Egyptian Guidelines for Clinical Practice for the Diagnosis & Management of Skin and Soft Tissue Infections

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INTRODUCTION

This practice guideline provides recommendations for the diagnosis and management of skin and soft tissue infections (SSTIs) in otherwise healthy hosts and compromised hosts of all age groups.

These recommendations take on new importance because of a dramatic increase in the frequency and severity of infections and the emergence of resistance to many of the antimicrobial agents commonly used to treat SSTIs in the past.

For example, in USA, there was a 29% increase in the total hospital admissions for these infections **between 2000 and 2004** [5]. In addition, 6.3 million physician's office visits per year are attributable to SSTIs [6]. Similarly, between 1993 and 2005, annual emergency department visits for SSTIs increased from 1.2 million to 3.4 million patients [7]. Some of this increased frequency is related to the emergence of community-associated methicillin resistant Staphylococcus aureus (MRSA) [5].

These infections have diverse etiologies that depend, in part, on different epidemiological settings. As a result, **obtaining a careful history that includes information about the patient's**

- Immune status,
- Geographic locale,
- Tavel history,
- Recent trauma or surgery,
- Previous antimicrobial therapy,
- Lifestyle,
- Hobbies, and
- Animal exposure or bites

Is essential when developing an **adequate differential diagnosis** and an appropriate index of suspicion for specific etiological agents.

Recognition of the physical examination findings and understanding the **anatomical relationships of skin and soft tissue** are crucial for establishing the correct diagnosis.
In some cases, this information is insufficient and biopsy or aspiration of tissue may be necessary.
In addition, **radiographic procedures** may be critical in a small subset of patients to determine:

- **The level of infection**,
- **The presence of gas**,
- **The presence of abscess**,
- **The presence of a necrotizing process**.

Last, **surgical exploration or debridement** is an important diagnostic, as well as therapeutic, procedure in patients with necrotizing infections or myonecrosis and may be important for selected immunocompromised hosts.

Clinical evaluation of patients with SSTI aims to establish the cause and severity of infection and must take into account pathogen- specific and local antibiotic resistance patterns.

Many different microbes can cause soft tissue infections, and although specific bacteria may cause a particular type of infection, considerable overlaps in clinical presentation occur. **Clues to the diagnosis and algorithmic approaches to diagnosis are covered in detail in the text to follow**.

Specific recommendations for therapy are given*, each* ***with a rating that indicates the strength of and evidence for recommendations according to the Infectious Diseases Society of America (IDSA)/US Public Health Service grading system for rating recommendations in clinical guidelines (Table 1) [2]****. The following 24 clinical questions are answered:***

Table 1. Strength of Recommendations and Quality of the Evidence

Strength of Recommendation and Quality of Evidence	Clarity of Balance Between Desirable and Undesirable Effects	Methodological Quality of Supporting Evidence (Examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low-quality quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Strong recommendation, very low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect for at least 1 critical outcome is very uncertain.
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patient's or societal values. Further research is unlikely to change our confidence in the estimate of effect
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Weak recommendation, low-quality evidence	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Weak recommendation, very low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain

Abbreviation: RCT, randomized controlled trial.

Table 2. Antimicrobial Therapy for Staphylococcal and Streptococcal Skin and Soft Tissue Infections

Disease Entity	Antibiotic	Dosage, Adults	Dosage, Children[a]	Comment
Impetigo[b] (*Staphylococcus* and *Streptococcus*)	Dicloxacillin	250 mg qid po	N/A	N/A
	Cephalexin	250 mg qid po	25–50 mg/kg/d in 3–4 divided doses po	N/A
	Erythromycin	250 mg qid po[c]	40 mg/kg/d in 3–4 divided doses po	Some strains of *Staphylococcus aureus* and *Streptococcus pyogenes* may be resistant.
	Clindamycin	300–400 mg qid po	20 mg/kg/d in 3 divided doses po	N/A
	Amoxicillin-clavulanate	875/125 mg bid po	25 mg/kg/d of the amoxicillin component in 2 divided doses po	N/A
	Retapamulin ointment	Apply to lesions bid	Apply to lesions bid	For patients with limited number of lesions
	Mupirocin ointment	Apply to lesions bid	Apply to lesions bid	For patients with limited number of lesions
MSSA SSTI	Nafcillin or oxacillin	1-2 g every 4 h IV	100–150 mg/kg/d in 4 divided doses	Parental drug of choice; inactive against MRSA
	Cefazolin	1 g every 8 h IV	50 mg/kg/d in 3 divided doses	For penicillin-allergic patients except those with immediate hypersensitivity reactions. More convenient than nafcillin with less bone marrow suppression
	Clindamycin	600 mg every 8 h IV or 300–450 mg qid po	25–40 mg/kg/d in 3 divided doses IV or 25–30 mg/kg/d in 3 divided doses po	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA
	Dicloxacillin	500 mg qid po	25–50 mg/kg/d in 4 divided doses po	Oral agent of choice for methicillin-susceptible strains in adults. Not used much in pediatrics
	Cephalexin	500 mg qid po	25–50 mg/kg/d 4 divided doses po	For penicillin-allergic patients except those with immediate hypersensitivity reactions. The availability of a suspension and requirement for less frequent dosing
	Doxycycline, minocycline	100 mg bid po	Not recommended for age <8 y[d]	Bacteriostatic; limited recent clinical experience
	Trimethoprim-sulfamethoxazole	1–2 double-strength tablets bid po	8–12 mg/kg (based on trimethoprim component) in either 4 divided doses IV or 2 divided doses po	Bactericidal; efficacy poorly documented
MRSA SSTI	Vancomycin	30 mg/kg/d in 2 divided doses IV	40 mg/kg/d in 4 divided doses IV	For penicillin allergic patients; parenteral drug of choice for treatment of infections caused by MRSA
	Linezolid	600 mg every 12 h IV or 600 mg bid po	10 mg/kg every 12 h IV or po for children <12 y	Bacteriostatic; limited clinical experience; no cross-resistance with other antibiotic classes; expensive
	Clindamycin	600 mg every 8 h IV or 300–450 mg qid po	25–40 mg/kg/d in 3 divided doses IV or 30–40 mg/kg/d in 3 divided doses po	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA. Important option for children
	Daptomycin	4 mg/kg every 24 h IV	N/A	Bactericidal; possible myopathy
	Ceftaroline	600 mg bid IV	N/A	Bactericidal
	Doxycycline, minocycline	100 mg bid po	Not recommended for age <8 y[d]	Bacteriostatic; limited recent clinical experience
	Trimethoprim-sulfamethoxazole	1–2 double-strength tablets bid po	8–12 mg/kg/d (based on trimethoprim component) in either 4 divided doses IV or 2 divided doses po	Bactericidal; limited published efficacy data

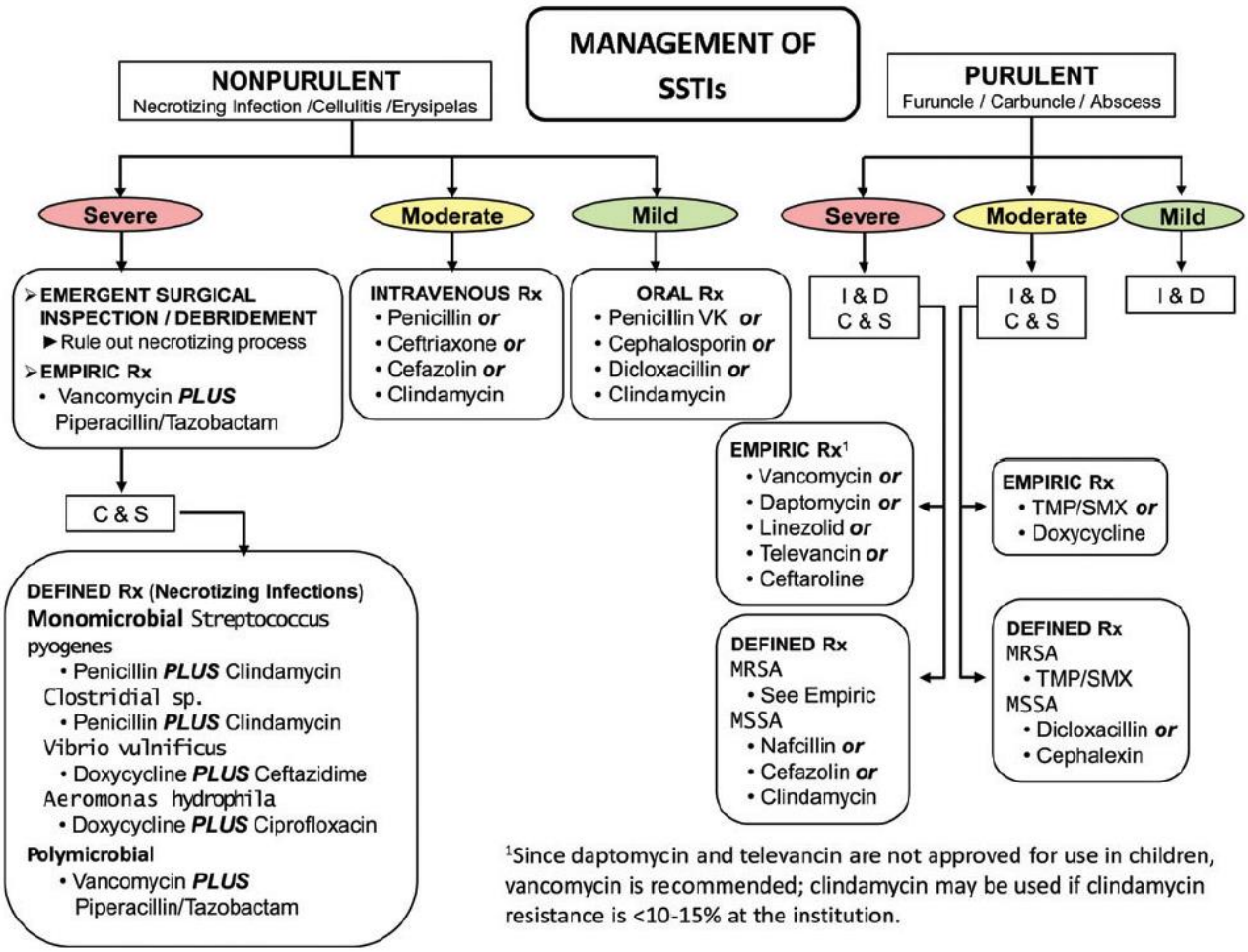

Figure 1. Purulent skin and soft tissue infections (SSTIs).

Mild infection: for purulent SSTI, incision and drainage is indicated. Moderate infection: patients with purulent infection with systemic signs of infection.

Severe infection: patients who have failed incision and drainage plus oral antibiotics or those with systemic signs of infection such as temperature >38°C, tachycardia (heart rate >90 beats per minute), tachypnea (respiratory rate >24 breaths per minute) or abnormal white blood cell count (<12 000 or <400 cells/µL), or immunocompromised patients.

Non purulent SSTIs. Mild infection: typical cellulitis/erysipelas with no focus of purulence.

Moderate infection: typical cellulitis/erysipelas with systemic signs of infection.

Severe infection: patients who have failed oral antibiotic treatment or those with systemic signs of infection (as defined above under purulent infection), or those who are immunocompromised, or those with clinical signs of deeper infection such as bullae, skin sloughing, hypotension, or evidence of organ dysfunction. Two newer agents, tedizolid and dalbavancin, are also effective agents in SSTIs, including those caused by methicillin-resistant Staphylococcus aureus, and may be approved for this indication by June 2014.

Abbreviations: C & S, culture and sensitivity; I & D, incision and drainage; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus; Rx, treatment; TMP/SMX, trimethoprim-sulfamethoxazole.

Part -1

1-What Is Appropriate for the Evaluation and Treatment of Impetigo and Ecthyma?

Recommendations:

1. Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma - especially when lesions are multiple or recurrent - are recommended to help identify whether Staphylococcus aureus and/or a β-hemolytic Streptococcus is the cause but treatment without these studies is reasonable in typical cases ***(strong and moderate).***

2. Ecthyma, Bullous and nonbullous impetigo : can be treated with oral or antimicrobials (with/or without topical saline soaks or betadine antiseptic paint) and sometimes combination therapy of both is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. For treatment of ecthyma an oral antimicrobial is a must.

> ***(a)Topical treatment of bullous and nonbullous impetigo should be with either mupirocin or Fucidin – cream form - twice daily (bid) for 5 days (with/or without topical saline soaks or betadine antiseptic paint*) *(strong & Hight)***
>
> ***(b) Oral therapy for ecthyma or impetigo should be a 7-day regimen with an agent active against S. aureus unless cultures yield streptococci alone (when oral penicillin is the recommended agent).***
> ***- Because S. aureus isolates from impetigo and ecthyma are usually methicillin susceptible: dicloxacillin or cephalexin is recommended.***
> ***- When MRSA is suspected or confirmed: doxycycline, clindamycin, or sulfamethoxazole-trimethoprim (SMX-TMP) is recommended (strong and moderate).***
>
> ***(c) Systemic antimicrobials should be used for infections during outbreaks of poststreptococcal glomerulonephritis to help eliminate nephritogenic strains of S. pyogenes from the community (strong, moderate).***

Evidence Summary
Impetigo can be either bullous or nonbullous *[12].*

Bullous impetigo *is caused by strains of S. aureus that produce a toxin that cleaves the dermal-epidermal junction to form fragile, thin roofed vesico - pustules. These lesions may rupture, creating crusted, erythematous erosions, often surrounded by a collar of the roof 's remnants.*

Nonbullous impetigo *can occur from infections with β-hemolytic streptococci or S. aureus, or both in combination [12]. Impetigo begins as erythematous papules that rapidly evolve into vesicles and pustules that rupture, with the dried discharge forming honey-colored crusts on an erythematous base.*

Ecthyma *is a deeper infection than impetigo, and S. aureus and/or streptococci may be the cause. Lesions begin as vesicles that rupture, resulting in circular, erythematous ulcers with adherent crusts, often with surrounding erythematous edema. Unlike impetigo, ecthyma heals with scarring [12].and/or streptococci may be the cause. Lesions begin as vesicles.*

Cultures of the vesicle fluid, pus, erosions, or ulcers establish the cause*. Unless cultures yield streptococci alone, antimicrobial therapy should be active against both S. aureus and streptococci[12].*
Oral penicillinase–resistant penicillin or first-generation cephalosporins are usually effective as most staphylococcal isolates from impetigo and ecthyma are methicillin susceptible [13]. Alternatives for penicillin-allergic patients or infections with MRSA include doxycycline, clindamycin, or SMX-TMP.
When streptococci alone are the cause, penicillin is the drug of choice, with a macrolide or clindamycin as an alternative for penicillin-allergic patients.

Topical treatment with mupirocin [12] or retapamulin *[14] is as effective as oral antimicrobials for impetigo. Clinical experience suggests that systemic therapy is preferred for patients with numerous lesions or in outbreaks affecting several people, to help decrease transmission of infection [15] (Table 2).*

Part -2

II. What Is the Appropriate

Evaluation and Treatment for Purulent SSTIs

(Cutaneous Abscesses, Furuncles, Carbuncles, and Inflamed Epidermoid Cysts)?

Recommendations:

3. Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases ***(strong and moderate).***

4. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended ***(strong and moderate).***

5. Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles, (Figure 1) ***(strong, high).***

6. The decision to administer antibiotics directed against S. aureus as an adjunct to incision and drainage should be made based upon presence or absence of **systemic inflammatory response syndrome (SIRS),** such as

- Temperature >38°C or <36°C,
- Tachypnea >24 breaths per minute,
- Tachycardia >90 beats per minute, or
- White blood cell count >12 000 or <400 cells/μL

(***moderate, strong, low).***

An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension ***(severe, strong, low).***

Evidence Summary

Cutaneous Abscesses*. Cutaneous abscesses are collections of pus within the dermis and deeper skin tissues. They are usually painful, tender, and fluctuant red nodules, often surmounted by a pustule and encircled by a rim of erythematous swelling. Cutaneous abscesses can be polymicrobial, containing regional skin flora or organisms from the adjacent mucous membranes, but S. aureus alone causes a large percentage of skin abscesses, with a substantial number due to MRSA strains [16–18].*

***Epidermoid (or epidermal inclusion) cysts**, often erroneously labeled sebaceous cysts, ordinarily contain skin flora in a cheesy keratinous material. When inflammation and purulence occur, they are a reaction to rupture of the cyst wall and extrusion of its contents into the dermis, rather than an actual infectious process [19].*

Incision, evacuation of pus and debris, and probing of the cavity to break up loculations provides effective treatment of cutaneous abscesses and inflamed epidermoid cysts. A randomized trial comparing incision and drainage of cutaneous abscesses to ultrasonographical guided needle aspiration of the abscesses showed that aspiration was successful in only 25% of cases overall and <10% with MRSA infections [20]. Accordingly, this form of treatment is not recommended. Simply covering the surgical site with a dry dressing is usually the easiest and most effective treatment of the wound [21, 22].

Some clinicians close the wound with sutures or pack it with gauze or other absorbent material. One small study, however, found that packing caused more pain and did not improve healing when compared to just covering the incision site with sterile gauze [23].

The addition of systemic antibiotics to incision and drainage of cutaneous abscesses does not improve cure rates [17, 21, 22, 24, 25], even in those due to MRSA, but did have a modest effect on the time to recurrence of other abscesses [17, 25]. However, systemic antibiotics should be given to patients with severely
impaired host defenses or signs or symptoms of systemic infection (Figure 1, Table 2).
In addition, multiple abscesses, extremes of age, and lack of response to incision and drainage alone are additional settings in which systemic antimicrobial therapy should be considered.

***Furuncles and Carbuncles. Furuncles (or "boils")** are infections of the hair follicle, usually caused by S. aureus, in which suppuration extends through the dermis into the subcutaneous tissue, where a small abscess form.*

***They differ from folliculitis**, in which the inflammation is more superficial and pus is limited to the epidermis. Clinically, furuncles are inflammatory nodules with overlying pustules through which hair emerges. Infection involving several adjacent follicles produces a carbuncle, a coalescent inflammatory mass with pus draining from multiple follicular orifices.*

***Carbuncles develop most commonly** on the back of the neck, especially in individuals with diabetes. These are typically larger and deeper than furuncles.*

Furuncles often rupture and drain spontaneously or following treatment with moist heat. Most large furuncles and all carbuncles should be treated with incision and drainage. Systemic antimicrobials are usually unnecessary, unless fever or other evidence of systemic infection is present (Figure 1).

Part -3

III. What Is the Appropriate Treatment for Recurrent Skin Abscesses? Recommendations

7. A recurrent abscess at a site of previous infection should prompt a search for local causes such as a **pilonidal cyst, hidradenitis suppurativa, or foreign material** ***(strong, moderate).***

8. Recurrent abscesses should be **drained** and **cultured early** in the course of infection ***(strong, moderate).***

9. After obtaining cultures of recurrent abscess, **treat with a 5- to 10-day course** of an antibiotic active against the pathogen isolated ***(weak, low).***

10. Consider a 5-day decolonization regimen :

- Twice daily of intranasal mupirocin,
- Daily chlorhexidine washes, and
- Daily decontamination of personal items such as towels, sheets, and clothes for recurrent S. aureus infection ***(weak, low).***

11. Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood (strong, moderate).

Evidence Summary

A recurrent abscess at a previous site of infection *may be caused by local factors such as foreign material, hidradenitis suppurativa, or pilonidal cyst [26, 27], eradication of which can be curative. Incision and drainage should be performed for recurrent abscesses.*

The benefits of adjunctive ***antimicrobial therapy*** *in preventing recurrences are unknown. Older randomized trials showed that twice-daily* ***intranasal mupirocin for 5 days each month*** *[28] or a* ***3-month*** *program of oral clindamycin 150 mg daily [29] reduced the rate of further infections. Whether such regimens are effective in the current era of community acquired MRSA is unclear [30].*

In one randomized trial, ***twice daily application of nasal mupirocin for 5 days among*** *military personnel who carried MRSA in the nose did not reduce the frequency of subsequent skin infections [30, 31].*

Scrubbing the body thrice weekly with chlorhexidine-impregnated cloths *after showering was also deemed ineffective [32].*

A 5-day decolonization with twice-daily intranasal mupirocin *and* ***daily bathing with chlorhexidine*** *[32] or* ***dilute bleach (1/4–1/2 cup of bleach per full bath)*** *for prevention of recurrences may be considered, but data about efficacy are sparse.*

One uncontrolled study reported termination of an epidemic of furunculosis in a village by use of ***mupirocin****, antibacterial* ***hand cleanser****, and* ***daily washing of towels****,* ***sheets****,* ***combs****, and* ***razors*** *[33].*

A recent study in children found employing preventive measures for the patient and the household contacts resulted in significantly fewer recurrences in the patient than employing the measures in the patient only [34]. Because ***patients with neutrophil dysfunction develop recurrent abscesses in early childhood****, patients who develop abscesses during adulthood do not needevaluation of neutrophil function*

Part -4

IV. What Is Appropriate for the Evaluation and Treatmentof Erysipelas and Cellulitis? Recommendations

12. Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended (***strong, moderate***).

13. Cultures of blood are recommended (***strong, moderate***), and cultures and microscopic examination of cutaneous aspirates, biopsies, or swabs should be considered in patients with:

- Malignancy on chemotherapy,
- Neutropenia,
- Severe cell-mediated immunodeficiency,
- Immersion injuries, and
- Animal bites

14. Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci (***strong, moderate***).

- For cellulitis with systemic signs of infection (moderate nonprurient), systemic antibiotics are indicated.
- Many clinicians could include coverage against methicillin-susceptible S. aureus (MSSA) (***weak, low***).
- For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS , vancomycin or another anti-microbial effective against both MRSA and streptococci is recommended (***strong, moderate***).
- In severely compromised patients as defined in question 13 , broad-spectrum antimicrobial coverage may be considered (***weak, moderate).***
- Vancomycin plus either piperacillin tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections (***strong, moderate***).

15. The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period (***strong, high***).

16. Elevation of the affected area and treatment of predisposing factors, such as edema or underlying cutaneous disorders, are recommended (***strong, moderate***).

17. Cellulitis of the lower-extremity, clinicians should carefully examine the interdigital toe spaces because treating fissuring, scaling, or maceration may eradicate colonization with pathogens and reduce the incidence of recurrent infection (***strong, moderate***).

18. **Outpatient therapy i**s recommended for patients who do not have:

- SIRS,
- Altered mental status, or
- Hemodynamic instability (***strong, moderate***).

Hospitalization is recommended if there is

- Concern for a deeper or necrotizing infection,
- For patients with poor adherence to therapy,
- For infection in a severely immunocompromised patient, or
- If outpatient treatment is failing (***strong, moderate***).

Evidence Summary

"Cellulitis" and "erysipelas" *refer to diffuse, superficial, spreading skin infections. The term*

*"**cellulitis" is not appropriate** for cutaneous inflammation associated with collections of pus, such as in septic bursitis, furuncles, or skin abscesses. For example, when cutaneous redness, warmth, tenderness, and edema encircle a suppurative focus such as an infected bursa, the appropriate terminology is "septic bursitis with surrounding inflammation," rather than "septic bursitis with surrounding cellulitis." This distinction is clinically crucial.*

For the primary treatment of cellulitis *is antimicrobial therapy, whereas for purulent collections the major component of management is drainage of the pus, with antimicrobial therapy either being unnecessary or having a subsidiary role (Figure 1 and Table 2).*

The term "erysipelas" has 3 different meanings*:*

> *(1) for some,* ***erysipelas*** *is an infection* ***limited to the upper dermis****, including the superficial lymphatics, whereas* ***cellulitis involves the deeper dermis and subcutaneous fat****, and on examination* ***erysipelas putatively has more clearly delineated borders*** *of inflammation than cellulitis;*
> *(2) for many,* ***erysipelas has been used to refer to cellulitis involving the face*** *only; and*
> *(3) for others, especially in European countries****, cellulitis and erysipelas are synonyms*** *[35].*

These infections cause rapidly spreading areas of erythema, swelling, tenderness, and warmth, sometimes accompanied by lymphangitis and inflammation of the regional lymph nodes. The skin surface may resemble an orange peel (peau d'orange) due to superficial cutaneous edema surrounding hair follicles and causing skin dimpling because the follicles remain tethered to the underlying dermis. Vesicles, bullae, and cutaneous hemorrhage in the form of petechiae or ecchymoses may develop.

Systemic manifestations are usually mild, but fever, tachycardia, confusion, hypotension, and leukocytosis are sometimes present and may occur hours before the skin abnormalities appear. These infections arise when microbes breach the cutaneous surface, especially in patients with fragile skin or diminished local host defenses from such conditions as obesity, previous cutaneous trauma (including surgery), prior episodes of cellulitis, and edema from venous insufficiency or lymphedema [36, 37].

The origin of the disrupted skin surface may be obvious, such as trauma, ulceration, and preexisting cutaneous inflammation, but often the breaks in the skin are small and clinically unapparent. These infections are most common on the lower legs.

Blood cultures are generally positive in ≤5% of cases [38]. The yield of cultures of needle aspirations of the inflamed skin ranges from ≤5% to approximately 40% [39–46].
The differences in diagnostic sensitivity and specificity are due to the variety of patient populations studied, the definitions of cellulitis, the inclusion or exclusion of cases with associated abscesses, and the determination of whether isolates are pathogens or contaminants.

Cultures of punch biopsy specimens yield an organism in20%–30% of cases [39, 47], but the concentration of bacteria in the tissues is usually quite low [47].

Combined data from specimen cultures, serologic studies [41, 48–51], and other methods (eg, immunohistochemical staining to detect antigens in skin biopsies [51, 52]), suggests that the vast majority of these infections arise from streptococci, often group A, but also from other groups, such as B, C, F, or G.

The source of these pathogens *is frequently unclear, but in many cases of leg cellulitis, the responsible streptococci reside in macerated, scaly, or fissured interdigital toe spaces [53, 54]. This observation underscores the importance of detecting and treating tinea pedis, erythrasma, and other causes of toe web abnormalities.*

Occasionally, ***the reservoir of streptococci is*** *the* ***anal canal*** *[55] or* ***the vagina****, especially for group B streptococcal cellulitis in patients with previous gynecologic cancer treated with surgery and radiation therapy.* ***Staphylococcus*** *aureus less frequently causes cellulitis, but cases due to this organism are typically associated with an open wound or previous penetrating trauma, including sites of illicit drug injection. Several other organisms can cause cellulitis, but usually only in special circumstances,* ***such as animal bites, freshwater or saltwater immersion injuries, neutropenia, or severe cell-mediated immunodeficiency****.*

Cultures o*f blood, tissue aspirates, or skin biopsies are unnecessary for typical cases of cellulitis.*

Blood cultures *should be obtained and cultures of skin biopsy or aspirate considered for patients with malignancy, severe systemic features (such as high fever and hypotension), and unusual predisposing factors, such as immersion injury, animal bites, neutropenia, and severe cell-mediated immunodeficiency [42].*

Therapy for typical cases of cellulitis *should include an antibiotic active against streptococci (Table 2). A large percentage of patients can receive oral medications from the start for typical cellulitis [56], and suitable antibiotics for most patients include penicillin, amoxicillin, amoxicillin-clavulanate, dicloxacillin, cephalexin, or clindamycin. In cases of uncomplicated cellulitis, a 5-day course of antimicrobial therapy is as effective as a 10-day course, if clinical improvement has occurred by 5 days [57].*

In retrospective study ***of cellulitis and abscesses requiring hospitalization****, the average duration of treatment* ***was 2 weeks*** *and only about one-third of patients received specific treatment for gram positive pathogens [58]. Two-thirds received very-broad-spectrum treatment, and the failure rate of 12% was not different regardless of spectrum of treatment.*

In some patients, cutaneous inflammation and systemic features ***worsen after initiating therapy****, probably because sudden destruction of the pathogens releases potent enzymes that increase local inflammation.*

MRSA is an unusual cause of typical cellulitis. *A prospective study of patients with cellulitis in a medical center with a high incidence of other MRSA-related SSTIs demonstrated that treatment with β-lactams, such as cefazolin or oxacillin, was successful in 96% of patients, suggesting that cellulitis due to MRSA is uncommon and treatment for that organism is usually unnecessary [50]. However, coverage for MRSA may be prudent in cellulitis associated with penetrating trauma, especially from illicit drug use, purulent drainage, or with concurrent evidence of MRSA infection elsewhere. Options for treatment of MRSA in those circumstances (Table 2) include*

intravenous drugs (vancomycin, daptomycin, linezolid, or telavancin) or oral therapy with doxycycline, clindamycin, or SMX-TMP.

If coverage for both streptococci and ***MRSA is desired for oral therapy, options*** *include clindamycin alone or the combination of either SMX-TMP or doxycycline with a β-lactam (eg, penicillin, cephalexin, or amoxicillin). The activity of doxycycline and SMXTMP against β-hemolytic streptococci is not known, and in the absence of abscess, ulcer, or purulent drainage, β-lactam monotherapy is recommended. This is further substantiated by a recent double-blind study showing that a combination of SMX-TMP plus cephalexin was no more efficacious than cephalexin alone in pure cellulitis [59].*

Elevation of the affected area hastens improvement by promoting gravity drainage *of edema and inflammatory substances. Patients should also receive therapy for any predisposing conditions, such as tinea pedis, trauma, or venous eczema ("stasis dermatitis").*

Part -5

V. Should Anti-inflammatory Agents Be Used to Complement Antibiotic Treatment of Cellulitis?

Recommendation

19. Systemic corticosteroids (e.g., prednisone 40 mg daily for 7 days) could be considered in nondiabetic adult patients with cellulitis (***weak, moderate***).

Part -6

VI. What Is the Preferred Evaluation and Management of Patients With Recurrent Cellulitis?

Recommendations

20. Identify and treat predisposing conditions such as
    - Edema,
    - Obesity,
    - Eczema,
    - Venous insufficiency, and
    - Toe web abnormalities (***strong, moderate***).

    These practices should be performed as part of routine patient care and certainly during the acute stage of cellulitis (***strong, moderate***).

21. Administration of prophylactic antibiotics, such as
    - Oral penicillin or
    - Erythromycin bid for 4–52 weeks, or
    - Intramuscular benzathine penicillin every 2–4 weeks,

    should be considered in patients who have 3–4 episodes of cellulitis per year despite attempts to treat or control predisposing factors (***weak, moderate***).

    This program should be continued so long as the predisposing factors persist (***strong, moderate***).

Evidence Summary

Patients with a previous attack of cellulitis, especially involving the legs, have annual recurrences rates of about 8%–20% *[65–67]. The infection usually occurs in the same area as the previous episode. Edema, especially lymphedema and other local risk factors such as* ***venous insufficiency****, prior* ***trauma*** *(including surgery) to the area,* ***and tinea pedis*** *or other toe* ***web abnormalities*** *[65–71], increase the frequency of recurrences.*
Other predisposing conditions include ***obesity****, tobacco use, a* ***history of cancer****, and* ***homelessness*** *[66, 67, 71].*

Addressing these factors might decrease the frequency of recurrences, but evidence for any such a benefit is sparse. For patients with recurrences despite such efforts, ***antimicrobial prophylaxis may reduce the frequency of future episodes****. Two randomized trials using twice-daily oral penicillin or erythromycin demonstrated a substantial reduction in recurrences among the antibiotic recipients compared to controls [72, 73]. An observational trial of monthly*
intramuscular injections of 1.2 million units of benzathine penicillin found that this regimen was beneficial only in the subgroup of patients who had no identifiable predisposing factors for recurrence *[74]. In a study of patients with recurrent cellulitis involving arm lymphedema caused by breast cancer treatment, 2.4 million units of biweekly intramuscular benzathine penicillin seemed to reduce the frequency of episodes, but here was no control group [75].*
The duration of therapy is indefinite*,* ***and infections may recur once prophylaxis is discontinued****. For example, a recent double-blind comparative trial demonstrated that phenoxy methyl-penicillin given as 250 mg twice daily for 12 months increased the time to recurrence to 626 days compared with 532 days in the control group and decreased the frequency of recurrence from 37% to 22% [76].*

Part -7

VII. What Is the Preferred Management of Surgical Site Infections? Recommendations

22. Suture removal plus incision and drainage should be performed for surgical site infections (***strong, low***).

23. Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response such as:

- Erythema and induration extending >5 cm from the wound edge,
- Temperature >38.5°C,
- Heart rate >110 beats/minute, or
- White blood cell (WBC) count >12 000/µL (weak, low).

24. A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections **following clean operations on the trunk, head and neck, or extremities** that also have systemic signs of infection (strong, low).

25. Treatment with:

- A first-generation cephalosporin or
- An anti-staphylococcal penicillin for MSSA, or
- Vancomycin, linezolid, daptomycin, telavancin, or
- Cefazoline where risk factors for MRSA are high
- (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended ***(strong, low***)..

26. Agents active against gram-negative bacteria and anaerobes, such as a **cephalosporin** or **fluoroquinolone** in **combination with metronidazole**, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract (***strong, low***).

Table 3. Antibiotics for Treatment of Incisional Surgical Site Infections

Surgery of Intestinal or Genitourinary Tract
Single-drug regimens
Ticarcillin-clavulanate 3.1 g every 6 h IV
Piperacillin-tazobactam 3.375 g every 6 h or 4.5 g every 8 h IV
Imipenem-cilastatin 500 mg every 6 h IV
Meropenem 1 g every 8 h IV
Ertapenem 1 g every 24 h IV
Combination regimens
Ceftriaxone 1 g every 24 h + metronidazole 500 mg every 8 h IV
Ciprofloxacin 400 mg IV every 12 h or 750 mg po every 12 h + metronidazole 500 mg every 8 h IV
Levofloxacin 750 mg IV every 24 h + metronidazole 500 mg every 8 h IV
Ampicillin-sulbactam 3 g every 6 h + gentamicin or tobramycin 5 mg/kg every 24 h IV
Surgery of trunk or extremity away from axilla or perineum
Oxacillin or nafcillin 2 g every 6 h IV
Cefazolin 0.5–1 g every 8 h IV
Cephalexin 500 mg every 6 h po
SMX-TMP 160–800 mg po every 6 h
Vancomycin 15 mg/kg every 12 h IV
Surgery of axilla or perineum[a]
Metronidazole 500 mg every 8 h IV
plus
Ciprofloxacin 400 mg IV every 12 h or 750 mg po every 12 h IV po
Levofloxacin 750 mg every 24 h IV po
Ceftriaxone 1 g every 24 h

Abbreviations: IV, intravenous; po, by mouth; SMX-TMP, sulfamethoxazole trimethoprim.
a May also need to cover for methicillin-resistant Staphylococcus aureus with vancomycin 15 mg/kg every 12 h.

Surgery of Intestinal or Genitourinary Tract

Single-drug regimens

- Ticarcillin-clavulanate 3.1 g every 6 h IV
- Piperacillin-tazobactam 3.375 g every 6 h or 4.5 g every 8 h IV
- Imipenem-cilastatin 500 mg every 6 h IV
- Meropenem 1 g every 8 h IV
- Ertapenem 1 g every 24 h IV

Combination regimens

- Ceftriaxone 1 g every 24 h + metronidazole 500 mg every 8 h IV
- Ciprofloxacin 400 mg IV every 12 h or 750 mg po every
- 12 h + metronidazole 500 mg every 8 h IV
- Levofloxacin 750 mg IV every 24 h + metronidazole 500 mg every 8 h IV
- Ampicillin-sulbactam 3 g every 6 h + gentamicin or tobramycin 5 mg/kg every 24 h IV

Surgery of trunk or extremity away from axilla or perineum

- Oxacillin or nafcillin 2 g every 6 h IV
- Cefazolin 0.5–1 g every 8 h IV
- Cephalexin 500 mg every 6 h po
- SMX-TMP 160–800 mg po every 6 h
- Vancomycin 15 mg/kg every 12 h IV
- Surgery of axilla or perineuma
- Metronidazole 500 mg every 8 h IV plus
- Ciprofloxacin 400 mg IV every 12 h or 750 mg po every 12 h IV po
- Levofloxacin 750 mg every 24 h IV po
- Ceftriaxone 1 g every 24 h

Part -8

VIII. What Is the Preferred Evaluation and Treatment of Necrotizing Fasciitis, Including Fournier Gangrene?

Recommendations

27. Prompt **surgical consultation is recommended** for patients with aggressive infections associated with signs of systemic toxicity or suspicion of necrotizing fasciitis or gas gangrene (***strong, low***).

28. **Empiric antibiotic treatment should be broad** (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA) (***strong, low***)..

29. **Penicillin plus clindamycin is recommended** for treatment of documented group A streptococcal necrotizing fasciitis (***strong, low***).

Table 4. Treatment of Necrotizing Infections of the Skin, Fascia, and Muscle

Type of Infection	First-line Antimicrobial Agent	Adult Dosage	Pediatric Dosage Beyond the Neonatal Period
Mixed infections	Piperacillin-tazobactam plus vancomycin	3.37 g every 6–8 h IV 30 mg/kg/d in 2 divided doses	60–75 mg/kg/dose of the piperacillin component every 6 h IV 10–13 mg/kg/dose every 8 h IV
	Imipenem-cilastatin	1 g every 6–8 h IV	N/A
	Meropenem	1 g every 8 h IV	20 mg/kg/dose every 8 h IV
	Ertapenem	1 g daily IV	15 mg/kg/dose every 12 h IV for children 3 mo-12 y
	Cefotaxime plus metronidazole or clindamycin	2 g every 6 h IV 500 mg every 6 h IV 600–900 mg every 8 h IV	50 mg/kg/dose every 6 h IV 7.5 mg/kg/dose every 6 h IV 10–13 mg/kg/dose every 8 h IV
Streptococcus	Penicillin plus clindamycin	2–4 million units every 4–6 h IV (adult) 600–900 mg every 8 h IV	60 000–100 000 units/kg/dose every 6 h IV 10–13 mg/kg/dose every 8 h IV
Staphylococcus aureus	Nafcillin	1–2 g every 4 h IV	50 mg/kg/dose every 6 h IV
	Oxacillin	1–2 g every 4 h IV	50 mg/kg/dose every 6 h IV
	Cefazolin	1 g every 8 h IV	33 mg/kg/dose every 8 h IV
	Vancomycin (for resistant strains)	30 mg/kg/d in 2 divided doses IV	15 mg/kg/dose every 6 h IV
	Clindamycin	600–900 mg every 8 h IV	10–13 mg/kg/dose every 8 h IV
Clostridium species	Clindamycin plus penicillin	600–900 mg every 8 h IV 2–4 million units every 4–6 h IV (adult)	10–13 mg/kg/dose every 8 h IV 60 000–100 00 units/kg/dose every 6 h IV
Aeromonas hydrophila	Doxycycline plus ciprofloxacin or ceftriaxone	100 mg every 12 h IV 500 mg every 12 h IV 1 to 2 g every 24 h IV	Not recommended for children but may need to use in life-threatening situations
Vibrio vulnificus	Doxycycline plus ceftriaxone or	100 mg every 12 h IV 1 g qid IV 2 g tid IV	Not recommended for children but may need to use in life-threatening situations
	Cefotaxime	2 g tid IV	

Table 4.Continue…..
Treatment of Necrotizing Infections of the Skin, Fascia, and Muscle
Antimicrobial Agent for Patients with Severe Penicillin Hypersensitivity

Type of Infection	Antimicrobial Agent for Patients With Severe Penicillin Hypersensitivity
Mixed infections	Clindamycin or metronidazole[a] with an aminoglycoside or fluoroquinolone N/A N/A
Streptococcus	Vancomycin, linezolid, quinupristin/dalfopristin, daptomycin
Staphylococcus aureus	Vancomycin, linezolid, quinupristin/dalfopristin, daptomycin Bacteriostatic; potential cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA[b]
Clostridium species	N/A
Aeromonas hydrophila	N/A
Vibrio vulnificus	N/A

Abbreviations: IV, intravenous; MRSA, methicillin-resistant Staphylococcus aureus; N/A, not applicable; qid, 4times daily; tid, 3 times daily. A) If staphylococcus present or suspected, add an appropriate agent. B) If MRSA is present or suspected, add vancomycin not to exceed the maximum adult daily dose

Part -9

IX. What Is the Appropriate Approach to the Management of Pyomyositis?

Recommendations

30. Magnetic resonance imaging (MRI) is the recommended imaging modality for establishing the diagnosis of pyomyositis. Computed tomography (CT) scan and ultrasound studies are also useful (***strong, moderate***).

31. Cultures **of blood** and **abscess material** should be obtained (***strong, moderate***).

32. **Vancomycin is recommended for initial empirical therapy**. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles (***strong, moderate).***

33**. Cefazolin or anti staphylococcal penicillin** (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis **caused by MSSA** (***strong, moderate***).

34**. Early drainage** of purulent material should be performed (***strong, high***).

35. **Repeat imaging studies should be performed in the patient with persistent bacteremi**a to identify undrained foci of infection (***strong, low***).

36**. Antibiotics should be administered intravenously initially**, but once the patient is clinically improved**, oral antibiotics** are appropriate for patients in whom bacteremia cleared promptly and there is **no evidence of endocarditis** or **metastatic abscess**. **Two to 3 weeks of therapy** is recommended (***strong, low***).

X. What Is the Appropriate Approach to the
Evaluation and Treatment of Clostridial Gas Gangrene or Myonecrosis?

Recommendations

37. **Urgent surgical exploration of the suspected gas gangrene site and surgical debridement** of involved tissue should be performed (***strong, moderate***).

38**. In the absence of a definitive etiologic diagnosis**, broad spectrum treatment with

- Vancomycin plus either piperacillin/ tazobactam,
- Ampicillin/sulbactam, or
- Carbapenem antimicrobial is recommended (***strong, low***).
- Definitive antimicrobial therapy with penicillin and clindamycin \ is recommended for treatment of clostridial myonecrosis (***strong, low***).

39. **Hyperbaric oxygen (HBO) therapy is not recommended** because it has not been proven as a benefit to the patient and may delay resuscitation and surgical debridement (***strong, low***)

Part -11

XI. What Is the Role of
Preemptive Antimicrobial Therapy to Prevent Infection for Dog or Cat Bites?

Recommendations

40. Preemptive **early antimicrobial therapy for 3–5** days is recommended for patients who

(a) Immunocompromised;
(b) A splenic;
(c) Have advanced liver disease;
(d) Have preexisting or resultant edema of the affected area
(e) Have moderate to severe injuries, especially to the hand or face; o
(f) Have injuries that may have penetrated the periosteum or joint capsule (***strong, low***).

41. **Postexposure prophylaxis for rabies** may be indicated; consultation with local health officials is recommended to determine if vaccination should be initiated (***strong, low***).

Part -12

XII. What Is the Treatment for Infected Animal Bite–Related Wounds?

Recommendation

42. An **antimicrobial agent or agents active against both aerobic and anaerobic** bacteria such as amoxicillin-clavulanate (***strong, moderate***).

Part -13

XIII. Should Tetanus Toxoid Be Administered for Animal Bite Wounds?

Recommendation

43. Tetanus toxoid **should be administered to patients without toxoid vaccination within 10 years.**
Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given (***strong, low***).

Part -14

XIV. In Which Patients Is Primary Wound Closure Appropriate for Animal Bite Wounds?

Recommendation

44. Primary wound closure is not recommended for wounds, with the exception of those to the face, which should be managed with copious irrigation, cautious debridement, and preemptive antibiotics (***strong, low***)
Other wounds may be approximated (***weak, low***).

Table 5. Recommended Therapy for Infections Following Animal or Human Bites

Antimicrobial Agent by Type of Bite	Therapy Type		
	Oral	Intravenous	Comments
Animal bite			
Amoxicillin-clavulanate	875/125 mg bid	. . .	Some gram-negative rods are resistant; misses MRSA
Ampicillin-sulbactam	. . .	1.5–3.0 g every 6–8 h	Some gram-negative rods are resistant; misses MRSA
Piperacillin-tazobactam	. . .	3.37 g every 6–8 h	Misses MRSA
Carbapenems		See individual info.	Misses MRSA
Doxycycline	100 mg bid	100 mg every 12 h	Excellent activity against *Pasteurella multocida*; some streptococci are resistant
Penicillin plus dicloxacillin	500 mg qid/500 mg qid	. . .	
SMX-TMP	160–800 mg bid	5–10 mg/kg/day of TMP component	Good activity against aerobes; poor activity against anaerobes
Metronidazole	250–500 mg tid	500 mg every 8 h	Good activity against anaerobes; no activity against aerobes
Clindamycin	300 mg tid	600 mg every 6–8 h	Good activity against staphylococci, streptococci, and anaerobes; misses *P. multocida*
Second-generation cephalosporin			Good activity against *P. multocida;* misses anaerobes
Cefuroxime	500 mg bid	1 g every 12 h	
Cefoxitin	. . .	1 g every 6–8 h	
Third-generation cephalosporin			
Ceftriaxone	. . .	1 g every 12 h	
Cefotaxime	. . .	1–2 g every 6–8 h	
Fluoroquinolones			Good activity against *P. multocida;* misses MRSA and some anaerobes
Ciprofloxacin	500–750 mg bid	400 mg every 12 h	
Levofloxacin	750 mg daily	750 mg daily	
Moxifloxacin	400 mg daily	400 mg daily	Monotherapy; good for anaerobes also
Human bite			
Amoxicillin-clavulanate	875/125 mg bid	. . .	Some gram-negative rods are resistant; misses MRSA
Ampicillin-sulbactam	. . .	1.5–3.0 g every 6 h	Some gram-negative rods are resistant; misses MRSA
Carbapenems			Misses MRSA
Doxycycline	100 mg bid	. . .	Good activity against *Eikenella* species, staphylococci, and anaerobes; some streptococci are resistant

Abbreviations: bid, twice daily; MRSA, methicillin-resistant *Staphylococcus aureus*; qid, 4 times daily; SMX-TMP, sulfamethoxazole-trimethoprim; tid, 3 times daily.

Part -15

XV. What Is the Appropriate Treatment of Cutaneous Anthrax?

Recommendations

45. **Oral penicillin V 500 mg 4 times daily (qid) for 7–10 days** is the recommended treatment for naturally acquired cutaneous anthrax (***strong, high***).

46. Ciprofloxacin 500 mg by mouth (po) bid or levofloxacin 500 mg intravenously **(IV)/po every 24 hours × 60 days is recommended** **for bioterrorism** cases because of presumed aerosol exposure (***strong, low***).

Evidence Summary

One of several clinical manifestations of anthrax is a cutaneous lesion :

- After **an incubation period** of 1–12 days,
- **Pruritus** begins at the entry site,
- Followed by **a papule**, development **of vesicles on top of the papule**, and, finally, a **painless ulcer with a black scab**.
- This eschar generally separates and sloughs after 12–14 days.
- Variable amounts of swelling that range from minimal to severe **("malignant edema")** surround the lesion.
- Mild to moderate **fever, headaches, and malaise** often accompany the illness.
- **Regional lymphadenopathy** is common,
- **Pus in the lesion is absent unless a secondary infection occurs**.
- **White blood cell counts are generally** normal, but mild leukocytosis can occur.
- **Blood cultures** are almost always negative.
- **Cultures of untreated lesions**, depending upon the stage of evolution, are positive >80% of the time.
- **Methods of specimen collection for culture depend on the type of lesion**. Regarding vesicles, the blister should be unroofed and 2 dry swabs soaked in the fluid. At a later stage, 2 moist swabs should be rotated in the ulcer base or beneath the eschar's edge.
- **Patients who have previously received antimicrobials or have negative studies**, but still have suspected cutaneous anthrax, **should undergo a punch biopsy that can be submitted for special studie**s (eg, immunohistochemical staining and/or polymerase chain reaction [PCR]). When obtaining specimens, lesions should not be squeezed to produce material for culture.
- **Additional diagnostic methods may include serological and skin tests**.

- Most published data indicate that **penicillin is effective therapy and will** "sterilize" most lesions within a few hours to 3 days but does not accelerate healing. Its value seems to be primarily in reducing mortality from as high as 20% to zero. **Based on even less evidence, tetracyclines, chloramphenicol, and erythromycin** also appear effective.
- **Some have suggested systemic corticosteroids for patients who develop malignant edema**, especially of the head and neck, but studies supporting this recommendation are lacking.
- Airway compromise **requiring intubation or tracheostomy** may occur with malignant edema

Part -16

XVI. What Is the Appropriate Approach for the Evaluation and Treatment of Bacillary Angiomatosis and Cat Scratch Disease?

Recommendations

47. Azithromycin is recommended for cat scratch disease (***strong, moderate***) according to the following dosing protocol:

- Patients >45 kg: 500 mg on day 1 followed by 250 mg for 4 additional days (strong, moderate).
- Patients <45 kg: 10 mg/kg on day 1 and 5 mg/kg for 4 more days (strong, moderate). 48. Erythromycin 500 mg qid or doxycycline 100 mg bid for 2 weeks to 2 months is recommended for treatment of bacillary angiomatosis (strong, moderate).

Part -17

XVII. What Is the Preferred Treatment for Erysipeloid?

Recommendation

49. **Penicillin (500 mg qid) or amoxicillin (500 mg 3 times daily [tid]) for 7–10 days** is recommended for treatment of erysipeloid (***strong, high***).

Part -18

XVIII. What Is the Appropriate

Treatment of Glanders?

Recommendation

50. Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility (***strong, low***)

Part -19

XIX. What Is the Appropriate

Diagnosis and Treatment of Bubonic Plague?

Recommendation

51. Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a **suppurative lymph node** (***strong, moderate***).

- Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or
- Doxycycline (100 mg bid po) is recommended for treatment of bubonic plague (***strong, low***).
- Gentamicin could be substituted for streptomycin (***weak, low***).

Part -20

XX. What Is Appropriate for

Diagnosis and Treatment for Tularemia?

Recommendations

52. Serologic tests are the preferred method of diagnosing tularemia (***weak, low***).

53. Streptomycin (15 mg/kg every 12 hours IM) or gentamicin (1.5 mg/kg every 8 hours IV) is recommended for treatment of severe cases of tularemia (***strong, low***).

54. Tetracycline (500 mg qid) or doxycycline (100 mg bid po) is recommended for treatment of mild cases of tularemia (***strong, low***).

55. Notify the microbiology laboratory if tularemia is suspected (***strong, high***)

Part -21

XXI. What Is the Appropriate Approach to Assess SSTIs in Immunocompromised Patients?

Recommendations

56. In addition to infection, differential diagnosis of skin lesions should include

- Drug eruption,
- Cutaneous infiltration with the underlying malignancy,
- Chemotherapy- or radiation-induced reactions,
- Sweet syndrome,
- Erythema multiforme,
- Leukocytoclastic vasculitis, and
- Graft-vs-host disease among allogeneic transplant recipients (strong, high).

57. Differential diagnosis for infection of skin lesions should include

- Bacterial,
- Fungal,
- Viral, and
- Parasitic agents (***strong, high***).

58. Biopsy or aspiration of the lesion to obtain material for histological and microbiological evaluation should always be implemented as an early diagnostic step (***strong, high***).

Part -22

XXII. What Is the Appropriate Approach to Assess SSTIs in Patients with Fever and Neutropenia?

Recommendations

59. Determine whether the current presentation of fever & neutropenia is :

- **Initial episode** of fever and neutropenia, or
- **Unexplained f**ever of their initial episode (after 4–7 days) or
- **Subsequent episode** of fever and neutropenia (recurrent)

(***strong, low***).

60. Aggressively determine the etiology of the SSTI by

1-Aspiration and/or

2-Biopsy of skin and soft tissue lesions

Then submit these for thorough:

- Cytological/histological assessments,
- Microbial
- Staining, and
- Cultures

(***strong, low***).

61. Risk-stratify patients with fever and neutropenia according to susceptibility to infection:

high-risk patients are those with

- Anticipated prolonged (>7 days) and profound neutropenia
- Absolute neutrophil count <100 cells/µL) or
- With a Multinational Association for Supportive Care (MASCC) score of <21;

low-risk patients are those: with

- Anticipated brief (<7 days) periods of neutropenia and few comorbidities (**strong, low)** or

- With a MASCC score of ≥21 (strong, moderate).

62. Determine the extent of infection through a thorough
    - Physical examination,
    - Blood cultures,
    - Chest radiograph, and
    - Additional imaging (including chest CT) as indicated by clinical and symptoms

    (***strong, low***).

Evidence Summary

SSTIs in patients with fever and neutropenia have rarely been carefully studied as a "separate entity." Rather, recommendations for these infections are extrapolated from broad group guidelines that include references to SSTIs and have been developed by professional organizations including:

- IDSA,
- National Comprehensive Cancer Network (NCCN),
- American Society of Blood and Marrow Transplantation,
- American Society of Clinical Oncology,
- The Centers for Disease Control and Prevention [187–193].

These guidelines are focused on the diagnosis and management of specific patient groups:

- fever and neutropenia,
- Infection in recipients of hematopoietic stem cell transplan,
- Specific infections (e.g., candidiasis, aspergillosis),
- Iatrogenic infections (e.g., intravascular catheter– related infection).

They are based on published clinical trials, descriptive studies, or reports of expert committees, and the clinical experience and opinions of respected authorities. Therefore, this section of the SSTI guideline will focus on existing recommendations that demand reinforcement, or that are truly specific to SSTIs.

Neutropenia is defined as an ANC <500 cells/ µL, or a neutrophil count that is expected to decrease to <500 cells/µL within associated neutropenia is common, but many patients do not have an infectious etiology determined [184, 194].

More than 20% of patients with chemotherapy-induced neutropenia develop a clinically documented infection involving the skin and soft tissues, but many are due to hematogenous dissemination [179].

Cancer patients with fever and neutropenia can be divided into low- and high-risk groups [187]. The determination of differences in patient risk of infection and infectious complications levels (high risk and low risk) during the period of neutropenia has been recognized and further validated since this clinical guideline was last updated [195, 196].
The MASCC developed and validated a scoring method that formally differentiates between high-risk and low-risk patients [195, 196]. High-risk patients have a MASCC score <21. Low-risk patients have a MASCC score ≥21. Disseminated or complex SSTIs are more likely to occur among high-risk patients.

Part -23

XXIII. What Is the Appropriate Antibiotic Therapy for Patients With SSTIs During the Initial Episode of Fever and Neutropenia?

Recommendations

63. Hospitalization and empiric antibacterial therapy with vancomycin plus anti pseudomonal antibiotics such as cefepime, a carbapenem (imipenem-cilastatin or meropenem or doripenem) or piperacillin-tazobactam is recommended (***strong, high***).

64. Documented clinical and microbiologic SSTIs should be treated based on antimicrobial susceptibilities of isolated organisms (***strong, high***).

65. It is recommended that the treatment duration for most bacterial SSTIs should be 7–14 days (***strong, moderate***).

66. Surgical intervention is recommended for drainage of soft tissue abscess after marrow recovery or for a progressive polymicrobial necrotizing fasciitis or myonecrosis (***strong, low***).

67. Adjunct colony-stimulating factor therapy

- Granulocyte colony-stimulating factor [G-CSF],
- Granulocyte macrophage colony-stimulating factor [GM-CSF]) or
- Granulocyte transfusions are not routinely recommended (***weak, moderate***).

68. ***Acyclovir should be administered*** **to patients suspected or confirmed to have cutaneous or disseminated varicella zostervirus (herpes simplex virus [HSV] or varicella zoster virus [VZV]) infection** (***strong, moderate***).

Part -24

XXIV. What Is the Appropriate Antimicrobial Therapy for Patients With SSTIs During Persistent or Recurrent Fever and Neutropenia? Recommendations

69. ***Yeasts and molds*** **remain the primary cause of infection associated with persistent and recurrent fever and neutropenia;** therefore,

(a) **Empiric antifungal** therapy should be added to the antibacterial regimen (***strong, high***).

(b) **Empiric administration of vancomycin** or other agents with gram-positive activity (linezolid, daptomycin, or ceftaroline, should be added if not already being administered (***strong, high***)

(c) **Candida species SSTIs should be treated** with an echinocandin or, if Candida Para psilosis has been isolated, lipid formulation amphotericin B (***strong, high***) with fluconazole as an acceptable alternative (***strong, moderate***).
Treatment should be administered for 2 weeks after clearance of bloodstream infection or resolution of skin lesions (***strong, moderate***).

(d) **Aspergillus SSTIs should be treated with** voriconazole (***strong, high***), or alternatively, lipid formulations of amphotericin B, Posaconazole, or echinocandin for 6–12 weeks (strong, low). **Mucor/Rhizopus infections** should be treated with lipid formulation amphotericin B (***strong, moderate)*** or Posaconazole (***strong, low***) The addition of an echinocandin could be

considered based on synergy in **murine models of mucormycotic**, and observational clinical data (***weak, low***).

(e) **Fusarium species infections** should be treated with high-dose IV voriconazole or Posaconazole (***strong, low***).

(f) **Begin treatment for antibiotic-resistant bacterial organisms** in patients currently on antibiotics (***strong, moderate***).

(g) **Intravenous acyclovir should be added to the patient's antimicrobial regimen** for suspected or confirmed cutaneous or disseminated HSV or VZV infections (***strong, moderate***).

70. Blood cultures should be obtained and skin lesions in this population of patients should be aggressively evaluated **by culture aspiration, biopsy, or surgical excision**, as they may be caused by resistant microbes, yeast, or molds (***strong, moderate***).

71. **The sensitivity of a single-serum fungal antigen test** (1,3-β-D-glucan or **galactomannan tests**) is low particularly in patients receiving antifungal agents, and benefits from laboratory tests for fungal antigen or DNA detection remain inconsistent (***strong, moderate***).

72. **Polymerase chain reaction (PCR) in peripheral blood for HSV and VZV** might be helpful in establishing a diagnosis of disseminated infection in patients with unexplained skin lesions
(***weak, moderate***).

Evidence Summary

In patients with persistent unexplained fever of their first episode (after 4–7 days) or recurrent fever, yeast and molds are the major cause of infection-related morbidity and mortality (Table 7) [187, 189, 203]. These later infections are most common among high-risk patients with prolonged and profound neutropenia and they should be considered in any patient with neutropenia and skin and soft tissue lesions suggestive of infection.

In addition, MRSA should also be considered if patients are not receiving antimicrobial agents with activity

Antibiotic selection should follow the clinical care guidelines developed by IDSA and the NCCN [187, 189]. Excellent results have been reported for gram-negative infections using broad spectrum monotherapy with **carbapenems**, **cephalosporins** that possess antipseudomonal activity, or **piperacillin/tazobactam**.

For patients in whom vancomycin may not be an option, daptomycin, ceftaroline, or linezolid should be added to the initial empiric regimen. Linezolid, daptomycin, or ceftaroline have activity against MRSA [204] and have received FDA approval for the treatment of SSTIs, but have not been comprehensively studied in patients with neutropenia. The use of linezolid in this patient population has been associated with delayed ANC recovery [205, 206]. The combination of ciprofloxacin and amoxicillin-clavulanate is the preferred oral antibiotic regimen for low-risk patients [207, 208]. Levofloxacin has better gram-positive activity than ciprofloxacin, but is less potent than ciprofloxacin against P. therapy (750 mg daily) may be required. Fluoroquinolone prophylaxis should preclude the use of fluoroquinolones For empiric therapy, and instead broad-spectrumβ-lactam antibiotics should be considered. Intravenous acyclovir
should be added to the empiric antimicrobial regimen of the
rare patient who has not been receiving antiviral prophylaxis effective
against HSV or VZV, but has developed skin lesions suspected
or confirmed to be caused by these viruses.

Part -25

XXV. What Is the Appropriate Approach to Assess SSTIs inPatients with Cellular Immunodeficiency? Recommendations

73. **Consider immediate consultation** with a dermatologist familiar with cutaneous manifestations of infection in patients with cellular immune defects e.g., those with

- Lymphoma,
- Lymphocytic leukemia,
- Recipients of organ transplants, or
- With immunosuppressive drugs such as anti–tumor necrosis factors or certain monoclonal antibodies.

(***weak, low***).

74. **Consider biopsy and surgical debridement early** in the management of these patients (***weak, low***).

75. **Empiric antibiotics, antifungals, and/or antivirals** should be considered in life-threatening situations (***weak, moderate***). The use of specific agents should be decided with the input of *the primary team, dermatology, infectious disease*, and *other consulting teams* (***strong, moderate***).

Table 6. Standard Doses of Antifungal Agents

Antifungal Agent	Oral Dose	IV Dose	Comments
Fluconazole	100–400 mg every 24 h	800 mg loading dose, then 400 mg daily	*Candida krusei* and *Candida glabrata* are resistant
Voriconazole[a]	400 mg bid × 2 doses, then 200 mg every 12 h	6 mg/kg IV every 12 h for 2 doses, followed by 4 mg/kg IV every 12 h	Accumulation of cyclodextrin vehicle with IV formulation with renal insufficiency
Posaconazole	400 mg bid with meals	N/A	Covers *Mucorales*
Lipid complex amphotericin B	N/A	5 mg/kg/d	Not active against fusaria
Liposomal amphotericin B	N/A	3–5 mg/kg/d	Not active against fusaria

Abbreviations: bid, twice daily; IV, intravenous; N/A, not applicable.

[a] The use of patient-specific pharmacokinetics is recommended to improve clinical outcome [247].

Table 7. Standard Doses of Antimicrobial Agents Active Against Multidrug-Resistant Organisms

Antimicrobial	IV Dose	Comments
Vancomycin	30–60 mg/kg/d in 2–4 divided doses	Target serum trough concentrations of 15–20 μg/mL in severe infections
Daptomycin	4–6 mg/kg/d	Covers VRE, strains nonsusceptible to vancomycin may be cross-resistant to daptomycin
Linezolid	600 mg every 12 h	100% oral bioavailability; so oral dose same as IV dose. Covers VRE and MRSA
Colistin	5 mg/kg load, then 2.5 mg/kg every 12 h	Nephrotoxic; does not cover gram-positives or anaerobes, *Proteus*, *Serratia*, *Burkholderia*

Abbreviations: IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

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