. Uncomplicated SSTIs can present as furuncles, carbuncles, cutaneous abscesses, or cellulitis, whereas complicated SSTIs are deeper, with the potential of systemic issues. Complicated SSTIs include necrotizing fasciitis, resulting in emergent surgical treatment. Imaging studies, such as plain X-rays, MRI, or CT scan, can be performed to rule out underlying issues that can alter the course of treatment. It is important to note that MRSA can cause both complicated and uncomplicated SSTIs and need to be considered as an etiology in both situations. Immunocompromised patients are a special population that requires swift identification and management, recognizing their atypical presentation and propensity for rapid decline. Successful treatment of SSTIs is crucial to diminish the likelihood of complications and hospital admissions.

## INTRODUCTION

SSTIs include a wide range of diseases, from cellulitis to necrotizing fasciitis. SSTIs often involve microbial infections of the skin, subcutaneous tissue, fascia, and muscle.<sup>1</sup> Given the high rates of morbidity and mortality caused by SSTIs among hospitalized patients, physicians should take care to properly diagnose and treat SSTIs. Non-life threatening SSTIs can be managed in the outpatient setting, but more serious cases will require more sophisticated care.<sup>2</sup> Family physicians, in particular, can play an important role in the early detection and appropriate microbial management of SSTIs.

The workup of a patient with a skin infection requires a high degree of clinical vigilance, so that complicated and more serious infections may be excluded. Any patient presenting with signs of a systemic infection will require a full work up, to include blood cultures, complete blood count, creatinine phosphokinase, bicarbonate and C-reactive protein.<sup>3</sup> These clinical studies are necessary to exclude any systemic illness.

## UNCOMPLICATED SKIN & SOFT TISSUE INFECTIONS

Uncomplicated SSTIs (uSSTIs) are a common reason for physician office visits. Determining the etiology and appropriate treatment is important to rule out the potential presence of a more serious infection. Less serious skin infections typically do not invade

below the skin or subcutaneous tissue layers and respond well to outpatient antibiotic therapies. Risk factors that predispose a patient to developing a soft tissue infection include health conditions that contribute to poor tissue perfusion and venous stasis, such as obesity, diabetes mellitus, peripheral vascular disease and peripheral neuropathy. Health conditions that contribute to poor wound healing, such as a compromised immune system, inadequate nutrition and cirrhosis, can also predispose a patient to soft tissue infections.<sup>4</sup> Diagnosis of soft tissue infections is largely clinical. Wound and blood cultures, as well as imaging, are not indicated in patients who do not exhibit signs of systemic infection.

The common etiological agents causing these infections are strains of *Staphylococcus aureus* and  $\beta$ -hemolytic streptococcus.<sup>5</sup> Community Acquired Methicillin Resistant *Staphylococcus aureus* (CA-MRSA) is associated with a variety of uncomplicated SSTIs including, but not limited to, furuncles, carbuncles, cutaneous abscesses, and cellulitis.<sup>6,7</sup> Furuncles are transdermal hair follicle infections that typically present as draining, pustular or nodular lesions. Carbuncles are the result of the coalescence of furuncles. Cutaneous abscesses typically present as single or multiple fluctuant, erythematous nodules that are tender to palpation and contain purulent material. Most cutaneous abscesses are caused by *staphylococcus* spp., especially MRSA. The recommended treatment for uncomplicated furuncles, carbuncles, and cutaneous abscesses is incision and drainage. Wound culture is also recommended at the time of incision and drainage. Use of antibiotics for uncomplicated cutaneous abscesses caused by MRSA does not improve patient outcomes or prognosis and is not recommended. If antibiotic treatment is considered, empiric treatment for suspected CA-MRSA SSTIs in the ambulatory setting include oral trimethoprim sulfamethoxazole,

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doxycycline, and clindamycin. Cellulitis generally presents with unilateral cutaneous edema, erythema, and warmth. The purulent exudate that attends cellulitis may suggest MRSA as a cause, but the more common causes include *Streptococcus* spp., especially *S. pyogenes*. However, at this time, cases of uncomplicated purulent cellulitis do continue to warrant culture and empiric treatment for CA-MRSA.

## COMPLICATED SKIN & SOFT TISSUE INFECTIONS

Skin and soft tissue infections should be considered complicated if systemic signs of illness such as fever or elevated WBC count are present, and in more severe cases, if tachycardia and hypotension are present.<sup>8</sup> These types of infections account for a significant percentage of the morbidity and mortality rates in this patient population. These infections are also responsible for longer hospital stays and loss of revenue for hospitals.<sup>9</sup> A timely diagnosis is critical in establishing a successful therapeutic intervention. Complicated soft tissue infections are defined by the presence of microbiome invasion beyond deep layers of the skin, or by an infection requiring surgical intervention.<sup>10</sup> These infections can be the result of burns, skin ulcerations, or poorly-healing abscesses. Soft tissue infections can also be classified as complicated in cases where the patient's ability to fight infection is compromised by various health conditions. Thus, co-morbid diseases, such as diabetes mellitus, immunodeficiency states, and arteriovenous insufficiencies, can all be contributing factors in the development of soft tissue infections that are clinically more difficult to treat. Furthermore, epidermal infections with accompanying fever, hypothermia, tachycardia, and hypotension would be highly indicative of an associated sepsis and are likely to create an infection that would be considered highly complicated.<sup>11</sup>

As with the case of uncomplicated soft tissue infections, the most common etiologic agents for complicated skin and soft tissue infections (cSSTIs) are gram positive microbes, such as *Staphylococcus aureus* and the  $\beta$ -Hemolytic streptococci strains (including group A, B, C and G). Strains of *Staphylococcus aureus* and  $\beta$ -Hemolytic streptococcus are capable of producing exotoxins that can result in a necrotizing infection. Necrotizing infections are medical and surgical emergencies, which require prompt treatment with aggressive surgical debridement. These infections involve fascial planes, leaving the skin intact. In these infections, a dermatological exam may reveal a mild cellulitis, but a more insidious infection is often present. Clinical exam findings can include systemic signs of infection, as well as pain that is out of proportion with clinical findings. In addition to rapid surgical debridement, intravenous antibiotics, analgesics, and electrolyte management are the standard of care for the treatment of necrotizing infections.

Imaging studies may be useful in the setting of complicated SSTIs. Plain x-rays are indicated if there is known trauma at the site of the SSTI, or may be considered if there is a preexisting chronic wound. Xrays may uncover a fracture, foreign body, or osteomyelitis. Magnetic resonance imaging (MRI) is the best choice to show the extent of corporal involvement. Soft tissue is also well visualized with computed tomography (CT), if shorter image time is warranted. Both MRI and CT are usually not necessary, but an option if needed for further evaluation.<sup>13</sup>

Unusual pathogens are a significant source of complicated soft tissue infections and are often overlooked in the clinical setting. Inquiring into a patient's recent history of travel, antibiotic usage, hospitalizations and exposure to animals may yield highly valuable information for purposes of determining etiologies. A list of unusual pathogens is listed in *Table 1*. Animal bites represent a common etiology of skin and soft tissue infections. Bites from felines are quite common and frequently get infected with *Pasteurella Multocida* and *Bartonella Henselae*, which are the most common pathogens in this situation. Dog bites are also commonly encountered in clinical settings but are less likely to become infected. No specific workup is necessary for animal bites in patients who are not exhibiting signs of systemic infection.

## NOTABLE CONSIDERATIONS ON MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become an increasingly common cause of SSTIs in both outpatient and inpatient settings and has become associated with high morbidity and mortality rates.<sup>14,15</sup> The continuing rise of MRSA cases in ambulatory settings has been attributed to the widespread emergence of community-associated (CA-MRSA) strains. Traditionally, risk factors for MRSA SSTIs included nasal colonization, previous MRSA infection, recent antibiotic therapy, hospitalization, and intravenous drug use;<sup>16</sup> CA-MRSA is, however, frequently isolated from SSTIs in individuals who lack these traditional risk factors.<sup>17</sup> Favorable patient outcome following an SSTI from MRSA depends on early diagnosis by a physician, followed promptly by appropriate management.<sup>18</sup>

## NOTABLE CONSIDERATIONS ON IMMUNOCOMPROMISED PATIENTS

A patient population that requires additional surveillance includes patients who are immunocompromised. This includes, but is not limited to, patients who are receiving immunosuppressant medication, radiation therapy, corticosteroids, chemotherapy, and those who are infected with HIV/AIDS. Immunocompromised patients require extra vigilance from the clinician in order to facilitate prompt management and to identify appropriate

TABLE 1:

Unusual Pathogens<sup>30,31</sup>

BITES (ANIMAL)	<i>Bacteroides</i> , <i>Bartonella henselae</i> , <i>Capnocytophaga canimorsus</i> , <i>Eikenella corrodens</i> , <i>Pasteurella multocida</i> , <i>Peptostreptococcus</i> , <i>S. aureus</i> , <i>Streptobacillus moniliformis</i> ;
FOLLICULITIS	<i>Candida</i> , dermatophytes, <i>Pseudomonas aeruginosa</i> , <i>S. aureus</i>
CLOSTRIDIAL MYONECROSIS	<i>C. perfringens</i> , <i>C. septicum</i>

pharmaceuticals for unusual and diverse microorganisms. For such patients, infections can quickly become life-threatening and are challenging to treat solely through antimicrobial therapy.<sup>19</sup> Common opportunistic organisms causing SSTIs in immunocompromised patients include drug resistant gram negative bacteria such as *Pseudomonas* species, anaerobes such as *Clostridium* species, and fungi such as *Cryptococcus* species. While cultures may not be indicated in most healthy patients, they are useful for immunocompromised patients who are at risk for sepsis, cellulitis, lymphangitis, and recurrent persistent abscesses.<sup>20</sup> It is important to note that immunocompromised patients will not exhibit the classic symptoms of SSTIs, owing to their diminished immune system's response. For this reason, diagnostic tests should be completed in a timely fashion to investigate the microbial landscape for susceptibility testing and to determine the appropriate pharmaceutical therapy.<sup>21</sup> This is a crucial step especially considering that many microorganisms may be acquired in the hospital and are strongly resistant to common antimicrobial drugs. Consequently, empiric treatment in immunocompromised patients may prove problematic, if not downright difficult.<sup>22</sup> What may appear as a deceptively simple skin infection in an immunocompromised patient can quickly progress to systemic infection or, even worse, to necrotizing fasciitis. This accelerated progression is due to the immunocompromised patient's weakened immune capacity, which reduces the patient's ability to stave off an infection that begins in the skin or soft tissues.<sup>23</sup> An important sign of a systemic infection is pain that is out of proportion to the presenting SSTI, and such a sign should prompt extensive investigation into the underlying cause. Other signs of systemic complications include bacteremia, leukocytosis, and fever.<sup>24</sup> Even if the original bacterial SSTI is resolved, it can return with a concurrent secondary fungal infection.<sup>25</sup> When managing SSTIs in immunocompromised patients, antibiotic therapy should encompass both gram positive and gram negative bacteria, using agents such as higher generation cephalosporins or imipenem. Patients allergic to penicillin-based medications can receive fluoroquinolones. When considering MRSA in the immunocompromised patient, the clinician may utilize vancomycin, clindamycin, or daptomycin, as appropriate and depending on the patient. The use of such antibiotics to treat MRSA-associated carbuncles and furuncles is recommended for immunocompromised patients and for infections with associated septic phlebitis or concomitant systemic inflammatory response syndrome.<sup>26,27</sup> Fungi can be managed with amphotericins, triazoles, or echinocandins.<sup>28,29</sup>

## DIFFERENTIAL DIAGNOSIS

There are other lesions and conditions that can mimic both uncomplicated and complicated SSTIs. This includes, but is not limited to, herpes zoster, acne, deep vein thrombosis (DVT), gout, contact dermatitis, autoimmune etiologies, allergic dermatitis, and venous stasis.

## TREATMENT

The treatment of skin and soft tissue infections will vary depending on local patterns of antibiotic resistance and sensitivity, as determined by local health officials. See *Table 2* for the management of common SSTIs.

## CONCLUSION

The increasing prevalence of SSTIs requires primary care clinicians to be well versed in the inpatient and outpatient management of these diseases. When appropriate, surgical referrals may be needed in order to effectively treat SSTIs and minimize further complications. If antimicrobial therapy is determined to be the appropriate treatment, the patient's health status and condition should be considered to increase the likelihood of a successful outcome. Symptoms such as fever, tachycardia, hypotension, or any other indications of systemic infection should prompt investigation of the underlying cause.

## AUTHOR DISCLOSURES:

No relevant financial affiliations

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TABLE 2:

Management of Common SSTIs<sup>30</sup>

MANIFESTATION	COMMON ETIOLOGY	MANAGEMENT OPTIONS	COMMENTS
<b>Nonpurulent SSTIs</b>			
Cellulitis	$\beta$ -hemolytic streptococci, polymicrobial	Oral penicillin, amoxicillin, cephalexin, clindamycin	A 5 day course is recommended for uncomplicated cases
Erysipelas	$\beta$ -hemolytic streptococci	Oral cefazolin, ceftriaxone, penicillin, amoxicillin	If indistinguishable from purulent cellulitis, cefazolin is preferred due to coverage for <i>S. aureus</i> for 7-10 days
Folliculitis	<i>S. aureus</i>	Topical clindamycin, mupirocin	Recurrent cases require systemic treatment with cephalexin or dicloxacillin for up to 4-6 weeks
Impetigo	<i>S. pyogenes</i> , <i>Staphylococcus</i> spp.	Topical mupirocin, retapamulin. Oral dicloxacillin, cephalexin, penicillin	Oral penicillin is preferred for cases of isolated streptococci impetigo 7-10 days
Necrotizing Infection	Mixed anaerobic bacteria, <i>S. pyogenes</i>	Surgical tissue debridement, empiric broad-spectrum antibiotics such as clindamycin plus vancomycin plus meropenem	Hyperbaric oxygen is used in necrotizing fasciitis
<b>Purulent SSTIs</b>			
Carbuncle/Furuncle	MSSA producing PVL, MRSA	Incision and drainage with addition of oral TMP-SMX, doxycycline, clindamycin	Oral antibiotics are required only for complicated cases
Cellulitis	CA-MRSA	Oral clindamycin, doxycycline, TMP-SMX	Additional coverage for streptococci is warranted in addition to MRSA coverage for 7-14 days
Cutaneous Abscess	MSSA producing PVL, MRSA	Incision and drainage	Addition of antibiotics for coverage of MRSA is indicated in immunocompromised patients or patients with systemic inflammatory response syndrome for 7-14 days

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