Alembic
Touching Lives over 100 years

ACP[SM]
American College of Physicians
Leading Internal Medicine, Improving Lives

India Chapter

Infectious Disease Excellence Program (IDEP)

Certification in Infectious Disease Management

MODULE 2

MODULE 2

Addressing Skin Infections in General Practice

Contents

Bacterial skin and soft tissue infections in adults: A review of their epidemiology, pathogenesis, diagnosis, treatment and site of care

Vincent Ki MD1, Coleman Rotstein MD FRCPC2

Reference: Can J Infect Dis Med Microbiol.2008 Mar;19(2):173-84. doi: 10.1155/2008/846453.

ABSTRACT

Skin and soft tissue infections (SSTIs) involve microbial invasion of the skin and underlying soft tissues. They have variable presentations, etiologies and severities. The challenge of SSTIs is to efficiently differentiate those cases that require immediate attention and intervention, whether medical or surgical, from those that are less severe. Approximately 7% to 10% of hospitalized patients are affected by SSTIs, and they are very common in the emergency care setting. The skin has an extremely diverse ecology of organisms that may produce infection. The clinical manifestations of SSTIs are the culmination of a two-step process involving invasion and the interaction of bacteria with host defences. The cardinal signs of SSTIs involve the features of inflammatory response, with other manifestations such as fever, rapid progression of lesions and bullae. The diagnosis of SSTIs is difficult because they may commonly masquerade as other clinical syndromes. To improve the management of SSTIs, the development of a severity stratification approach to determine site of care and appropriate empirical treatment is advantageous. The selection of antimicrobial therapy is predicated on knowledge of the potential pathogens, the instrument of entry, disease severity and clinical complications. For uncomplicated mild to moderate infections, the oral route suffices, whereas for complicated severe infections, intravenous administration of antibiotics is warranted. Recognition of the potential for resistant pathogens causing SSTIs can assist in guiding appropriate selection of antibiotic therapy.

Key Words: Bacterial, Infections, Management, Skin

Skin and soft tissue infections (SSTIs) are clinical entities of variable presentation, etiology and severity that involve microbial invasion of the layers of the skin and underlying soft tissues. SSTIs range from mild infections, such as pyoderma, to serious life-threatening infections, such as necrotizing fasciitis. The minimum diagnostic criteria are erythema, edema, warmth, and pain or tenderness. The affected area may also become dysfunctional (eg, hands and legs) depending on the severity of the infection. A patient's comorbidities (eg, diabetes mellitus and AIDS) can easily transform a normally mild infection into a rapidly advancing threat to life [1]. SSTIs present clinically diverse challenges requiring management strategies that efficiently and effectively identify those cases requiring immediate attention and intervention, whether medical or surgical, from those less severe cases.

The difficulty stems from the paucity of robust research to support any particular approach [2,3]. Current guidelines for stratifying SSTI patients to specific treatments are based primarily on retrospective data and clinical experience. Eron et al [2] have presented a preliminary algorithm for managing SSTIs based on a crude numerical scale. The goal of the algorithm is to evaluate patients expeditiously and refer them to a specific site of care treatment. Although this algorithm provides an approach to patient stratification, it is overly sim-plified and takes into account very few patient characteristics in the different classifications. Another schema designed for dermatologists by Elston [4] makes no attempt to differentiate complicated from uncomplicated SSTIs.

The primary purpose of the present paper is to review current practice and then formulate a more comprehensive clinical ap-proach to managing patients with SSTIs. Given the higher preva-lence of bacterial infections, the present review does not include a discussion of viral, fungal or parasitic SSTIs. This approach involves an assessment of patient characteristics in assigning infection severity through an algorithm that parallels the commu-nity-acquired pneumonia algorithm of severity proposed by Fine et al [5], and Halm and Teirstein [6].

EPIDEMIOLOGY

Given the variable presentation of SSTIs, an assessment of their incidence and prevalence has been difficult. The estimated inci-dence rate of SSTIs is 24.6 per 1000 person-years (7). Because a majority of SSTIs tend to resolve within seven to 10 days, an estimate of prevalence is highly variable.

Key points

- Risk factors influence SSTI likelihood but do not directly correlate with disease severity; multiple patient-related factors can worsen prognosis and treatment response.
- Etiological risk factors, including trauma and specific microbial exposures, should guide empirical antibiotic selection and clinical decision-making.

Among hospitalized pa-tients, the estimated prevalence of SSTIs is 7% to 10% (8,9). Among all hospitalized patients with infections only, SSTIs take on a more prominent role. In the emergency care setting, SSTIs represent the third most common diagnosis after chest pain and asthma [2]. There is an increased preva-lence among men (60% to 70% of all cases) and patients between 45 and 64 years of age. Approximately 70% to 75% of all cases are managed in the outpatient setting [2,7], with many cases of SSTIs involving the lower leg region [7,9–11]. Overall, the rate of complicat-ed cellulitis is low (erysipelas 0.09 per 1000 person-years; lymphadenitis 0.16% of all cel-lulitis cases; lymphangitis 0.16 per 1000 per-son-years and necrotizing fasciitis 0.04 per 1000 person-years) [7].

RISK FACTORS

The presence of specific risk factors may po-tentiate SSTIs, and may dictate their etiolo-gy, the course of disease and the response to specific treatments. The presence of risk factors for developing an SSTI has not been shown to correlate with disease severity [9]. Thus, the use of risk factors for diagnostic purposes requires further investigation.

Risk factors may be organized into two categories. First, there are patient-related factors, which may predispose to disease or have prognostic implications. Risk factors in this cate-gory include critical illness, elderly age, immunocompromised state, liver and kidney disease, and vascular (especially lymphatic or venous) insufficiency [1-3,9,12]. Because the lower leg has been shown to be the most frequent location for SSTIs, studies have described specific patient-related risk factors for such infections. A recent study by Björnsdóttir et al [11] was able to quantify the likelihood of an SSTI of the lower limbs based on the presence of Staphylococcus aureus and/or beta-hemolytic streptococcus in toe webs, leg erosions or ulcers, and/or prior saphenectomy. These factors independently corre-lated with the development of SSTI of the lower leg. In the same population, if toe web bacteria were absent, the presence of tinea pedis had moderate predictive power for an SSTI. Moreover, multiple patient-related risk factors may correlate to a poorer prognosis, more rapid progression of disease, slower healing and, also, more resistant pathogens. Certain risk factors (chronic renal or liver failure, asplenia, immunocom-promised state, vascular insufficiency or neuropathy) should be considered in the determination of disease severity.

The second category is etiological risk factors. The mecha-nism of injury (trauma or others) or specific exposures increases the likelihood of SSTIs caused by specific microbes. There is overlap between risk factors in this grouping and those listed in the above group. A comprehensive list of these etiological risk factors and their associated bacterial causes are presented by Eron et al [2] in Table 1.

TABLE 1
List of etiological risk factors for skin and soft tissue infections and their associated bacterial causes

Risk factor	Associated etiological pathogen
Diabetes mellitus	Staphylococcus aureus , group B streptococci, anaerobes, Gram-negative bacilli
Cirrhosis	Campylobacter fetus, Klebsiella pneumoniae, Escherichia coli , Capnocytophaga canimorsus , other Gram-negative bacilli, Vibrio vulnificus
Neutropenia	Pseudomonas aeruginosa
Human bite wounds	Oral flora (Eikenella corrodens)
Cat bite wounds	Pasteurella multocida
Dog bite wounds	C canimorsus , P multocida
Rat bite wounds	Streptobacillus moniliformis
Animal contact	Campylobacter species
Reptile contact	Salmonella species
Hot tub exposure/ loofah sponge	P aeruginosa
Freshwater exposure	Aeromonas hydrophila
Seawater (fish tank) exposure	V vulnificus , Mycobacterium marinum
IV drug abuse	MRSA, P aeruginosa
Subcutaneous drug abuse	Anaerobes, especially E corrodens

IV Intravenous; MRSA Methicillin-resistant S aureus . Adapted from reference 2

MICROBIOLOGY

The principal barrier against microbial invasion is the skin. It constantly interacts with the external environment and is colonized with a diverse population of microbes. The vast majority of colonizing flora consists of bacteria. To help organize the distribution of flora, one can divide the body into two halves

at the waistline. The typical organisms that colonize the skin above the waist are usually Gram-positive species such as Staphylococcus epidermidis, Corynebacterium species, S aureus and Streptococcus pyogenes [13]. The latter two species are par-ticularly significant because they contribute to a majority of SSTIs.

On the other hand, the typical organisms that colonize the skin below the waist are both Gram-positive and Gram-negative species. It is speculated that this difference is second-ary to the proximity to the anorectal region. Enteric species, such as Enterobacteriaceae and Enterococcus species, gravitate to and colonize this area of the skin, the so-called 'fecal veneer'.

The usual pattern of distribution consists of larger populations in the axilla, groin and intertriginous areas, where there is a higher moisture level. The microflora tend to occupy the stratum corneum and the upper parts of the hair follicles. Specific microbes tend to colonize specific anatomical structures depend-ing on tropic stimuli, site-specific biochemical interactions and tissue-specific biofilm formation. The composition of the flora can vary drastically depending on climate, genetics, age, sex, stress, hygiene, nutrition and hospitalization [13].

The exact mechanisms of interaction between the normal microflora and the human skin are not well understood. A mutual relationship exists between the flora and the human host. In humans, the complex interactions with skin flora promote protection against colonization by other pathogenic species through site competition and production of antimicrobial substances [13]. The latter process produces cross-reactive antibodies, which are active against other invasive microbes.

The microbiology of SSTIs may also vary with the means of entry (Table 1) (2). Thus, the etiology of SSTIs may be normal host flora transferred from the instrument of entry or transferred from the environment. In addition, etiologies differ between community-acquired and hospital-acquired SSTIs. Hospital-acquired SSTIs in North America showed an increase in more resistant organisms (14). Specifically, S aureus (45.9%) (approxi-mately 40% of all cases were methicillin resistant), Pseudomonas aeruginosa (10.8%) and Enterococcus species (8.2%) ranked sig-nificantly higher than beta-hemolytic streptococci (2.3%), which constitute the majority of community-acquired SSTIs. New evidence suggest an increase in methicillin-resistant S aureus (MRSA) in community-acquired SSTIs (15-17). This isolate is characterized by the insertion of the staphylococcal chromosomal cassette mecA type IV and is associated with the Panton-Valentine leukocidin virulence factor (Table 2) (18).

Key points

- The microbiology of SSTIs varies by anatomical location, means of entry, and setting (community vs. hospital-acquired), influencing treatment selection.
- There is a rising prevalence of methicillin-resistant **Staphylococcus aureus** (MRSA) in both community- and hospital-acquired SSTIs, requiring vigilant antimicrobial stewardship.

TABLE 2
Examples of bacteria-specific virulence factors

Classification	Bacteria	Virulence factor	Details
Adherence factors	*S pyogenes*	Fimbrillae	Allow adherence to host epithelial cells
		M protein	Prevent phagocytosis
		Protein F	Allow access into epithelial cells to avoid detection
	S aureus	Clumping factor	Allow adherence to host epithelial cell
		Protein A	Prevent antibody opsonization and phagocytosis
Exotoxins	*S aureus*	Serine protease	Digest desmosome proteins and cause bullous disease (44)
		Lipases	Digest skin fatty acids to invade through skin barrier
		Panton-Valentine leukocidin	Membrane pore formation, especially in neutrophils and skin tissues leading to cell lysis (45); predilection for mitochondria may lead to elaboration of oxidative species leading to skin necrosis
	Clostridium species	Collagenases	Connective tissue digestion, which can cause rapidly progressive disease
		Hyaluronidases	Matrix protein digestion, which can cause rapidly progressive disease
		Alpha-toxin	Cell membrane and nerve sheath degradation; induce metabolic dysfunction through prostaglandin elaboration
	E coli	Nonspecific exotoxin	Intracellular signalling disruption leading to cell death

E coli Escherichia coli; S aureus Staphylococcus aureus; S pyogenes Streptococcus pyogenes. *Adapted from reference 19*

Key points

- SSTI severity depends on depth, with deeper infections (fasciitis, myositis) requiring urgent intervention.
- Skin barrier disruptions (lacerations, burns, instrumentation) are key entry points, necessitating preventive measures.
- Exotoxins from **S. aureus** and **S. pyogenes** drive rapid necrosis, increasing the risk of toxic shock syndrome.
- Rapidly progressive SSTIs **(Vibrio vulnificus)** demand immediate recognition to prevent sepsis and multi-organ failure.

PATHOGENESIS

Human skin serves as the first line of defence against microbial infection as a physical barrier; by secreting low pH, sebaceous fluid and fatty acids to inhibit growth of pathogens; and by possessing its own normal flora, thus deterring colonization by other pathogenic organisms [19]. Unfortunately, having penetrated the integumentary barrier, infecting organisms may cause tissue damage and may incite an inflammatory response.

Bacteria, initially in low numbers, colonize different layers of the skin architecture (ie, epidermis, dermis, subcutaneous and adipose tissues, and muscle fascia). As bacteria increase in number where the integumentary barrier is disrupted, invasion by these colonizing bacteria ensues and an SSTI develops. Involvement of pores in the epidermis may lead to folliculitis, furuncles or carbuncles. Infection of the superficial layers of skin is labelled erysipelas, whereas deeper involvement of the dermis and/or subcutaneous tissues is labelled cellulitis. Finally, involvement of yet deeper skin structures may lead to fasciitis and even myositis. For individuals with thick adipose tissues (eg, overweight or obese individuals), involvement of fat tissue causes panniculitis [20].

The clinical presentation of most SSTIs is the culmination of a two-step process. First, invasion occurs, and then a process follows that culminates in clinical effects resulting from the interaction of the bacteria and the host defences.

There are several means by which bacteria penetrate the skin barrier. The most common route is through a break in the barrier. Lacerations, bite wounds, scratches, instrumentation (eg, needles), pre-existing skin conditions, wounds (eg, chicken pox or ulcer), burns and surgery are the common mechanisms of compromising the skin barrier. These mecha-nisms permit the entry of normal skin flora and indigenous flora from the instrument of penetration. Other routes of penetration include contiguous spread from an adjacent infec-tion (eg, osteomyelitis), entry of water into skin pores (eg, hot-tub folliculitis) and, rarely, hematogenous seeding (ie, emboli)[1-3].

Bacterial infection

The development of an SSTI depends on three steps – bacterial adherence to host cells, invasion of tissue with evasion of host defences and elaboration of toxins [19]. Virulence genes, in most pathogenic bacteria, encode special proteins that confer these properties. Specific examples of the following virulence factors are found in Table 2.

Among the bacterial arsenal of virulence proteins, the toxins are most potent and responsible for clinical disease [19]. There are two main classes of toxins endotoxins and exotoxins. Endotoxins are lipopolysaccharide chains found abundantly in Gram-negative bacterial cell walls. In modest quantities, lipopolysaccharides may be beneficial by activating the immune system. They cause the release of chemoattractants and enhance T lymphocyte activation by inducing the expression of costimulatory molecules. Massive elaboration of liposaccharides may, however, lead to detrimental overstimula tion of host immune and inflammatory systems. For example, the potent endotoxin expressed by Vibrio vulnificus usually causes rapidly progressive SSTIs, leading to necrotizing fasciitis [21], and culminating in septic shock, disseminated intravas-cular coagulation and adult respiratory distress syndrome.

Exotoxins, on the other hand, are actively secreted proteins that cause tissue damage or dysfunction through various mechanisms [19]. They may cause tissue damage through enzymatic reactions, cellular dysregulation or pore formation, with subsequent cell lysis. A special group of exotoxins is the superantigens. These are most notably produced by virulent S aureus and S pyogenes strains [19]. These antigens bind conserved portions of T cell receptors and are, therefore, able to activate a large number of T lymphocytes. The massive release of cytokines causes a grossly exaggerated inflammatory response. SSTIs caused by these strains develop rapidly and are associated with severe tissue necrosis. This phenomenon precipitates toxic shock syndrome.

Inflammation

The other portion of the infection process involves the host response to tissue invasion and damage. As a protective response, the goals of inflammation are to rid the body of the inciting organisms and begin tissue repair.

Microbial invasion or tissue damage in skin or soft tissues induces changes in vascular tone to increase blood flow to the injured site. Additional changes in microvasculature promote and assist the extravasation of plasma proteins and leukocytes. These cells and proteins migrate, accumulate and are activated at the site of injury. With activation, cells phagocytize, and destroy foreign matter, dead tissue or microbes. Certain pyrogenic cytokines or exotoxins cause the febrile response. The orches-tration of cells and cytokines is highly sophisticated and beyond the scope of the present review. Ultimately, the site of injury is quarantined, cleared and repaired gradually [19].

Unfortunately, there may be circumstances when this process continues unfettered. With diabetic foot ulcer infections, S aureus infections with Panton Valentine leukocidin produc-tion and toxic shock syndrome, the persistence of tissue damage or pathogens may perpetuate the inflammatory response. As a result, inflammation may be the source of ongoing tissue damage [19]. The tissue eventually becomes devitalized and hypoxia ensues, which predisposes to anaerobic infections, such as with Clostridium species. Urgent medical attention, including surgical debridement of necrotic tissues and aggressive antibiotic therapy, is essential to arrest inflammation and promote healing.

Clinical manifestations of inflammation

The cardinal manifestations of inflammation are warmth, erythema, edema, pain and dysfunction [22]. Prolonged inflam-mation can lead to chronic edema, especially in the lower extremities, and can result in a postcellulitic syndrome. Ancillary systemic signs, such as fever, hypotension and tachy-cardia, result from cytokine-induced changes in thermoregula-tion and vascular resistance. The release of cytokines may be mediated by the normal immune cell function or by bacterial toxin stimulation. Out-of-proportion pain results from severe damage of the deep layers of skin produced by bacterial toxins, while bullous lesions are produced by toxin mediated epidermal cleavage. Skin anesthesia, which may be present during the course of necrotizing fasciitis, occurs secondary to toxin-mediated nerve tissue damage. Also, violaceous lesions result from toxin mediated lysis of erythrocytes and hemorrhage [3,8].

Clinical presentation

SSTIs produce a diversity of clinical manifestations. Typical presenting features, as mentioned above, are nonspecific, and include erythema, edema, pain and warmth. In contrast, more severe infections may present with more systemic signs and symptoms, including temperature higher than 40°C or lower than 35°C, hypotension, heart rate faster than 100 beats/min, altered mental status, with a rapidly progressive course and extreme pain (necrotizing fasciitis and myonecrosis) [3,8]. On examination of severe infections, one may be able to palpate crepitus and fluctuance secondary to gas or fluid collections. With subsequent necrosis of the dermis, bullae form, which are initially filled with clear fluid and then with hemorrhagic, violaceous fluid [3,8]. As mentioned above, skin anesthesia may be a late finding in severe skin SSTIs. Finally, ulcers develop in areas of high mechanical pressure [23], progressing to ischemia and necrosis [24,25].

DIFFERENTIAL DIAGNOSIS

Because of its delicate and intricate anatomy and physiology, the skin is very prone to irritation, abrasions or trauma, as well as the development of lesions generated from within its own structures (eg, folliculitis). Erythematous skin lesions do not always represent infections. A broad range of differential diagnoses exist, which may present similar to impetigo, erysipelas or even cellulitis. Falagas and Vergidis [26] have discussed various common and rare diseases that may mimic SSTIs (Table 3).

The general lack of data has precluded the development of a standardized approach to categorizing the different skin diseases. For this reason, an approach to the differential diagnosis of SSTIs may be based on the specific anatomical site affected. First, for skin lesions that affect the upper extremities, venous thrombophlebitis, contact dermatitis, envenomations, Sweet's syndrome, gouty arthritis, pseudogout, erythromelalgia and familial Hibernian fever should be considered. Second, for lesions that affect the head, acne, drug reactions, relapsing polychondritis, herpes zoster and psoriasis should be considered. Third, for chest and abdominal skin lesions, drug reac-tions, foreign body reactions, the familial

Key points

- Severe SSTIs show systemic signs (fever, hypotension, tachycardia) and toxin effects like bullae and skin anesthesia, requiring urgent care.
- Out-of-proportion pain, crepitus, and hemorrhagic bullae indicate necrotizing fasciitis, demanding immediate surgical evaluation.
- Chronic inflammation in SSTIs can cause postcellulitic syndrome with persistent edema and tissue damage.
- A broad differential diagnosis is crucial to distinguish SSTIs from inflammatory or vascular mimics, preventing misdiagnosis.

TABLE 3
Differential diagnoses of skin and soft tissue lesions

Disease entity	Description
Superficial thrombophlebitis	Inflammation of superficial vein associated with thrombus
	Usually caused by intravenous needle or catheter; may become secondarily infected
	Red, indurated area; tender, palpable vein
Deep venous thrombosis	Blood clot formation in deep veins leading to venous obstruction and inflammation
	Usually occurs in the setting of hypercoagulability, endothelial dysfunction and stasis
	Erythema, edema and warmth; palpable clot (rare); mild fever and leukocytosis
Contact dermatitis	Irritant or allergic skin reaction to environmental agents
	Sharply demarcated area of erythema and pruritis; may become secondarily infected
Pyoderma gangrenosum	Ulcerative skin condition associated with systemic disease with unknown etiology
	Commonly occurs with IBD, leukemia, monoclonal gammopathies and rheumatoides
	Papule or pustule progress to ulceration with violaceous or vesiculopustular borders
Drug reactions	Erupt secondary to hypersensitivity reaction to consumption of specific medication
	Usually associated with sulfur-based antibiotics and anti-inflammatory agents
	Pruritic or burning, well-demarcated plaque that recurs at the same site and spreads slowly
Eosinophilic cellulitis (Wells' syndrome)	Idiopathic acute dermatitis with dermal eosinophilic infiltration and eosinophilia
	Associated with myeloproliferative, immunological and infectious disorders
	Recurrent; 2–8 weeks' duration; multiple, pruritic, erythematous plaques
Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Idiopathic neutrophilic skin plaque eruption
	Associated with hematological malignancy (acute myelogenous leukemia)
	Red, tender plaques on face, neck and arms; fever; ocular, oral and joint pathology
Gouty arthritis	Joint inflammation causing cutaneous erythema
	Caused by joint space urate crystal precipitate-induced inflammatory response
	Erythema, warmth and tenderness; mild fever, chills and leukocytosis; urate crystals
Erythromelalgia	Idiopathic paroxysmal foot or hand cutaneous disorder
	Associated with myeloproliferative disorders; triggered by heat, fever and exercise
	Foot and hand burning, erythema and elevated skin temperature
Relapsing polychondritis	Idiopathic inflammatory disease affecting cartilaginous structures
	Commonly affects the ears, with ear lobe sparing
	Inflammatory lesions, nonerosive polyarthritis, ocular disease and aortic insufficiency
Carcinoma erysipeloides (inflammatory carcinoma)	Metastatic disease invading into skin lymphatic vessels
	Associated most with breast carcinoma
	Erythematous plaque on or under breast without fever or leukocytosis
Familial Mediterranean fever	Autosomal recessive disease with self-limited fever, synovitis and serositis
	Self-limited, recurrent, erysipelas-like skin lesions commonly below the knee
	Responds well to colchicines
Familial Hibernian fever	Idiopathic, genetic disease with fever and similar symptoms as above
	Erysipelas-like lesion on limb, which migrates distally from origin
	Does not respond to colchicines
Foreign body reactions	Rare hypersensitivity reactions to metallic implants
	Associated with hypersensitivity to nickel, chromium and cobalt
	Reaction causes overlying cutaneous, cellulitis-like erythema
Polyarteritis nodosa	Multisystemic, necrotizing vasculitis
	Subcutaneous, inflammatory nodules along affected artery that coalesce into plaques
	Often bilateral and involve lower extremities
Erythema nodosum	Septal panniculitis, usually secondary to systemic disease
	Associated with IBD, sarcoidosis and Behçet's syndrome
	Coalescent raised, painful lesions, usually in arms and legs bilaterally; 4–6 weeks' duration

IBD Inflammatory bowel disease. Adapted from reference 26

fever syndromes, eosinophilic cellulitis, herpes zoster infection and carcinoma erysipeloides should be considered. Finally, for lower extremity skin lesions, deep venous thrombosis, gouty arthritis, pseudogout, relapsing polychondritis and erythromelalgia should be considered.

DIAGNOSIS

The diagnosis of most SSTIs is based on clinical impression. Laboratory investigations help to confirm the diagnosis and elucidate characteristics of specific etiologies. A diagnostic approach

to a suspected SSTI is provided in Figure 1.

The first step is clinical suspicion of an SSTI. The minimum criterion is a skin lesion with the typical inflammatory tetrad – tenderness, erythema, edema and warmth. Depending on the extent and location of infection, dysfunc-tion of the affected area (eg, hand or foot) may also be present. The symptom that high-ly increases the suspicion of an SSTI is fever. Other signs and symptoms, including crepi-tus, bullae, anesthesia and hemorrhage, aug-ment the suspicion and confirm the diagnosis.

Investigations may include blood cultures, tissue swab with culture, needle aspiration, x-ray, ultrasound and computed tomography (CT) scan or magnetic resonance imaging (MRI) screen, depending on the clinical manifestations. In the presence of systemic symptoms, such as fever and hypotension, blood cultures help to assess for bacteremia. Blood cultures produce a low yield, with less than 5% of cases being positive [27].

Swabs of tissue with culture, such as blood cultures, are also low-yield tests [27]. Before swabbing, an ulcerated wound ought to be debrided and cleansed with normal saline irriga-tion. The difficulty with this test is determining which posi-tive swab cultures represent pathogenic agents and which represent merely skin colonization. In wounds with skin breakdown characterized by the cardinal manifestations of SSTIs, tissue swabs are most useful, given the high pretest probability of infection. In addition, positive swabs of superficial ulcers without penetration to the bone in diabetic patients are also useful in determining the microbiological etiology of the underlying infection [28]. However, such swabs may not be indicative of the etiology of underlying osteomyelitis [29].

Needle aspiration is a controversial investigation, and different approaches exist. Some studies advise a leading edge aspirate, while others attempt a central aspirate. The evidence, however, demonstrates no added benefit to either method. In one study, positive cultures were attained in approximately 10% of patients, regardless of method [30]. Furthermore, it has also been demonstrated that patients with underlying diseases or fever are more likely to have positive needle aspirate cultures [31]. Needle aspirations may be most useful in patients presenting with skin infections associated with fluid-filled vesicles.

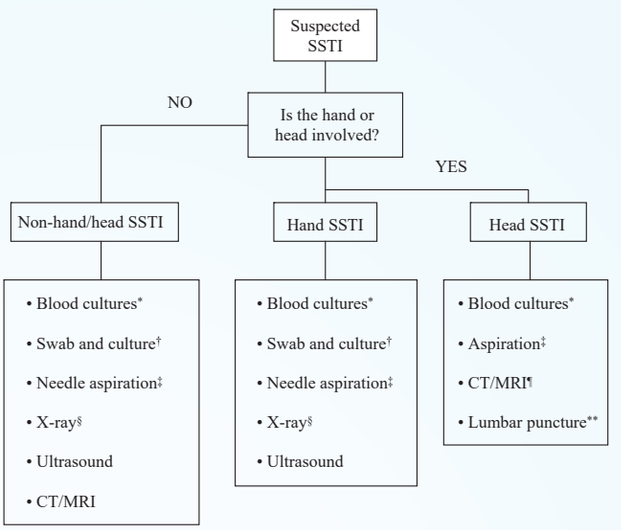


Figure 1: *Diagnostic evaluation of skin and soft tissue infections (SSTIs). *As clinically indicated; †Ulcerated lesions should be cleaned and debrided before having wound base swabbed; ‡Most useful if vesicle/bullae or fluid abscess present; §Seek out bone trauma and air fluid levels; ¶Indications – neurological deficits, vision nonassessable, proptosis/deteriorating acuity or colour/bilateral edema/ophthalmoplegia, no improvement after 24 h and swinging pyrexia not resolving within 36 h (for head only); **Only if central nervous system involvement suspected and intracranial pressure excluded. CT Computed tomography; MRI Magnetic resonance imaging*

An x-ray or ultrasound may be used to explore subdermal involvement. The x-ray may reveal bony involvement such as with osteomyelitis, although its sensitivity and specificity is limited [32]. In addition, x-rays may reveal air in the tissues or air fluid levels, which are indicative of gas-producing organ-isms such as Clostridium species. Ultrasound, on the other hand, may be used to investigate fluctuance and crepitus. This modality is useful for detecting abscess formation or fascial inflammation [9,33]. For more detailed exploration of deeper soft-tissues, a CT scan or an MRI screen may be useful. These latter two modalities are most helpful in diagnosing patients with rapidly progressive skin infections, because these lesions do not present superficially until later in their course (3,8,9). For these rapidly progressive lesions, such as necrotizing fasci-itis, early surgical exploration may be prudent, because usual diagnostic testing may prove equivocal (2,3). In patients with cranial lesions suspected of being SSTIs, head CT scans and/

Key points

- SSTI diagnosis is based on clinical signs (erythema, edema, warmth, tenderness) with fever and systemic symptoms increasing suspicion.
- Imaging (X-ray, ultrasound, CT, MRI) and tissue swabs aid diagnosis, though blood cultures and needle aspiration have low yield.

Key points

- Severity stratification in SSTIs helps determine site of care and empirical treatment, but existing grading systems lack clear clinical applicability.
- A structured severity scoring system, like those used for pneumonia, is proposed but requires validation for practical use.

or MRI screens are indicated in patients with the following findings: neurological deficits, nonassessable vision, proptosis, deteriorating visual acuity, bilateral ocular edema or ophthalmoplegia, head lesions with no improvement after 24 h or swinging pyrexia not resolving within 36 h [34]. In patients suspected of central nervous system involvement, a lumbar puncture may be necessary after the exclusion of increased intracranial pressure.

Because involvement of the head or hand is associated with a higher perceived risk for loss of function, it is vital to assess patients with such infections vigilantly. Increased diagnostic testing is needed to determine the depth and extent of infection. This information is vital for the timely administration of treatment to prevent short- and long-term morbidity.

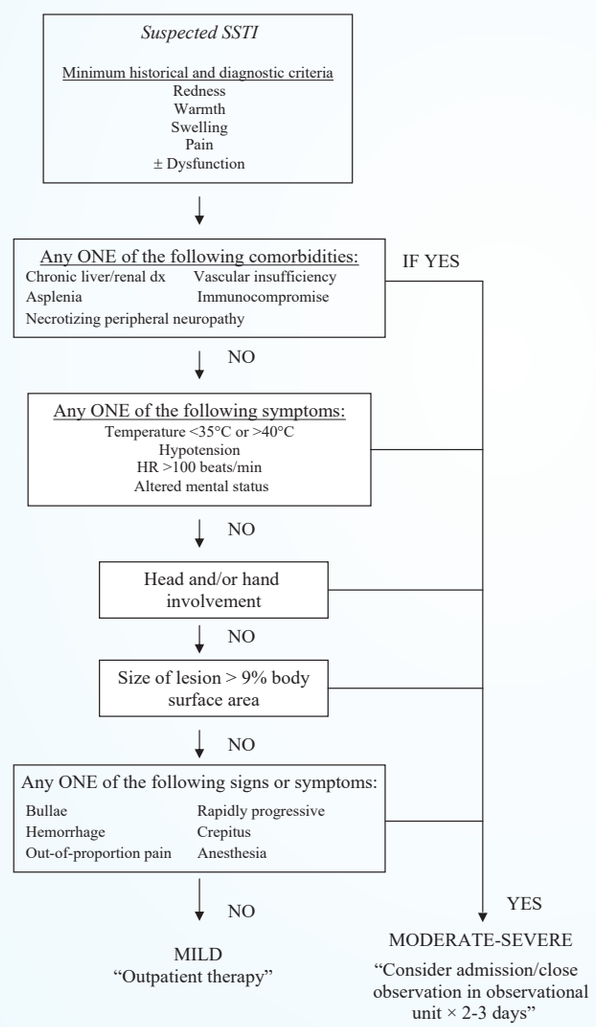


Figure 2: *Evaluation algorithm for severity of skin and soft tissue infection (SSTI). dx Dysfunction; HR Heart rate*

SEVERITY STRATIFICATION

Due to the diverse presentation of SSTIs, it has proven difficult to adopt a severity stratification approach. To improve the management of SSTIs, it is vital to develop an appropriate severity stratification approach to assist in determining the site of care and appropriate empirical treatment.

Eron et al [2] formulated a grading system of SSTIs based on a four-grade clinical description of the lesion and the patient. Once the severity grade of the infection is determined, an algorithm exists to assist in specifying the site of care. Unfortunately, because the descriptions of patient clinical presentations are quite ambiguous, the system is not very practical in its application.

To improve on the schema of Eron et al, a severity stratification system is proposed that mirrors the system designed by Fine et al [5] and Hahn and Teirstein [6] for grad-ing community acquired pneumonias (Figure 2). This system grades severity according to the presence or absence of specific historical and clinical findings. Its practical applicability requires further testing and validation.

To be considered an SSTI, the presenting skin or soft tissue lesion must meet the minimum criteria outlined above, but depending on the infection, not all of these signs are required. In addition, patient comorbidities may impact on the progression and the course of SSTIs. There are specific comorbid conditions that increase the risk of acquiring severe SSTIs (see above). The presence of these conditions must be assessed and factored in when judging severity for potential admission to the hospital.

The systemic manifestations of fever (lower than 35°C or higher than 40°C), hypotension, tachycardia (heart rate faster than 100 beats/min) or altered mental status represent sys-temic tox-

icity, and portend deeper penetration and invasion of the infection. If allowed to progress, patients with these clinical signs may go on to develop severe sepsis and/or shock, which carry high morbidity and mortality rates.

The next step in determining the severity of the infection is to assess the site of the lesion. The most common site for an SSTI is in the lower extremities. In contrast, involvement of the whole hand or head has the potential for more significant damage. Even if such infections seem clinically less severe, they should prompt more vigilant investigation and treatment. Head and hand SSTIs, therefore, carry a greater clinical severity.

The size of the lesion is a very important determinant of dis-ease severity. Certain SSTIs, such as necrotizing fasciitis, have a tendency to involve large areas of skin and soft tissue, even though in their early stages, this may not be apparent (3,8,9). Large and rapidly progressive SSTIs require more urgent man-agement, observation and intervention. To help distinguish large from smaller lesions, the use of the 'rule of nines' as previously applied to burn victims is recommended (35). For adults, each arm and the head constitute approximately 9% of body surface area, whereas each leg, the upper torso and the abdomen (when including both anterior and posterior aspects) each constitute approximately 18% of body surface area, respectively. Any SSTI that involves more than 9% of body surface area should be viewed as severe (Figure 3). The excep-tion to this rule are head and hand infections. The whole head and the whole hand constitute approximately 9% and 2% of body surface area, respectively. The potential morbidity of these infections, as previously mentioned, requires a lower threshold for increasing severity. Therefore, for these regions, lesions covering the whole hand or one-half of the head should be considered to be as more severe infections.

Finally, one must consider specific signs and symptoms in determining disease severity. The presence of bullae, hemor-rhage, out-of-proportion pain, crepitus, anesthesia and rapidly progressive character herald the presence of greater disease severity.

Following the determination of severity based on the pro-posed algorithm, one can establish the appropriate site of care. If the infection is mild, outpatient management is appropriate, which includes an antibiotic regimen (oral or intravenous) with or without specific wound care. If, however, the infection is severe, it is prudent to consider hospital admission or at least admission to an observational unit. If left untreated, mild infections may progress to severe infections.

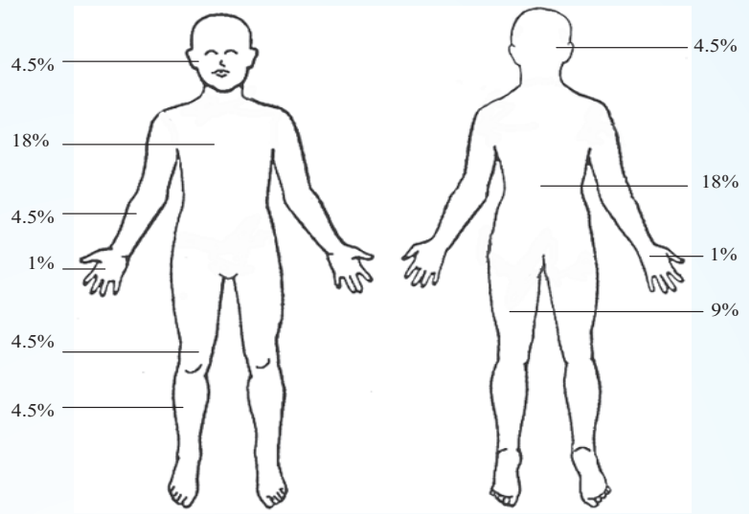


Figure 3: *Body surface area – the rule of nines*

ANTIMICROBIAL TREATMENT

Traditionally, pharmacotherapeutic recommendations have been based on bacterial etiology. Unfortunately, most often, the specific bacterial etiology of an SSTI is unknown and clinicians are forced to prescribe empirically. As a result, treat-ment recommendations based solely on organisms are difficult to apply clinically.

An approach based on clinical presentation offers a practical framework by which to organize SSTI treatment to help guide empirical therapy. However, deviations from this framework do occur under special circumstances. These special considerations may include the following – diabetic lower limb infections, no

Key points

- Severe SSTIs are indicated by systemic toxicity (fever <35°C or >40°C, hypotension, tachycardia, altered mental status) and require urgent intervention to prevent sepsis and shock.
- Head and hand infections are inherently high-risk due to potential functional impairment and should be treated with heightened vigilance.
- Lesions covering >9% of body surface area (rule of nines) or showing rapid progression, bullae, hemorrhage, or anesthesia signal severe disease.
- Mild SSTIs may be managed outpatient, but severe cases require hospital admission for close monitoring and aggressive treatment.

Key points

- Empirical antibiotic selection for SSTIs is primarily based on clinical presentation rather than confirmed bacterial etiology, with initial coverage targeting **Staphylococcus aureus** and **Streptococcus** species.
- Head and hand infections require special attention, with cefazolin or ceftriaxone (± clindamycin) as first-line therapy, and cefuroxime for suspected **Haemophilus** infections in children.
- Below-the-waist SSTIs involve more diverse flora, including Gram-negative and anaerobic organisms, necessitating adjusted antimicrobial selection.

-socomial infections, infections secondary to specific environmental exposures, necrotizing infections and colonization with resistant organisms (eg, MRSA). Recommendations for treating routine SSTIs are presented first, followed by recommendations for managing SSTIs in special circumstances.

As presented earlier, the most common etiologies of SSTIs are the normal host flora. Above the waist, one should always consider staphylococcal and streptococcal species as the instigating organisms of SSTIs. Therefore, for all mild to moderate infections (according to the previous severity algorithm), empirical therapy should always be directed against these species (Table 4) [1-3,36].

Lesions affecting the head and hand deserve special mention. The typical etiologies are still staphylococcal and streptococcal species; however, for children, one ought to consider Haemophilus species infection that may involve the face. Current guidelines [36,37] recommend the use of intravenous cefazolin or ceftriaxone with or without clindamycin as the initial therapy, with cephalexin as the step-down agent of choice. For suspected Haemophilus infections, cefuroxime is the recommended empirical agent of choice.

For deeper and larger lesions above the waist associated with systemic signs and symptoms, but without other complicating factors or significant circumstances (refer to algorithm), the typical etiologies are similar. Empirical treatment of such lesions should still target staphylococcal and streptococcal species (especially S aureus and S pyogenes). Some would consider the addition of clindamycin to standard therapy for enhanced coverage of group A streptococcal species [3]. Inhospital treatment may be necessary depending on patient status. It should be noted that out-patient intravenous therapy is advisable in cases in which there are issues with oral tolerance or compliance. With clinical improvement and stabilization, oral step-down therapy is recommended.

For SSTIs below the waist, special consideration must be given to the change in flora. As described earlier, in addition to the typical Gram-positive species, one needs to also consider enteric species – the so-called 'fecal veneer'. Risk factors for increased Gram-negative or anaerobic coloniza-tion include bedridden patients, severe and chronic infec-tions requiring multiple courses of antibiotic treatment, and extensive necrosis. The treatment recommendations are shown in Table 5 [1-3,36,37]. Chronic diabetic ulcer infections, especially with extensive necrosis, warrant anaerobic coverage. With respect to beta-lactams or fluoroquinolones, there is evidence to suggest that these two agents have similar efficacy

TABLE 4
Antimicrobial table for different skin and soft tissue infections

Clinical entity or risk factor	Common etiology	Empirical antibiotic(s)
Mild infections (above waist)	*Staphylococcus aureus* *Streptococcus pyogenes*	Cloxacillin, cephalexin or clindamycin (if penicillin allergy)
Infections of hand and head	*S aureus* *S pyogenes** *Haemophilus influenzae* (head infection in children)	Cefazolin, ceftriaxone or cefuroxime (*H influenzae*) followed by cephalexin (step-down therapy)
Severe infections (above waist) without special considerations (see text below)	*S aureus* *S pyogenes**	Cefazolin, then cloxacillin or cephalexin (step-down therapy)
Mild infections (below waist)	*S aureus* *S pyogenes** Coliform species possible	Cloxacillin or cephalexin Add clindamycin or metronidazole (anaerobes) Add second-generation cephalosporin or fluoroquinolone (if Gram-negative)
Severe infections (below waist)	*Escherichia coli* *Enterococcus* species Other coliform species *S aureus* *S pyogenes**	Second-, third- or fourth-generation cephalosporin, fluoroquinolones or piperacillin-tazobactam (in addition to above Gram-positive coverage)

**± Clindamycin*

TABLE 5
Special considerations in treating skin and soft tissue infections

Prolonged hospitalization or antibiotic exposure	MSSA MRSA *Pseudomonas aeruginosa* *Enterococcus* species AR *Enterobacteriaceae* species	Second- or third-generation cephalosporin (mild to moderate), beta-lactam plus a fluoroquinolone or aminoglycoside; add vancomycin if MRSA suspected
New diabetic foot ulceration (antibiotic naive)	MSSA *Streptococcus pyogenes*	Cloxacillin or cephalexin
Chronic foot ulceration (antibiotic sensitive)	MSSA MRSA CNS *S pyogenes* AR *Enterobactericiae* species	Piperacillin-tazobactam, ceftriaxone, ciprofloxacin or meropenem with vancomycin (combination therapy recommended)
Chronic nonhealing foot ulceration (antibiotic sensitive)	*P aeruginosa* MSSA MRSA CNS *S pyogenes* AR *Enterobactericiae* species	Combination therapy (as above) with antipseudomonal activity: piperacillin-tazobactam, ceftazidime or ciprofloxacin
Necrotic or gangrenous foot infection	*Bacteroides* species Other anaerobes *P aeruginosa* MSSA MRSA CNS *S pyogenes* AR *Enterobactericiae* species	Add clindamycin or metronidazole to baseline therapy
Rapidly progressive infections or necrotizing fasciitis	Group A streptococcus species *Staphylococcus aureus* Anaerobic bacteria *Clostridium* species	Clindamycin with penicillin G or cefazolin (change depending on inciting event)
Bites	Animal bites *Streptococcus*/*Staphylococcus* species *Pasteurella* species *Capnocytophaga canimorsus* *Bacteroides* species *Porphyromonas* species *Fusobacterium species* *Prevotella heparinolytica* *Propionibacterium species* *Peptostreptococcus species* Human bites *Viridans streptococci* *Staphylococcus* species *Haemophilus* species *Eikenella corrodens*	Amoxicillin-clavulanate (mild lesions), ceftriaxone plus metronidazole (moderate to severe lesions), clindamycin plus TMP-SMX (penicillin allergy)
Exposure to salt water or freshwater	*Aeromonas hydrophila* (freshwater) *Vibrio vulnificus* (salt water)	Ciprofloxacin (freshwater) Doxycycline (salt water)
Injection drug use	*S aureus* *S pyogenes* Gram-negative and anaerobic species (usually polymicrobial)	Cephalexin or cloxacillin with metronidazole Ceftriaxone with metronidazole (marked necrosis)
HIV	Gram-positive, Gram-negative and anaerobic polymicrobial infections	Piperacillin-tazobactam
Community-associated MRSA	Community-associated MRSA	Soaks, incision plus drainage, topical mupirocin (minor infections); clindamycin, TMP-SMX or doxycycline (mild infections); vancomycin, clindamycin or TMP-SMX (severe infections)

AR Antibiotic resistant; CNS Coagulase-negative Staphylococcal species; MRSA Methicillin-resistant Staphylococcus aureus*; MSSA Methicillin-sensitive* S aureus*; TMP-SMX Trimethoprim-sulphamethoxazole*

Key points

- Resistant pathogens (MRSA, **Pseudomonas aeruginosa**, Enterobacteriaceae) must be considered in patients with prolonged hospitalization or multiple antibiotic exposures, requiring targeted therapy.
- Diabetic lower limb SSTIs should be carefully monitored, with early intervention to prevent chronic ulceration and complications.
- Rapidly progressive SSTIs require immediate surgical debridement, as timely removal of necrotic tissue is critical for recovery.
- Bite wounds should be thoroughly cleaned and assessed early to prevent secondary infections, with prophylactic antibiotics considered based on the source of the bite.
- Patients with recurrent or resistant SSTIs should undergo targeted microbial testing to guide precise treatment and avoid unnecessary antibiotic exposure.

in empirical therapy [38]. In fact, given the increased adverse event profile for fluoroquinolones, beta-lactams should be the preferred empirical agents in immunocompetent patients.

Special considerations

With increased antibiotic exposure or prolonged hospitalization, patients are at an increased risk for infections with resistant organisms (Table 5). The pathogens in these infections are S aureus (including MRSA), P aeruginosa, Enterococcus species, Escherichia coli and other antibiotic-resistant Enterobacteriaceae species [37]. Guidelines recommend second- or third-generation cephalosporins as first-line agents for mild to moderate infections. In P aeruginosa infections, combination therapy may be considered. A recent study [39] of Paeruginosa bacteremia demonstrated a significant mortality benefit with combination therapy directed against the pathogen. However, no studies have examined the impact of combination therapy on SSTIs. With more severe or rapidly deteriorating infections, therapy should be expanded to broad-spectrum agents. In the case of MRSA, vancomycin should be added to first-line therapy.

Diabetic lower extremity SSTIs are highly prevalent worldwide. Appropriate management of these infections requires targeted pharmacotherapy [2,3,27,36]. First, for superficial infections suggestive of cellulitis, or new ulcer and antibiotic naivity, therapy should still target staphylococcal and streptococcal species. Second, for a chronic ulcer infection in a patient with a history of multiple antibiotic courses, one also needs to consider Enterobacteriaceae species (especially resist-ant strains), coagulase-negative staphylococcus and MRSA as etiological pathogens. Piperacillin-tazobactam, ceftriaxone, fluoroquinolones and the carbapenems, such as ertapenem, imipenem or meropenem, may be considered as first-line empirical agents for these lesions. For MRSA, vancomycin is the mainstay of therapy. Third, for the chronic nonhealing ulcer infections in patients with prolonged antibiotic exposure, one needs to consider the possibility of P aeruginosa infection. For these SSTIs, combination therapy should contain an antipseudomonal beta-lactam agent such as piperacillin, piperacillin-tazobactam, ceftazidime or a carbapenem, plus a fluoroquinolone such as ciprofloxacin. Finally, for SSTIs show-ing evidence of necrosis, the etiology is usually polymicrobial, and consists of both aerobic and anaerobic organisms. Initial therapy in these patients should be intravenous; however, with clinical improvement, therapy may be streamlined to oral antibiotics. The management of such infections requires care-ful monitoring and frequent therapeutic titration.

Rapidly progressive and necrotic SSTIs require urgent intervention. Because of their tendency to present with non-specific signs and symptoms, a delay in diagnosis may lead to severe complications. The management of these SSTIs requires early surgical consultation and supportive care meas-ures, including fluid management, vasopressor agents and antibiotics. Many lesions require extensive debridement before any healing may begin [3,8]. With regard to adjuvant medical therapy, antibiotic agents should target Gram-positive organ-isms: group A streptococcus, S aureus, group B streptococcus and Clostridium species. Current guidelines recommend intra-venous clindamycin in combination with either penicillin G or cefazolin. Depending on the inciting event (eg, bite or environmental exposures), empirical therapy may need to be altered to cover for specific bacterial etiology [3]. Ancillary intravenous immunoglubulin may also prove to be useful in severely septic patients [40].

Bite wounds are at risk for developing SSTIs. In these cases, it is important to determine the cause of the bite wound. Organisms involved in these SSTIs depend on the source agent as mentioned above.

SUMMARY

SSTIs are a highly prevalent but complex and diverse group of infections. As a result of the diversity of their presentation, clinical management is challenging. Furthermore, their management is complicated by the paucity of evidence from well-documented studies, and decisions regarding site of care and appropriate antimicrobial therapy may be inconsistent and inefficient.

One method of addressing site of care decisions is to determine disease severity based on the combination of several clinical findings. Disease severity should consider location, size, systemic symptoms, comorbidities and significant characteristics of the infection. Based on these criteria, SSTIs may be classified as either mild or moderate to severe. Following this stratification, one can determine the site of care: mild lesions can be treated in the outpatient setting with oral therapy, whereas moderate to severe lesions may require hospitalization or outpatient intravenous therapy.

Appropriate antibiotic therapy is the key to infection treatment. Empirical therapy should depend on several factors: potential pathogens, disease severity, clinical complications and the instrument of entry (eg, animal bite). For all uncomplicated lesions, empirical therapy should target the typical Gram-positive skin flora, such as S pyogenes and S aureus. For lesions below the waist, therapy should also be directed against enteric species. Characteristics that complicate SSTIs include prolonged hospitalization and antibiotic therapy, diabetes, rapidly progressive and necrotic lesions, bite wounds, exposure to salt water or freshwater, injection drug use, HIV and risk factors for community-associated MRSA. Empirical therapy for SSTIs in the above settings must include coverage of the commonly encountered pathogens. Finally, the duration of therapy and use of oral therapy are best determined by careful follow-up and astute clinical judgement. It is also unknown whether current therapy guidelines for outpatient and hospitalized patient care are optimal with respect to treatment efficacy and health care costs.

Key points

- SSTI management requires stratification based on severity (mild vs. moderate/severe) to determine the appropriate site of care and treatment approach.
- Empirical antibiotic selection should be guided by location, likely pathogens, complicating factors (e.g., diabetes, bite wounds, MRSA risk), and site-specific flora.

REFERENCES

1. Swartz MN. Clinical practice. Cellulitis. N Engl J Med. 2004;350:904–12. doi: 10.1056/NEJMcp031807.

2. Eron LJ, Lipsky BA, Low DE, Nathwani D, Tice AD, Volturo GA Expert panel on managing skin and soft tissue infections. Managing skin and soft tissue infections: Expert panel recommendations on key decision points. J Antimicrob Chemother. 2003;52:i3–17. doi: 10.1093/jac/dkg466.

3. Stevens DL, Bisno AL, Chambers HF, et al. Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005;41:1373–406. doi: 10.1086/497143.

4. Elston DM. Optimal antibacterial treatment of uncomplicated skin and skin structure infections: Applying a novel treatment algorithm. J Drugs Dermatol. 2005;4

5. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243–50. doi: 10.1056/NEJM199701233360402.

6. Halm EA, Teirstein AS. Clinical practice. Management of community-acquired pneumonia. N Engl J Med. 2002;347:2039–45. doi: 10.1056/NEJMcp020499.

7. Ellis Simonsen SM, van Orman ER, Hatch BE, et al. Cellulitis incidence in a defined population. Epidemiol Infect. 2006;134:293–9. doi: 10.1017/S095026880500484X.

8. Vinh DC, Embil JM. Rapidly progressive soft tissue infections. Lancet Infect Dis. 2005;5:501–13. doi: 10.1016/S1473-3099(05)70191-2.

9. Baddour LM. Epidemiology, clinical features, and diagnosis of cellulitis. < http://www.utdol.com/utd/content/topic.do?topicKey=skin.inf/11185&selectedTitle=1150&source=searc_result2008>

10. Cox NH. Management of lower leg cellulitis. Clin Med. 2002;2:23–7. doi: 10.7861/clinmedicine.2-1-23.

11. Björnsdóttir S, Gottfredsson M, Thórisdóttir AS, et al. Risk factors for acute cellulitis of the lower limb: A prospective case-control study. Clin Infect Dis. 2005;41:1416–22. doi: 10.1086/497127.

12. Horowitz Y, Sperber AD, Almog Y. Gram-negative cellulitis complicating cirrhosis. Mayo Clin Proc. 2004;79:247–50. doi: 10.4065/79.2.247.

13. Todar K. The bacterial flora of humans. < http://textbookofbacteriology.net/normalflora. html> (Version current at February 12, 2008).

14. Rennie RP, Jones RN, Mutnick AH SENTRY Program Study Group (North America) Occurrence and antimicrobial susceptibility patterns of pathogens isolated from skin and soft tissue infections: Report from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 2000) Diagn Microbiol Infect Dis. 2003;45:287–93. doi: 10.1016/s0732-8893(02)00543-6.

15. King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant Staphylococcus aureus USA 300 clone as the predominant cause of skin and soft-tissue infections. Ann Intern Med. 2006;144:309–17. doi: 10.7326/0003-4819-144-5-200603070-00005.

16. Frazee BW, Lynn J, Charlebois ED, Lambert L, Lowery D, Perdreau-Remington F. High prevalence of methicillin-resistant Staphylococcus aureus in emergency department skin and soft tissue infections. Ann Emerg Med. 2005;45:311–20. doi: 10.1016/j. annemergmed.2004.10.011.

17. Eady EA, Cove JH. Staphylococcal resistance revisited: Community-acquired methicillin resistant Staphylococcus aureus –an emerging problem for the management of skin and soft tissue infections. Curr Opin Infect Dis. 2003;16:103–24. doi: 10.1097/00001432- 200304000-00007.

18. Moroney SM, Heller LC, Arbuckle J, Talavera M, Widen RH. Staphylococcal cassette chromosome mec and Panton-Valentine leukocidin characterization of methicillin-resistant Staphylococcus aureus clones. J Clin Microbiol. 2007;45:1019–21. doi: 10.1128/JCM.01706- 06.

19. McAdam AJ, Sharpe AH. Infectious diseases – bacterial infections. In: Kumar V, Abbas AK, Fausto N, editors. Robbins & Cotran Pathologic Basis of Disease. Philadelphia: Elsevier Inc; 2005. pp. 371–96.

20. Nauta RJ. A radical approach to bacterial panniculitis of the abdominal wall in the morbidly obese. Surgery. 1990;107:134–9.

21. Oliver JD. Wound infections caused by Vibrio vulnificus and other marine bacteria. Epidemiol Infect. 2005;133:383–91. doi: 10.1017/s0950268805003894.

22. Acute and chronic inflammation. In: Kumar V, Abbas AK, Fausto N, eds. Robbins & Cotran Pathologic Basis of Disease. Philadelphia: Elesvier Inc, 2005:47-86.

23. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. Lancet. 2005;366:1725–35. doi: 10.1016/S0140-6736(05)67699-4.

24. Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot? Diabetes Metab Res Rev. 2000;16:S75–83. doi: 10.1002/1520-7560(200009/10)16:1+<::aid-dmrr139>3.0.co;2-8.

25. Lipsky BA, Berendt AR, Deery HG, et al. Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004;39:885–910. doi: 10.1086/424846.

26. Falagas ME, Vergidis PI. Narrative review: Diseases that masquerade as infectious cellulitis. Ann Intern Med. 2005;142:47–55. doi: 10.7326/0003-4819-142-1-200501040-00011.

27. Hook EW, III, Hooton TM, Horton CA, Coyle MB, Ramsey PG, Turck M. Microbiologic evaluation of cutaneous cellulitis in adults. Arch Intern Med. 1986;146:295–7.

28. Slater RA, Lazarovitch T, Boldur I, et al. Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone. Diabet Med. 2004;21:705–9. doi: 10.1111/j.1464-5491.2004.01221.x.

29. Senneville E, Melliez H, Bertrand E, et al. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: Concordance with ulcer swab cultures. Clin Infect Dis. 2005;42:47–62. doi: 10.1086/498112.

30. Newell PM, Norden CW. Value of needle aspiration in bacteriologic diagnosis of cellulitis in adults. J Clin Microbiol. 1988;26:401–4. doi: 10.1128/jcm.26.3.401-404.1988.

31. Sachs MK. The optimum use of needle aspiration in the bacteriologic diagnosis of cellulitis in adults. Arch Intern Med. 1990;150:1907–12.

32. Lipsky BA. Osteomyelitis of the foot in diabetic patients. Clin Infect Dis. 1997;25:1318–26. doi: 10.1086/516148.

33. Tsai CC, Lai CS, Yu ML, Chou CK, Lin SD. Early diagnosis of necrotizing fasciitis by utilization of ultrasonography. Kaohsiung J Med Sci. 1996;12:235–40.

34. Howe L, Jones NS. Guidelines for the management of periorbital cellulitis/abscess. Clin Otolaryngol Allied Sci. 2004;29:725–8. doi: 10.1111/j.1365-2273.2004.00889.x.

35. Berkow SG. A method of estimating the extensiveness of lesions, burns and scalds, based on surface area proportions. Arch Surg Lond. 1924;8:138–48.

36. Fung HB, Chang JY, Kuczynski S. A practical guide to the treatment of complicated skin and soft tissue infections. Drugs. 2003;63:1459–80. doi: 10.2165/00003495-200363140- 00003.

37. Rosser WW, Pennie RA, Pila NJ The Anti-Infective Review Panel. Anti-Infective Guidelines for Community-Acquired Infections. Toronto: MUMS Guideline Clearinghouse; 2005.

38. Falagas ME, Matthaiou DK, Vardakas KZ. Fluoroquinolones vs beta-lactams for empirical treatment of immunocompetent patients with skin and soft tissue infections: A meta-analysis of randomized controlled trials. Mayo Clin Proc. 2006;81:1553–66. doi: 10.4065/81.12.1553.

39. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteremia? A meta-analysis. Lancet Infect Dis. 2004;4:519–27. doi: 10.1016/S1473-3099(04)01108-9.

40. Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. Cochrane Database Syst Rev. 2002(1):CD001090. doi: 10.1002/14651858.CD001090.

41. Barton M, Hawkes M, Moore D, et al. Guidelines for the prevention and management of community-associated methicillin-resistant Staphylococcus aureus: A perspective for Canadian health care practitioners. Can J Infect Dis Med Microbiol. 2006;17

42. Jewesson PJ. Pharmaceutical, pharmacokinetic and other considerations for intravenous to oral stepdown therapy. Can J Infect Dis. 1995;6(Suppl):11A–6A. [Google Scholar]

43. Desai M, Franklin BD, Holmes AH, et al. A new approach to treatment of resistant gram-positive infections: Potential impact of targeted IV to oral switch on length of stay. BMC Infect Dis. 2006;6:94. doi: 10.1186/1471-2334-6-94.

44. Hanakawa Y, Schecter NM, Lin C, et al. Molecular mechanisms of blister formation in bullous impetigo and staphylococcal scalded skin syndrome. J Clin Invest. 2002;110:53–60. doi: 10.1172/JCI15766.

45. Kaneko J, Kamio Y. Bacterial two-component and hetero-heptameric pore-forming cytolytic toxins: Structures, pore-forming mechanism, and organization of the genes. Biosci Biotechnol Biochem. 2004;68:981–1003. doi: 10.1271/bbb.68.981. (Erratum in 2004;68:A4)

Azithromycin Pulse Therapy in Acne Vulgaris: Better Outcomes with Fewer Side Effects

Compared to Doxycycline Daily Therapy in a Non-Randomized Clinical Study

Reference: Singhi MK, Ghiya BC, Dhabhai RK. Comparison of oral azithromycin pulse with daily doxycycline in the treatment of acne vulgaris. Indian J Dermatol Venereol Leprol. 2003;69(4):274-276.

ABSTRACT

Acne vulgaris, a prevalent dermatological condition, often necessitates systemic therapy in moderate to severe cases. This non-randomized clinical trial aimed to evaluate the clinical effectiveness and safety profile of oral azithromycin pulse therapy (500 mg OD for 3 days in 10-day cycles) versus daily doxycycline (100 mg OD), both alongside topical erythromycin.

Out of 70 enrolled patients, 62 completed the 3-month study. Results revealed that the azithromycin group experienced a 77.26% reduction in acne severity, which was significantly superior to the 63.74% improvement in the doxycycline group. Moreover, azithromycin demonstrated a lower incidence of side effects, with only mild gastrointestinal symptoms, while doxycycline was associated with more frequent and severe adverse events.

This study suggests that azithromycin, with its unique pharmacokinetics and pulse regimen, offers a more effective and patient-compliant option for the management of inflammatory acne.

Study Methodology

Study Design & Background

A non-randomized, open-label comparative trial was conducted to explore alternatives to traditional long-term antibiotic regimens in acne treatment. The rationale stemmed from the need for simplified dosing, better patient adherence, and reduced antimicrobial resistance risks.

Patient Population

- Total enrolled: 70 patients (45 female, 25 male)
- Completed study: 62 patients (38 in azithromycin group, 26 in doxycycline group)
- Inclusion: Patients with moderate to severe acne vulgaris (as per consensus classification) resistant to previous treatments
- Exclusion: Concurrent antibiotic use, liver disease, pregnancy

Most patients had longstanding acne, with many showing truncal involvement (chest and back), indicating more severe disease.

Treatment Protocols

Group A: Azithromycin Pulse

- 500 mg orally once daily for 3 consecutive days every 10 days.
- 7-day drug-free interval between each cycle
- Duration: 3 months (total 9 cycles)

Group B: Doxycycline Continuous

- 100 mg once daily after meals
- Daily dosing for 3 months

Topical Therapy:
All patients in both groups received topical erythromycin twice daily throughout the study.

Assessment Tools & Endpoints

- Acne lesions were graded using the Michaelsson Severity Index, assigning weight to different lesion types (comedones, papules, pustules, nodules, cysts)
- Primary endpoint: Mean % reduction in total severity score over 3 months
- Secondary endpoints: Proportion of patients with >80% improvement, side-effect frequency, and dropout rates

Key points

- Pulse dosing: 500 mg OD × 3 days every 10 days.
- Designed for better adherence and reduced resistance.
- Anti-inflammatory + long half-life advantage.
- Suitable for moderate–severe, resistant acne.

Follow-ups were conducted at 10-day intervals, with assessments by two independent clinicians, and photographic documentation was maintained.

Findings & Outcomes

Parameter	Azithromycin (n=36)	Doxycycline (n=26)
Mean Severity Index (Pre-Treatment)	254.96	234.76
Mean Severity Index (Post-Treatment)	59.93	82.85
% Improvement	77.26%	63.74%
Patients with >80% Improvement	52.8%	19.2%
Mild GI Side Effects	3	4
Serious Side Effects	0	2 (oesophageal ulceration, photo-onycholysis)

Greater Baseline Severity Handled Better with Azithromycin

- The mean pre-treatment severity was higher in the azithromycin group (254.96) than in the doxycycline group (234.76), indicating more severe baseline disease.
- Despite this, azithromycin achieved superior clinical outcomes, suggesting greater therapeutic strength.

Superior Clinical Efficacy with Azithromycin

- The post-treatment severity index was significantly lower with azithromycin (59.93 vs. 82.85), demonstrating better lesion clearance.
- The overall improvement in severity score was 13.5% higher with azithromycin (77.26% vs. 63.74%), confirming statistically significant superiority ($p < 0.01$).

More Patients Achieved High-Level Clearance

- 52.8% of azithromycin-treated patients showed >80% improvement, compared to only 19.2% in the doxycycline group
- This outcome reflects rapid, deep, and visible improvement—especially relevant in adolescents and young adults seeking quick relief.

Better Safety Profile and Tolerability

- Azithromycin had no serious side effects, only 3 cases of mild GI discomfort, and no treatment discontinuations.
- In contrast, doxycycline was associated with 2 serious adverse events (esophageal ulceration and photo-onycholysis) and more frequent GI complaints, making it less favorable for long-term use.

Pulse Dosing Leads to Better Compliance

- The intermittent dosing of azithromycin (3 days per 10-day cycle) improves patient adherence, especially compared to daily doxycycline.
- Fewer pills, fewer side effects, and better outcomes make azithromycin more appealing to both clinicians and patients.

Discussion, Key Takeaways & Clinical Message

Discussion

Azithromycin's pharmacological advantages (long half-life, intracellular accumulation, anti-inflammatory properties) make it ideal for pulse therapy in dermatology. Unlike daily antibiotics, pulse dosing allows drug-free intervals without compromising efficacy, which helps reduce resistance development and treatment fatigue.

Patients in the azithromycin group not only experienced better clinical outcomes, but also fewer adverse events, enhancing quality of life and adherence. The combination with topical erythromycin further enhanced lesion clearance without increasing the antibiotic load.

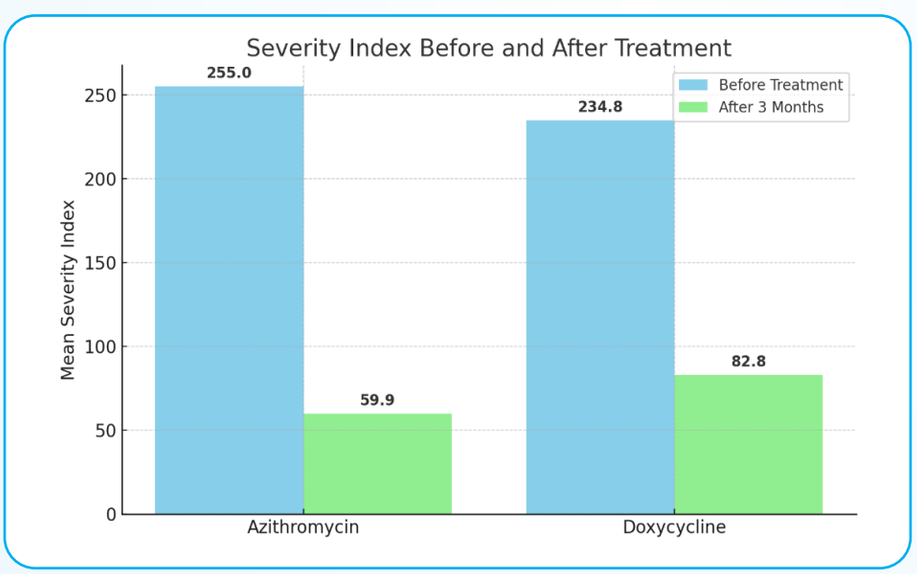
In contrast, while doxycycline remains a staple, its continuous administration led to more gastrointestinal disturbances, and even serious complications in two cases, emphasizing the need for safer alternatives.

Severity Index – Before vs After Treatment

- Azithromycin group had higher baseline severity yet showed greater reduction.
- Post-treatment index was 23 points lower in the azithromycin group.
- Indicates stronger lesion clearance and more robust anti-inflammatory response.
- Supports azithromycin as a preferred option in high-burden inflammatory acne.

Percentage Improvement in Acne Severity

- Azithromycin provided 13.5% more improvement, despite intermittent dosing.
- Reflects efficient skin tissue penetration and prolonged half-life.
- Clinical outcomes achieved without daily intake, improving patient comfort.
- Statistically significant ($p < 0.01$) – stronger efficacy profile.



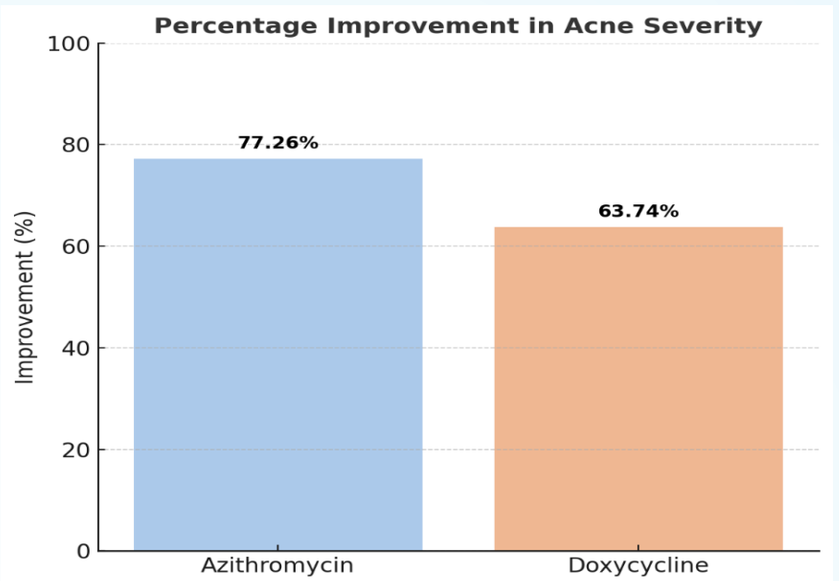
Group	Mean Severity Index (Before)	Mean Severity Index (After)
Azithromycin	254.96	59.93
Doxycycline	234.76	82.85

Key points

- Higher baseline severity with Azithro: 254.96 vs. 234.76.
- Yet showed stronger results post-treatment.
- 9 cycles over 3 months = fewer pills, better compliance.
- Drug-free intervals lower adverse event risks

Key points

- Acne reduction: **77.26% (Azithro)** vs. **63.74% (Doxy)**.
- 80% clearance: **52.8% (Azithro)** vs. **19.2% (Doxy)**.
- Serious AEs: **0 (Azithro)** vs. **2 (Doxy)**.
- Mild GI issues: **3 (Azithro)** vs. **4 (Doxy)**.



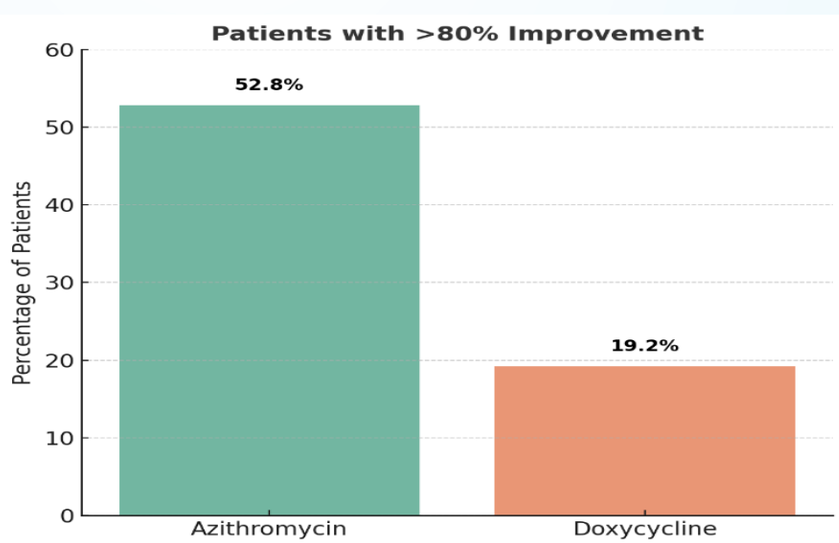
Group	% Improvement
Azithromycin	77.26%
Doxycycline	63.74%

- Rapid, visible results are especially crucial in cosmetic-sensitive young patients.
- Positions azithromycin as a first-choice agent in moderate–severe acne.

Patients Achieving >80% Improvement

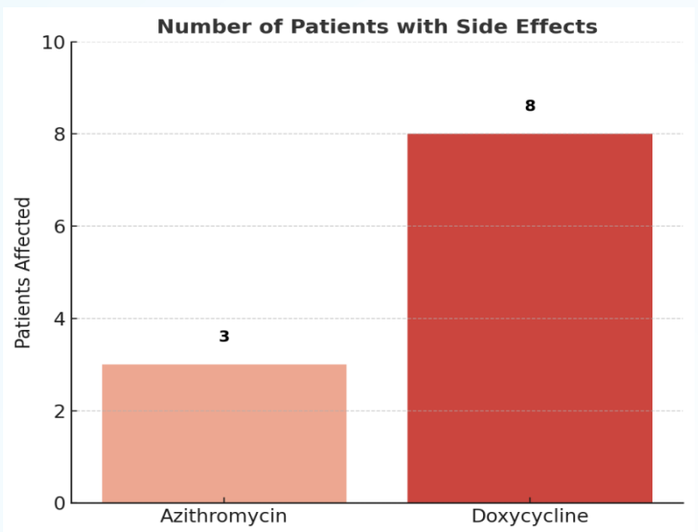
- More than half of azithromycin patients had near-complete resolution.
- Doxycycline lagged significantly—only 1 in 5 reached similar clearance.

Group	% Patients with >80% Clearance
Azithromycin	52.8%
Doxycycline	19.2%



Incidence of Side Effects

- Azithromycin exhibited a cleaner safety profile: no serious events, minor GI upset only.
- Doxycycline was linked to serious complications, affecting tolerability.
- Better safety allows azithromycin to be continued without interruption.
- Important consideration for long-term treatment plans and adherence.



Group	Mild Side Effects	Serious Adverse Events
Azithromycin	3	0
Doxycycline	4 (GI upset, diarrhea)	2 (esophageal ulceration, photo-onycholysis)

Key Takeaways for Clinical Practice

- Azithromycin pulse therapy led to a 77.26% reduction in acne severity in just 3 months
- Over 50% of patients achieved >80% lesion reduction
- Better safety profile with no severe side effects
- Pulse regimen improved adherence and minimized risk of antibiotic fatigue
- Practical alternative to long-term daily antibiotics for moderate-to-severe acne

Key points

- Azithro cleared tougher cases more effectively.
- Statistically superior ($p < 0.01$) vs. Doxy.
- Near-complete resolution in >50% of patients.
- Ideal for high-burden, cosmetic-sensitive cases.


Alembic
Touching Lives over 100 years