

skin and soft-tissue infections

The early clinical presentation of soft-tissue infections may be deceptive.

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Definitions and terminology

The skin and its appendages, and the subcutaneous tissue, deep fascia and muscle, can all develop infections under various circumstances. Patients with skin and soft-tissue infections (SSTIs) often initially present to family physicians. The signs and symptoms of SSTIs may overlap, making a comprehensive diagnosis difficult.^{1,2} Early clinical presentation may be deceptively innocent.³ Furthermore, at presentation it is often difficult to assess the depth, severity and specific structures or tissues involved. All SSTIs represent a continuum of symptoms and should be considered collectively:

- Erythema, warmth, oedema, skin discoloration and localised pain are common presenting signs in the case of superficial, complicated or deep infections.
- Some or all of the following signs are indicative of a necrotising condition affecting deep structures
 - when vesicles become manifest
 - when oedema is tense
 - when crepitus is present
 - when pain is extreme
 - when infection progresses.
- Failure of an SSTI to respond to antibiotics points to a necrotising infection.
- Signs of systemic infection, hypotension, tachycardia and organ dysfunction may indicate toxic shock (staphylococcal or streptococcal).

It is essential to maintain a high index of suspicion for these infections and be aware of possible presenting features.

Recognising the extent of the infection is imperative to ensure prompt and comprehensive therapy.² SSTIs may vary from less severe conditions to severe and invasive conditions, which may lead to soft-tissue loss or limb amputation and even death if not managed promptly. Therefore, patients with severe infections need early hospitalisation, surgery and antibiotics.

Early clinical presentation may be deceptively innocent.

Classification

SSTIs can be described as localised or spreading – this may be useful when considering surgical treatment.

SSTIs can be classified as uncomplicated, referring to infections affecting the superficial layers of the skin, and as complicated,

indicating infections extending to the deeper layers of the skin. Complicated SSTIs may involve the subcutaneous tissue, deep fascia and muscle.^{1,2} Uncomplicated SSTIs^{1,2} may be defined as conditions that respond to a course of antibiotics or to simple drainage. These include minor abscesses, impetigo, folliculitis, furuncles or boils, carbuncles, limited cellulitis, and even minor wound infections.

Examples of complicated SSTIs^{1,2} are the following:

- infections involving deep skin structures
- infections requiring significant surgical intervention, e.g. infected burns, major abscesses, infected ulcers, infections in diabetics, and deep-space wound infections
- otherwise uncomplicated infections occurring at anatomical sites (e.g. the rectal area) where the risk of anaerobes and Gram-negative pathogens is increased
- infections in the presence of significant underlying disease, e.g. diabetes mellitus, peripheral vascular disease, ischaemic ulceration and chronic lymphoedema, that may complicate the response to therapy
- where immunosuppression may enable unusual or normally non-pathogenic bacteria to cause infections or increase the likelihood of developing fulminant infections.

SSTIs may also be classified according to the presence or absence of necrotic or devitalised tissue. In necrotising soft-tissue infections (NSTIs) the devitalised tissue plays an important role in the pathophysiology of the disease, providing a growth medium for bacteria and preventing cellular and humoral defence mechanisms from reacting. The acidic pH of such tissue or wounds prevents the antimicrobial agents from being delivered effectively or inactivates these drugs. NSTIs may involve the dermal and subcutaneous layers (necrotising cellulitis), fascia (necrotising fasciitis), muscle (pyomyositis or myonecrosis) or any combination of these.²

The cardinal principles of controlling SSTIs are:⁴

- adequate drainage of infected fluid collections
- debridement of infected, necrotic or devitalised tissue
- removal of devices or foreign bodies
- early, appropriate antibiotic therapy.

Early aggressive surgery is indicated for both complicated SSTIs and NSTIs after prompt resuscitation, adjuvant antibiotic therapy and systemic support. Wound bed preparation and wound healing should receive particular attention.

Epidemiology

SSTIs are common bacterial infections seen by family practitioners and surgeons. They account for a substantial portion of

emergency department visits and hospital admissions.

SSTIs led to 29 820 hospital admissions in the UK during 1985, with a mean occupancy of 664 hospital beds each day. A more recent study in the UK indicated that SSTIs account for about 10% of hospital admissions, with a mean length of stay of 5 days. During 1995, 330 000 hospital admissions for SSTIs were reported.¹

Over recent decades physician visits for cellulitis and soft-tissue infections have increased from 32 to 48 per 1 000 population from 1997 to 2005. Necrotising fasciitis caused by group A streptococci is now endemic in the USA. Of great concern is that *Staphylococcus aureus*, the predominant cause of cellulitis, and abscesses or wound exudates, are becoming increasingly resistant to methicillin. Vancomycin and other newer antibiotics are therefore the drugs of choice.⁵ This is true even for community-acquired methicillin-resistant *S. aureus* (MRSA), demonstrating that MRSA is no longer a pathogen limited to hospitalised patients.

Pathogenesis

The role of the skin as an integral part of our host defence mechanisms cannot be underestimated. Intact skin serves as an effective physical barrier to the penetration of micro-organisms because of the tight junctions between epithelial cells. In addition, the acidic oily matrix produced by the sebaceous glands coats the epithelial cells. Commensal and saprophytic micro-organisms of the normal skin flora are interspersed in this matrix cell surface.¹ Bacteria involved are coagulase-negative staphylococci, corynebacteria, micrococci, diphtheroids and propionibacteria. They augment the defence of the skin by preventing colonisation and invasion by more virulent species. In moist skin areas such as the groin the normal flora may also include Gram-negative enteric bacteria, e.g. *Escherichia coli*.

To cause SSTIs invading organisms must penetrate the skin barrier through a breach caused by direct trauma or an underlying process such as ischaemia. The two most common pathogens in SSTIs are *S. aureus* and beta-haemolytic streptococci, e.g. *Streptococcus pyogenes*. The ability of all micro-organisms to cause SSTIs is related to their toxin production and resistance to host inflammatory responses.¹

Virulence factors may include secretion of substances that can induce extensive cytokine and chemokine responses in the host. They may also deter phagocytosis by host scavenger cells or produce extracellular toxins that damage the host

cellular response and lead to abscess formation or spreading of the infection. These exotoxins may be extremely potent and cause forms of toxic shock syndrome that may be fatal.¹

Physical examination

The following findings are important indicators of severity of infection:¹

- At the site of infection:
 - the type of lesion
 - whether fluctuation (fluid that has to be drained) is present
 - whether crepitus is present, indicating a gas-forming infection.
- The size and site of the lesion may indicate the severity of the infection. Some sites (face, fingers, toes, genitals) necessitate admission of the patient and vigilant observation.
- The degree of pain:
 - pain not in proportion to the appearance of the lesion may indicate a developing necrotising infection
 - loss of skin sensation around a wound may be an indication of dead tissue
 - in limbs with peripheral vascular disease the pain caused by SSTIs may be masked.
- Systemic infection, usually indicated by extremes of temperature (<35°C or >40°C), hypotension, tachycardia and changed levels of consciousness.

Uncomplicated SSTIs^{1,6}

Impetigo (Fig. 1) is a bacterial, inflammatory skin disease characterised by the appearance of pustules, typically on the face or the extremities. This condition is common during hot, humid conditions. It is highly communicable and facilitated by overcrowding and poor hygiene.

Erysipelas (Fig. 2) is a contagious infection of the superficial layers of the skin that may extend to the subcutaneous tissue and form vesicles or bullae. The predominant clinical features are sharply demarcated red edges and oedematous, indurated elevation of the affected area.

Erysipeloid dermatitis is infective, with an erythematous-oedematous appearance. It may occur on the hands of fishmongers or meat workers and is caused by *Erysipelothrix rhusiopathiae* from infected meat, bone or hides.

Cellulitis is a purulent inflammation of the loose subcutaneous tissue. The skin is warm, diffusely red and swollen. The area affected may be extensive and painful.



Fig. 1. Impetigo (US Department of Health and Human Services).



Fig. 2. Facial erysipelas (CDC/Dr Thomas F Sellers/Emory University).



Fig. 3. A carbuncle on the buttock of a diabetic patient (Wikimedia commons).

Folliculitis is a purulent inflammation of hair follicles.

A **furuncle or boil** is a painful skin nodule associated with circumscribed inflammation of the corium or dermis and subcutaneous tissue, enclosing a central slough or core. It is caused by bacteria that enter the skin through hair follicles.

A **carbuncle** (Fig. 3) is a necrotising infection of skin and subcutaneous tissue, usually caused by staphylococci. Typically, it has multiple formed or incipient drainage sinuses and an indurated border.

In general, the dermal layer of the skin may become infected (i.e. cellulitis) by traumatic injury, surgery or underlying skin disease such as psoriasis or peripheral vascular disease. Typical pathogens that cause cellulitis are *S. aureus* and *Streptococcus* spp. Sometimes Gram-negative bacteria and anaerobes may also be involved.⁶ Because of the lack of microbiological technology the aetiology can often not be determined. Specimens for culture and sensitivity must be taken because at present even community-acquired *S. aureus* infections are often resistant to methicillin (CA-MRSA). However, outbreaks of CA-MRSA have not been described in South Africa.

Infections 'above the belt' are more likely to be caused by *S. aureus*, whereas those 'below the belt', e.g. perianal abscesses and perineal hidradenitis suppurativa, often consist of mixed flora.

Clinically it is very difficult to distinguish between streptococcal and staphylococcal impetigo and cellulitis. As a microbiological diagnosis is often not possible or practical, empiric antibiotic treatment for streptococci and staphylococci should be commenced.

Complicated SSTIs may involve the subcutaneous tissue, deep fascia and muscle.

Treatment

- In general, antibiotics are indicated for the treatment of cellulitis. In cases of uncomplicated cellulitis outcome after 5 days of therapy is equivalent to 10 days' treatment.
- Typically, antimicrobial agents include antistaphylococcal penicillins or the cephalosporins. Broad-spectrum drugs such as the fluoroquinolones, e.g. moxifloxacin, should be reserved for organisms resistant to the more narrow-spectrum agents.
- Broad-spectrum beta-lactams, e.g. amoxicillin/clavulanic acid, are indicated for animal or human bites and intravenous drug users as Gram-negative and anaerobic bacteria are possibly involved.
- The threshold for treatment of MRSA infections should be low, i.e. if there is no improvement in 72 hours. Out-patient treatment for suspected CA-MRSA may include oral trimethoprim-sulfamethoxazole or clindamycin.

Linezolid may be used for hospital- or health care-associated MRSA (HA-MRSA) infections.

Simple drainage and wound care should suffice for most surgical site infections and subcutaneous abscesses.

- Antibiotics are indicated when:
 - signs of systemic infection are present (temperature >38°C, tachycardia, leukocytosis)
 - >5 cm erythema occurs around the wound
 - deep infections with implants or grafts are present.
- For wound infections developing after clean surgical procedures cefazolin or clindamycin should be sufficient.
- For wound infections developing after clean-contaminated surgical procedures Gram-negative and anaerobic cover should be provided, e.g. amoxicillin/clavulanic acid or a fluoroquinolone plus clindamycin.

Complicated SSTIs

These infections differ from uncomplicated infections in that the deeper structures such as muscle and fascia are typically involved. These infections often occur in immunocompromised or diabetic patients. The bacteria involved are the same as in superficial infections, although polymicrobial flora occur more often. These infections are debilitating, may be limb threatening or progress to systemic infection, and should be treated immediately.

Treatment

Principles of treatment for patients with complicated SSTIs are:⁶

- *Early* recognition of the need for surgical drainage and/or debridement. This may necessitate early specialist surgical consultation to ensure adequate source control because antibiotic treatment duration relies on this.
- Standard of care that includes early, appropriate antimicrobial therapy combined with drainage or debridement. Consider where the infection was acquired because it will determine the choice of antibiotic. The empiric choice of antibiotic therapy must cover the most likely organisms.
- Community-acquired infections are mostly due to CA-MRSA, MSSA and *Streptococcus* spp. Anti-staphylococcal penicillins, cephalosporins, or broad-spectrum fluoroquinolones, e.g. moxifloxacin,

should provide sufficient cover for non-MRSA SSTIs. In serious infections broad-spectrum penicillins (amoxicillin/clavulanic acid or piperacillin/tazobactam) or carbapenems (ertapenem) provide excellent cover for SSTIs. CA-MRSA can usually be treated with trimethoprim-sulfamethoxazole. This will also cover *Streptococcus* spp. and Gram-negative organisms except *Pseudomonas aeruginosa*. Clindamycin, which will cover Gram-positive organisms and anaerobes, may also be used. However, in South Africa, MRSA encountered are not clone-specific epidemics and may vary in their antimicrobial sensitivity. They may therefore be unpredictable in their response to trimethoprim-sulphamethoxazole.

- HA-MRSA should be treated with vancomycin or linezolid. A new drug, tigecycline (a semi-synthetic glycylcycline), also has broad-spectrum activity against MRSA.
- Nosocomial infections are often caused by MRSA or mixed flora, e.g. surgical site infections after intra-abdominal procedures. When MRSA is suspected, vancomycin or linezolid should be prescribed. When mixed flora are involved, extended-spectrum penicillins or carbapenems are indicated.

Duration of antibiotic therapy:

- Even in the case of deep-seated infections antimicrobial therapy should not exceed 7 - 10 days. As debridement may result in open wounds, dedicated wound care will play an important role in expediting healing.

Indications for hospitalisation:¹

- severity/size of the infection
- need for surgical drainage
- likelihood of disease progression
- presence of comorbid conditions
- results of microbiological culture and sensitivity testing
- assessment of the patient's treatment compliance
- level of support available at home.

Necrotising skin and soft-tissue infections⁶

Necrotising infections are fulminant, life-threatening forms of complicated SSTIs. They involve the fascia, resulting in thrombosis of subcutaneous blood vessels and necrosis of the underlying

tissue. Clinically, this condition should be suspected when erythema, oedema, skin discoloration or bullae are associated with more pain than indicated by signs and symptoms. This condition may progress rapidly to widespread tissue loss.

Classification of necrotising SSTIs^{1,3}

The nomenclature is confusing because these infections often occur along a continuum. Classically these infections are separated into necrotising fasciitis and myonecrosis:

- Meleney's synergistic gangrene, caused by *S. aureus* interacting with microaerophilic streptococci. Surgical patients are at risk and gangrene is observed as slowly expanding ulceration confined to the superficial fascia.
- Clostridial cellulitis, caused by *Clostridium perfringens*, occurs after local trauma or surgery. Gas is found in the skin, but not in the fascia.
- Non-clostridial anaerobic cellulitis, caused by mixed aerobes and anaerobes (*Bacteroides* spp. and *Peptostreptococcus* spp.). Diabetics are typically affected. The main clinical feature is gas in the tissues.
- Gas gangrene, caused by *Clostridium* spp. (*C. perfringens*, *C. histolyticum*, *C. septicum*) may occur after trauma, crush injuries, injections or spontaneously in oncology patients. It is characterised by myonecrosis, gas in the tissues and systemic toxicity. Clostridia produce a variety of toxins. The alpha toxin is responsible for rapid tissue necrosis, while the others often lead to systemic toxicity, which may be life threatening.
- Necrotising fasciitis type 1. This is a polymicrobial infection caused by Gram-negative aerobic bacilli and Gram-positive organisms along with strict anaerobes. Diabetics, patients with morbid obesity, alcoholics, parenteral drug abusers and those with peripheral vascular disease are at risk. It destroys the fat and fascia, sometimes sparing the skin of the lower extremities, perineum and abdominal wall.
- Necrotising fasciitis type 2 or streptococcal gangrene is primarily caused by group A beta-haemolytic streptococci (GAS), also known as *S. pyogenes*, alone or in combination with *S. aureus*. It may occur with penetrating injuries, surgery, burns, childbirth, pelvic inflammatory disease or varicella infections. The organism may be very contagious. The typical appearance of severe local pain and rapidly spreading erythema followed by necrosis is a result of the streptococcal haemolytic toxins, streptolysin O and S, which destroy tissue. Three exotoxins are also produced, which mediate shock and

multiple system organ failure. Fascial necrosis and myonecrosis occur, but there is no gas in the tissues.

Early diagnosis is essential to protect limbs and to save lives. All types of necrotising infections should be suspected on clinical grounds only. An aggressive approach, e.g. bedside incision, will contribute to the diagnosis. On incision, there is loss of fascial integrity, lack of bleeding and 'dishwater fluid' in the wound. No investigations or preparations should delay operative intervention. Early specialist surgical consultation for radical, repeated debridement takes precedence. Broad-spectrum antibiotics should be administered, as discussed in the previous section. Although antibiotics play an adjunctive role to surgery, they should be initiated when a diagnosis has been made.

Treatment^{3,4,6}

- Timing is critical for successful treatment – early recognition and aggressive medical and surgical therapy are the primary determinants of successful outcome.
- Early, aggressive surgical debridement, repeated within 6 - 48 hours in the operating theatre, is necessary to ascertain that the wound is clean. Source control is essential. This must be done regardless of how well the patient is at that time.
- Appropriate microbial samples must be taken.
- Early, appropriate empiric broad-spectrum antibiotics should be administered.
- Dedicated attention should be given to wound healing.
- There should be supportive systemic treatment in an ICU. Although controversial, the use of intravenous gamma-globulin may be considered. Hyperbaric oxygen should be used after surgery for clostridial gangrene.

Other causes of SSTIs¹

A thorough history must be taken in patients with SSTIs. There is a variety of infectious agents, other than bacteria, which may cause infection or play an important role in the development of infection, e.g. viruses, leprosy, animal bites, insect bites or stings, tick bites, fungi and injection drug use.

Wound healing

Although not the topic of this article, attention to wound healing plays an important role in the recovery of patients with severe SSTIs. The reader is encouraged to visit the website of the Wound Healing Association of Southern Africa (WHASA)

at www.whasa.org and Wound Healing Southern Africa at www.woundhealinga.co.za.

References

1. Aldridge KE, Pankey GA, Rodloff AC. *Lectures in Hospital Infections, part 4: Complicated Skin and Skin Structure Infections*. London: Current Medicine Group, 2006.
2. May AK. Skin and soft tissue infections. *Surg Clin N Am* 2009; 89: 403-420.
3. Majeski JA, John JF, jr. Necrotizing soft tissue infections: a guide to early diagnosis and initial therapy. *South Med J* 2003; 96(9): 900-905.
4. Marshall JC, Maier RV, Jimenez M, et al. Source control in the management of severe sepsis and septic shock: an evidence-based review. *Crit Care Med* 2004; 32(11) Suppl: S513-S526.
5. Eron LJ. Cellulitis and soft tissue infections. *Ann Intern Med* 6 January 2009; ITC1-1 – ITC1-16.
6. Hedrick TL, Smith PW, Gazoni LM, Sawyer RG. The appropriate use of antibiotics in surgery: a review of surgical infections. *Curr Probl Surg* 2007; 44: 635-675.

In a nutshell

- Important principles in the prevention of surgical site infections are good hand hygiene, good surgical technique and appropriate use of perioperative antibiotic prophylaxis.
- Typical pathogens associated with cellulitis are *S. aureus* and *Streptococcus* spp., but may include Gram-negative organisms and anaerobes.
- Culture identification of the pathogen should point to changing from broad-spectrum antibiotics to more narrow-spectrum regimens to avoid development of resistance.
- Standard of care is antimicrobial therapy with drainage or debridement for patients with complicated skin infection.
- Antibiotics serve an adjunctive role to surgical debridement in necrotising infections, but should be initiated immediately on diagnosis.⁶ Empiric therapy should target the suspected pathogen.
- Maintaining a high index of suspicion for deep and necrotising infections and an awareness of possible presenting features is essential.^{3,5}
- Rapid spreading of the infected area, violaceous bullae or reddish-purple discoloration of the skin, severe pain, or systemic toxicity suggest necrotising fasciitis that requires urgent surgical attention.⁵
- The cardinal principles of source control in SSTIs are:^{4,5}
 - adequate drainage of infected fluid collections
 - meticulous, complete surgical debridement of all infected, necrotic or devitalised tissue
 - removal of devices or foreign bodies
 - early, appropriate antibiotic therapy.