

A Practical Guide to Diagnosis and Treatment of Infection in the Outpatient Setting

Diagnosis and Treatment of Skin and Soft Tissue Infections

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Skin and soft tissue infections are frequently encountered in the offices of primary care physicians. The more severe cases cannot be treated with oral antibiotics and require administration of intravenous antibiotics. The mildest cases, such as folliculitis, may only require topical therapy.

In many instances, a mild cellulitis is encountered, but the patient is administered an inappropriate antibiotic, or the correct antibiotic at a suboptimal dose and the infection progresses to one that requires hospitalization. In order to keep patients from requiring intravenous antibiotics a proper understanding of bacteriology of skin and soft tissue infections (SSTI), antibiotic spectrum and tissue penetration of the drugs are essential.

Etiology and pathogenesis

Two conditions must exist for cellulitis to occur. First, pathogenic bacteria must be present on the skin. Second, there must be a loss of skin integrity.

Two types of microflora inhabit the skin. *Resident flora* are bacteria that are considered normal skin flora. They are organisms of very low pathogenicity. Coagulase negative staphylococci, diphtheroids, bacillus species and propionibacterium are examples. Although they are known to cause infections of prosthetic material, like IV catheters or prosthetic joints, these organisms basically never cause skin infections. Their presence in cultures of open wounds almost always represents mere surface colonization. The resident flora are always present on skin, and in fact, colonize the deeper layers of the stratum corneum.

Transient flora are bacteria that colonize the skin for short periods, then are eventually out-competed for nutrients by the better adapted resident flora and they fade from the microflora. From time to time a highly pathogenic organism colonizes the skin. When it does, it occupies the upper most layers of skin. Organisms like *Streptococcus pyogenes* and *Methicillin-resistant Staphylococcus aureus* find their way to the skin by direct contact with another person carrying these organisms, then multiply on the surface of the skin to set up a colonized state which can last for months.

These pathogenic bacteria are opportunists, and if not given the open door to cause an infection, they may exist on the surface of the skin until, starved for nutrients, they vanish. That open door is any breakdown of skin integrity. Open wounds, puncture wounds, cracks in dry skin and even barely discernable abrasions can allow pathogenic bacteria to penetrate to deeper layers where, because of more plentiful nutrients, they multiply rapidly. They then disseminate along tissue planes, and cause an intense inflammatory reaction – cellulitis.

Impaired local defense mechanisms can predispose an individual to recurrent cellulitis. Women with chronic lymphedema in the arm due to radical mastectomy and lymph node dissection, who therefore do not have an intact lymphatic system, have frequent episodes of cellulitis. Impaired venous return, such as in patients with venous insufficiency, also increases the risk of repeated skin infection. These patients often have skin breakdown (venous stasis ulcers) which acts as an open door for pathogenic bacteria.

An interesting phenomenon has been reported in the literature. A correlation has been found between tinea pedis in those who have had coronary artery bypass surgery with harvest of saphenous vein for grafting and increased risk of developing cellulitis in the leg from which the saphenous vein was removed. In this case, tinea pedis causes disruption of the skin barrier and removal of the saphenous vein impairs venous and lymphatic flow and such patients are prone to recurrent bouts of cellulitis. Treating the tinea pedis with topical antifungals significantly decreases the risk of recurrent infections.

Microbiology. By far the most common causes of SSTIs are *Staphylococcus aureus* and streptococcal species like *S. pyogenes* and *S. agalactia*. In diabetics, infections of foot ulcers are frequently polymicrobial involving gram positive organisms, gram negatives like the enterobacteriaceae group or pseudomonas and anaerobes. But, in cases of cellulitis in diabetics and also non-diabetics who do not have open wounds, staphylococcus and streptococcus cause almost all cases.

Methicillin-resistant Staphylococcus aureus (MRSA) must be considered any time a hospitalized, or recently hospitalized patient develops cellulitis related to an intravenous catheter site infection. The nosocomial origin of this organism is well known, however there is an increasing incidence lately of community-acquired MRSA (CAMRSA). CAMRSA is genetically distinct from hospital-acquired MRSA (HAMRSA), the former having been identified as carrying the *mec-IV* gene, the latter either the *mec-II*, or *mec-III* genes. These genes code for different patterns of antimicrobial resistance. Several groups have been identified as being at increased risk for SSTIs due to CAMRSA: men who have sex with men, IV drug abusers, institutionalized patients (prison inmates, nursing home residents, patients from mental institutions), and children in day-care. There have been reported outbreaks among athletes competing in contact sports (football, wrestling, etc) as well.

Pseudomonas aeruginosa can cause skin and soft tissue infections, but only in certain unique circumstances. Nail puncture cellulitis with or without resultant soft tissue abscess of a foot is almost always due to pseudomonas, especially when the nail penetrates through a shoe. Pseudomonas may cause a folliculitis when an individual has been in an inadequately chlorinated swimming pool or Jacuzzi, known as *hot tub folliculitis*. Pseudomonas and other gram negatives are also common causes of cellulitis involving burn wounds. And many times, open wounds incurred while swimming in lakes or rivers might become infected by various pseudomonads, particularly *Aeromonas hydrophila*.

Pasteurella multocida is the most common cause of cellulitis occurring after a cat bite. This organism can also cause infection after a dog bite along with *Capnocytophaga canimorsus*, formerly known as CDC group DF-2. Infection with *C. canimorsus* can progress rapidly to fulminant sepsis in splenectomized patients.

A returning tourist who, while swimming in the ocean, cut himself on coral or while handling fish or shellfish, may develop a cellulitis due to *Vibrio vulnificus*. They might also develop multiple painless papules that eventually ulcerate. These papules are most likely due to *Mycobacterium marinum*. *M. marinum* also causes a classic syndrome known as *fish tank granuloma* contracted by someone who has received an abrasion while cleaning their fish tank.

Clinical Manifestations

Cellulitis. Blanching redness, tenderness, local heat and sometimes induration are hallmarks of cellulitis. Lower extremity cellulitis is quite common in those with chronic edema such as right-sided congestive heart failure or venous stasis disease. In the case of the latter, when venous stasis dermatitis is present it is often difficult to determine when the person has cellulitis and when the redness and tenderness is merely due to the venous stasis disease. Probably the most reliable method of distinguishing this is by noting any *change* in the leg, such as increased pain, increased redness, or new purulent drainage from venous stasis ulcers.

Cellulitis of the hands or arms usually develop after trauma or after a nosocomial IV catheter infection. In the case of the latter, the cellulitis might be accompanied by septic thrombophlebitis in which a tender cord is palpable emanating from the site of the IV catheter. Recurrent arm cellulitis is common in women who have had a mastectomy with lymphnode dissection, and therefore have chronic lymphedema of the arm.

Facial cellulitis should raise the possibility of an underlying sinusitis. In the absence of sinusitis, facial cellulitis may also arise from an infected hair follicle, usually in the nares.

Erysipelas is a form of cellulitis characterized by confluent redness and well demarcated borders. Many times lymphangitis accompanies it. Streptococcus is almost always the cause. Facial erysipelas is commonly seen in diabetics.

Streptococcus also causes impetigo. The hallmark of this superficial skin infection is papular eruptions with honey yellow crusting. It is most common among children and is spread to other areas of an affected person's anatomy through the process of autoinoculation. Discomfort is mild and it is never accompanied by fever.

Abdominal wall cellulitis may be seen in morbidly obese patients and could arise from a bacterial superinfection of yeast skin infection in the areas within folds of fat. In a patient with recent abdominal surgery it could be done to a post-operative wound infection, or if it involves an area of the abdominal wall remote from the wound, could represent a severe intra-abdominal infection now extending through fascia to the epidermis.

Folliculitis/Furunculosis/Carbuncle. These three are combined because they are on a continuum. The duct of a sebaceous gland in a hair follicle becomes obstructed and, if the skin is colonized by a pathogenic organism, the follicle can become superinfected. In most cases a small pustule forms with a red base. This process frequently involves a solitary follicle, but multiple follicles can become involved. Lesions are mildly painful, or itchy. Sometimes the infection worsens and a subcutaneous abscess, or *furuncle*, forms. This is usually quite painful and is associated with a limited radius of surrounding cellulitis.

In special cases, particularly in diabetics, pus from a furuncle dissects along tissue planes and erupts through the skin with multiple draining sinus tracks. This *carbuncle* is associated with a wider area of cellulitis and induration.

Necrotizing fasciitis. Certain highly virulent bacteria can cause a necrotizing soft tissue infection. Two types of infection have been described. Type I is a polymicrobial infection involving enteric gram negative organisms and anaerobes. An example of a type I fasciitis is Fournier's gangrene, an aggressive, deep soft tissue infection of perineum primarily in diabetics. Although a potentially life-threatening infection, relative to type II infection, evolves fairly slowly. Type II is due predominantly to *Streptococcus pyogenes*. This second type of necrotizing fasciitis can involve any part of the skin and expands rapidly, many times over a period of only a few hours.

Virulence factors allow the infection to disseminate along fascial planes. Septic shock is not uncommon. Mortality is highest of all soft tissue infections and it is a true medical emergency.

Diagnosis is not always obvious as the skin overlying infected fascia may appear grossly normal. Induration, fever, prostration, severe pain of involved anatomy should be a clue. Hemorrhagic bullae on the overlying skin is an ominous sign and is virtually pathognomonic. This cannot be treated by antibiotics alone, but requires urgent surgical debridement, usually involving wide excision of infected tissue with resultant extensive skin loss.

Post-operative wound infection. Although occurring with an incidence of less than 5%, this is an unfortunate risk of all surgical procedures. Infection may be localized to the operative wound where abscesses may form, or it may spread laterally along tissue planes and cause cellulitis. The most common cause of hospital-acquired infections of all kinds, including post-op wound infections, are multi-drug-resistant (MDR) gram negatives, such as acinetobacter, enterobacter, and pseudomonas, and methicillin-resistant *Staphylococcus aureus*. Antimicrobial choices must be made with that in mind.

Animal/Human bite wounds. Dog and cat bites are the most common form of animal bite seen. Bacterial infections, especially due to *Pasteurella multocida* and *Capnocytophagus canimorphus*, as mentioned above, are the predominant result. Human bites can lead to soft tissue infection. Oral flora (viridans streptococcal species, fusobacterium, Eikenella, etc.) constitute the most common etiologic agents.

Insects. Insects do not carry the type of bacteria that cause skin and soft tissue infections. One might argue that erythema chronica migrans, the circular rash that develops after infection with *Burrelia burgorferi* after a tick bite, is a cellulitis of sorts. Indeed, a skin biopsy of the Lyme disease rash reveals many spirochetes, however, the rash is self limited and painless, whereas bacterial cellulitis is painful and progressive.

In defense of spiders, many patients with cellulitis come with a label of “spider bite”. The brown recluse spider is blamed for most of these. The spider, however, does not transmit infection. The recluse spiders (the Desert recluse is the species we have in the Desert Southwest) secrete a necrotizing toxin with their bite that causes progressive ulceration and tissue loss. The ulcer may become superinfected with bacteria, but infection is not the primary process.

Most people who have claimed to have had a spider bite never see the spider that bit them. In most cases of true recluse spider bite the spider *is* identified. The reason for this is that these spiders, by nature, are non-aggressive and only bite in defense. They love to seclude themselves in dark places (hence the name, recluse), usually under houses or rocks, but sometimes in shoes or under bed sheets. They bite when a foot enters the shoe, or bed sheets, where they are hiding. Their bite usually is the last thing that they do in their short lives just before they are squashed. A dead spider can usually be found, however it’s mangled carcass is frequently so deformed that it is impossible to speculate.

Most alleged spider bite victims never go on to develop the ulcer. The truth of the matter is that the majority of these cases do not represent true spider bites. What they are probably experiencing is the development of an acute folliculitis which involves a sudden onset of pain at a pinpoint location on their skin. Cellulitis then spreads from there.

Diagnosis

History. Establishing the fact that a SSTI exists is usually not the problem as the disease state is evident to the naked eye. The difficulty lies in determining the etiologic agent. Since cultures obtained in patients with SSTIs are frequently negative, the determination the etiologic agent, which then guides the proper choice of an antibiotic, must rely on obtaining a good exposure history.

Physical exam. Blanching redness, tenderness and local heat are hallmarks of cellulitis. Presence of red streaks, or lymphangitis, or tender regional lymph nodes is a clue that *Streptococcus pyogenes* is the likely etiologic agent. The patient should also be evaluated for crepitation, fluctuance, bullae and induration.

Cultures. Cultures of draining open wounds should be obtained. Caution needs to be taken in interpreting such cultures, however, since normal surface colonizers, or resident flora, also inhabit open wounds and might show up in cultures, but do not represent infecting organisms. Any pus draining from sinus tracts or aspirated from subcutaneous abscesses should also be cultured.

Blood cultures may be positive in patients with necrotizing fasciitis, but are rarely positive in other forms of SSTI. Studies have suggested that 25% of the time when the leading edge of a simple cellulitis is aspirated, the causative agent will be identified in culture. This procedure has been extremely painful for the patient and does nothing for the patient-doctor relationship. Plus, I have never seen a positive culture from this technique. The vast majority of the time spontaneous, uncomplicated cellulitis is due to *S. aureus* or *S. pyogenes*, so cultures would not tell us anything we didn’t already suspect. The only time skin aspirate would be useful would be in a recalcitrant case of cellulitis or in unusual circumstances such as a neutropenic patient where an unexpected organism might be the cause.

Radiographic studies. A three-phase bone scan should be done to rule out underlying osteomyelitis on any cellulitis associated with an infected chronic, non-healing ulcer, or a deep-penetrating wound (nail puncture or deeply penetrating animal bite). Magnetic resonance imaging can also identify infected bone, with the added advantage of detecting fasciitis and soft tissue abscesses that might require surgical debridement.

A plain film of an extremity involved in cellulitis might reveal gas in soft tissue plains which indicates the presence of fasciitis or soft tissue abscess. Soft tissue gas is generally enough to indicate the need for surgery with or without an MRI.

If a patient presents with lower extremity cellulitis it is advisable to order a venous duplex ultrasound to rule out a deep venous thrombosis which can accompany cellulitis or mimic it.

A CT scan of the sinuses should be done on any patient with a facial cellulitis to rule out underlying sinusitis.

Treatment

Since it is rare that a causative microorganism is identified in culture, antibiotic therapy is usually empiric, but is guided by exposure history. Central to choosing appropriate antibiotics is deciding when topical therapy will be sufficient, an oral antibiotic will be enough, or when an intravenous antibiotic will be necessary.

Impetigo can be treated with topical mupirocin (Bactroban) with or without an oral antibiotic, such as cephalexin or dicloxacillin. Oral clindamycin may be used in a penicillin-allergic patient.

Folliculitis may also be treated with topical antibiotics, but if it becomes too extensive and treatment with topical antibiotics becomes impractical, or if it recurs, then the above mentioned oral antibiotics may be necessary. It may be helpful to have the patient bathe with an antiseptic soap (PhisoHex or Hibiclens) daily for seven to ten days to reduce the colony counts of pathogenic bacteria on the skin.

Hot tub folliculitis is a self-limited disease that usually resolves without specific antimicrobial treatment.

A **furuncle** or **carbuncle** will require surgical drainage of the abscess. If only a mild cellulitis surrounds the lesion, an oral antibiotic, such as cephalexin, dicloxacillin or clindamycin might be adequate. Some carbuncles are complicated by significant surrounding cellulitis and induration and will require a short course of IV antibiotics followed by oral antibiotics.

Uncomplicated **cellulitis** may be treated by oral antibiotics only if the affected area of skin is small and there are no other systemic signs or symptoms. Again, the oral drugs of choice are cephalexin, dicloxacillin or clindamycin. Using the maximum dose is essential since tissue penetration is impaired by local edema. The dose for cephalexin and dicloxacillin is 500 mg PO QID. The dose for clindamycin should be at least 300 mg PO QID. Underdosing may lead to treatment failure.

Concomitant fever or a leukocytosis, failure of oral antibiotics, or cellulitis involving a large area of skin and induration are indications for IV antibiotics. If the patient is otherwise healthy and he/she has proper health insurance coverage, cellulitis could be treated with outpatient IV antibiotics, thus avoiding hospitalization. Drugs of choice would be cefazolin 1 to 2 grams IV Q 8 hours or clindamycin 600 to 900 mg IV Q 8 hours (higher dose of these antibiotics is preferred) as most cases of cellulitis are complicated by edema and induration which, as already mentioned, impair drug penetration to the site of infection). For convenience sake, 2 gm of ceftriaxone (Rocephin) or 1 gm of Ertapenem (Invanz), both dosed Q 24 hours, could be used. It is my opinion, however, that these two drugs are second line treatment for cellulitis and are to be avoided in the more serious cases.

We are seeing an increasing number of cases of cellulitis due to **MRSA**. In patients in one of the groups mentioned above at high risk for MRSA, trimethoprim/sulfamethoxazole (TMP/SMX) should be included in any oral regimen. Combining TMP/SMX with rifampin provides a synergistic regimen which is fairly effective in treating mild to moderate MRSA infections. Using TMP/SMX routinely even in low risk patients cannot be faulted. Note that although it is very effective against staphylococcus, TMP/SMX alone is unreliable in treating streptococcal infections, and unless cultures reveal that MRSA is the sole culprit, it should be combined with anti-streptococcal antibiotics (cephalexin or clindamycin). Certainly, MRSA coverage should be considered in anyone that fails cefazolin or clindamycin treatment. IV antibiotics for MRSA include Vancomycin, linezolid (Zyvox), daptomycin (Cubicin), and dalphopristin/quinupristin (Synercid). Brand new on the market, tigacycline (Tygacil), a glycoacycline antibiotic, also has MRSA coverage. It is an IV antibiotic which has broad spectrum gram positive, gram negative and anaerobic coverage. You will be hearing more about this drug in the near future.

In a patient at high risk for MRSA infection who is allergic sulfa drugs, oral Zyvox would be an appropriate alternative. The problem with Zyvox is that many times its cost is so prohibitive, an IV antibiotic may be required. Cubicin is dosed once daily, is highly efficacious, and has a low side effect profile. Depending on peaks and troughs, Vancomycin may be dosed once daily allowing convenience in outpatient administration, but its administration is complicated by the frequent need for obtaining peaks and troughs.

*** NOTE:** Although there is an FDA indication for using a quinolone, such as **Levaquin**, for SSTIs, **This author advises against it's regular use** in treating SSTIs for two reasons: 1) Levaquin's efficacy against staphylococcus is unreliable and I have seen numerous treatment failures, and 2) quinolone overuse is leading to some major resistance problems. It behooves all clinicians to use quinolone-sparing regimens unless a quinolone is clearly the drug of choice as in specific cases listed below.

As mentioned above, **necrotizing fasciitis** requires urgent hospitalization, emergency surgery and broad-spectrum IV antibiotics. Necrotizing cellulitis of the perineum in a diabetic likely represents a type I infection and broad gram-positive, gram-negative, and anaerobic coverage is required. It is highly recommended that aside from a surgical consult, infectious disease consultation should be obtained. Antibiotic coverage may be complicated as choice of appropriate antibiotics depends on surrounding circumstances. Piperacillin/tazobactam (Zosyn), imipenem (Primaxin), or meropenem (Merrem) plus or minus Vancomycin are common choices.

Necrotizing cellulitis of an extremity is likely to be a type II infection due to *S. pyogenes*. Clindamycin at high dose needs to be a part of any antibiotic regimen early on as it inhibits protein synthesis. The necrotizing nature of this infection is due to release of proteinaceous exotoxins synthesized by the organism whose production is blocked by clindamycin, thus reducing the degree of tissue damage. I like to use high dose cefazolin plus clindamycin.

Animal or human bites do not necessarily become infected, so prophylactic antibiotics are not generally recommended. Prophylaxis is only indicated in cases when the bite results in crushed tissue, or if the animal tooth penetrated deeply. Antibiotic therapy should otherwise only be instituted when signs of infection are present. *Pasteurella multocida*, the primary agent in cat bite infections, is innately resistant to first generation cephalosporins and clindamycin. Therefore, the usual treatment for cellulitis would be ineffective. Ampicillin, or amoxicillin, is the drug of choice.

Amoxicillin/clavulenate (Augmentin) adds coverage for methicillin-sensitive *S. aureus* (MSSA) and oral anaerobes which might also be contributing to infection resulting from animal or human bites. Therefore, the first line drug for any animal bite should be Augmentin, or in the IV form (should the infection be severe enough to require it), ampicillin/sulbactam (Unasyn). In the penicillin-allergic patient, a quinolone, like Levaquin, will cover pasteurella, and clindamycin can be given to cover MSSA and oral anaerobes.

Cases in which ***pseudomonas aeruginosa* or *aeromonas*** may be a prominent pathogen, such as nail puncture infections, burn wound infections, or lacerations incurred during exposure to fresh water lakes or rivers, may also involve gram positive infections. Thus, empiric therapy should include coverage for both classes of organisms. Quinolones are first line drugs for community-acquired pseudomonas infections. Since quinolones are not completely trustworthy in treating staphylococcal infections, however, I recommend combining a quinolone with a first generation cephalosporin, clindamycin, or even TMP/SMX.

Infections related to lacerations or abrasions received while swimming in **sea water** are best treated with doxycycline, which is effective against vibrio. As with fresh water-related infections, the more severe infections should also include pseudomonad and gram positive coverage.

Below is a table summarizing antibiotic choices depending on exposure history.

<u>Exposure</u>	<u>Organism</u>	<u>Antibiotic</u>
Spontaneous	Staph, strep	1 st gen ceph, clinda
Facial (sinusitis)	Staph, strep, Oral anaerobes	Augmentin, Unasyn, clindamycin

Nail puncture	pseudomonas	Zosyn, quinolone, Cefepime
Cat, dog, human bite	pasteurella, Capnocytophaga) Oral flora	Augmentin, Unasyn, or clind + quinolone
Ocean laceration	Vibrio	Doxycycline
Fresh water laceration	aeromonas	quinolone, Zosyn
Post-op wound	MRSA, MDR-GNRs	Vanco, Zyvox, or Cubicin Plus Cefepime, Zosyn, Primaxin
Drug abuser, athlete, Institutionalized, day-care	MRSA	TMP/SMX + Rif (mild) Vanco, Zyvox, Cubicin (severe cases)

The perennial question presented about treatment of SSTIs is “how long do we treat?” There is no magic **duration of therapy**. Each infection is different and requires a different approach. The answer to the question of “how long” is an emphatic “until the infection is gone!” If after ten days of therapy, there is still redness, tenderness and induration, stopping antibiotics at that point with most certainly lead to a relapse. Cellulitis should be treated until redness and tenderness are gone, whether it takes three days or thirty days.

Summary

Most SSTIs are treated empirically since cultures are usually not positive. Choice of antibiotics depends on exposure history. The first decision point in treatment is what level of treatment will be required: 1) topical therapy alone, 2) oral antibiotics, or 3) IV antibiotics. Mild to moderate infections involving small areas of tissue and which are absent of systemic signs and symptoms may be treated with oral antibiotics with reasonable success. Progression of infection in spite of oral antibiotics, large areas of tissue infected and patients with systemic symptoms should be treated with intravenous antibiotics.