Is Cellulitis part of the Differential Diagnosis?

Factors to consider in Skin, Soft Tissue, Bone and Joint Infection

In response to concerns raised about optimal diagnosis and management of skin/soft tissue, bone and joint infections, CPSM sought assistance in providing advice to the profession. Although a brief summary in the CPSM Newsletter cannot address all of the nuances of these infections, what follows is a practical guide with tips in the context of local pathogens. CPSM extends thanks to Dr. John Embil for preparing this article and to the 24 physicians who collaborated with Dr. Embil in offering multiple specialty perspectives.

Skin and Soft Tissue Infections

The most likely pathogens responsible for community acquired skin/soft tissue, bone and joint infections are *Staphylococcus aureus* (methicillin susceptible or resistant) and the beta-hemolytic streptococci. There are, of course, multiple factors that influence the nature of the pathogens responsible for infection. Please note that *S. aureus* and the beta-hemolytic streptococci must be considered in all of these infections as they are organisms routinely found on the skin and can be introduced into the skin with injury. Factors that influence the nature of the pathogens include the following:

- Penetrating Trauma: Consider anaerobes and Gram-negative bacteria, in addition to *S. aureus* and beta-hemolytic streptococci
- Water exposure: Consider *Aeromonas hydrophila* and *Vibrio spp*
- Swimming pool/fish tank exposure: Consider *Mycobacterium marinum*
- Nail Puncture through Footwear: Consider *Pseudomonas aeruginosa*
- Exposure in northwestern Ontario/southeastern Manitoba: Consider *Blastomyces dermatitidis*
- Animal bites and scratches: Cats (*Pasteurella multicida*), dogs (*Pasterurella canis/multicida*, *Neisseria weaveri* and *Capnocytophaga canimorsus*)
- Human bites: oral anaerobes, *S. aureus* and beta-hemolytic streptococci

There are numerous conditions that can mimic acute skin and soft tissue infections that also need to be considered, specifically:

- **Contact dermatitis:** Please note that many topical antimicrobials can be potent skin sensitizers, causing contact dermatitis that can mimic cellulitis. One example is bacitracin present in Polysporin™ and other combination antimicrobial ointments.
- **Stasis dermatitis:** This condition is usually bilaterally symmetrical, warm, and violaceous, with dry crusted skin and can be very itchy.
- **Dependent rubor:** Usually unilateral, with a cool pulseless leg and associated pain when the leg is elevated and relief of discomfort with the leg being dependent. The presence of palpable pedal pulses suggests adequate circulation to foot and leg and eliminates the need for further vascular investigations. Please note that peripheral arterial disease may present separately or in conjunction with infections, particularly those combined with ischemic ulcers or gangrene (such as diabetic foot ulcers). Please reach out to vascular surgery on call if any concerns.
- **Foot Fractures:** Charcot arthropathy in the person with diabetes can manifest with a hot swollen foot with associated leg edema. A plain radiograph will help in establishing the diagnosis.

The general classification of skin and soft tissue infections is as follows:

- **Mild:** Localized swelling and induration with limited erythema. There is no hemodynamic instability. These infections can be treated with oral antibiotic therapy.
- **Moderate:** More extensive erythema, with involvement of deeper tissues. Depending upon the patient's hemodynamic status, moderate infections can be treated orally, but, if there is any evidence that the patient is unstable, intravenous antibiotics should be administered.
- **Severe:** Associated with potential fever, tachycardia, tachypnea, elevation of white blood cell count, and possibly hypotension. These patients require admission to hospital, intravenous antibiotics and possibly more extensive investigation.

When considering treatment of an acute skin and soft tissue infection, it is important to consider whether the individual has risk factors for colonization or infection with methicillin resistant *Staphylococcus aureus* (MRSA) such as those who are haemodialysis dependent, residents in congregate settings, or where there are multiple people in the household, institutionalization in healthcare facilities, and penitentiaries. Previous infection with MRSA must also be considered as MRSA will not respond to beta-lactam antibiotics such as amoxicillin-clavulanic acid, cephalexin, cefazolin and ceftriaxone but should respond to doxycycline, trimethoprim-sulfamethoxazole (TMP/SMX), clindamycin, vancomycin, and daptomycin.

Please consider the following guiding principles when initiating therapy for the treatment of acute skin and soft tissue infections:

- Mild/limited infections can be treated orally and if the patient does not have any risk factors for infection with MRSA, then cephalexin, or amoxicillin-clavulanic acid can certainly be considered. If there is allergy to the beta-lactam agents, consider clindamycin or doxycycline. In situations where there may be simultaneous infection with *S. aureus* (methicillin susceptible or resistant) and the beta-hemolytic streptococci such as in residents from remote and Northern communities, treatment for both pathogens must be considered. Please note that neither doxycycline, nor TMP/SMX are considered as reliable agents for treatment of infections caused by streptococci.
- Simple abscess with limited cellulitis in healthy patients can usually be treated with incision and drainage alone, but adjunctive antibiotics may be of benefit.
- For patients with more significant infections, intravenous antibiotic therapy may be required. For those for whom MRSA is not a concern consideration can be given to the use of intravenous ceftriaxone 2 grams once daily which allows for the convenience of once daily treatment. However, if the patient requires admission to hospital cefazolin 2 grams intravenously every 8 hours can be used as an alternative. When MRSA is a consideration vancomycin or daptomycin can be used as single agents or in combination with ceftriaxone or cefazolin.
- Please ensure that all antibiotic dosing is adjusted for renal function.
- In the past, cefazolin would be combined with probenecid to extend the effect of cefazolin, however, probenecid has many medication interactions and therefore, this combination should be avoided.
- If there is concern about MRSA, clindamycin, vancomycin or daptomycin can be considered as alternatives to ceftriaxone. In the vast majority of acute skin and soft tissue infections, gram negative microorganisms do not play a role and therefore, the combination of vancomycin and ceftriaxone can be started as empiric therapy but should be de-escalated once culture results become available.
- With the exception of impetigo, topical antibacterial creams and ointments have no role in management of skin/soft tissue infection and should not be prescribed. They may lead to adverse reactions (dermatitis, allergy) and provide no treatment benefit.

- If there is pain out of proportion to clinical findings, the diagnosis of necrotizing fasciitis must be entertained and immediate action taken. Do not delay establishing the diagnosis by requesting diagnostic imaging. Reach out to the on-call consultant in Plastic Surgery, Orthopedics and/or Infectious Diseases to discuss the situation.

Bone and Joint Infections

Patients who present with a hot, swollen, and painful joint may have septic arthritis, however, this must be differentiated from an overlying bursitis or cellulitis. If there is pain with axial loading, decreased range of motion and pain with any form of weight bearing, the diagnosis of septic arthritis must be entertained. A high index of suspicion is necessary in elderly patients, those being treated with immunosuppressive medications, persons with diabetes, and those with using injection street drugs. Please note, however, that crystalline arthropathy, gout (caused by monosodium urate crystal deposition) or pseudogout (caused by calcium pyrophosphate crystal deposition) can also present in a similar fashion. Crystalline arthropathy, however, usually occurs involving the first metatarsal phalangeal joint (MTPJ), with other joints less likely. Gout usually occurs first in the first MTPJ of ambulatory patients. Pseudogout can present first in the first MTPJ or other medium or large joints (e.g. knees), especially in elderly individuals. Please consider the following guiding principles when evaluating a person with a hot, painful, and swollen joint, with decreased range of motion around the joint:

- If the diagnosis of septic arthritis is considered and there is an associated joint effusion, aspiration of the joint (if amenable) should be undertaken with the specimen being submitted for:
    - Gram stain, culture, cell count and crystal analysis.
    - If the index of suspicion for septic arthritis is high, contact an orthopedic surgeon for review as irrigation and debridement of the affected joint is the standard of care, unless there are other prevailing circumstances.
    - Septic arthritis is generally not treated with antibiotics alone. Antibiotics serve as an adjunct to irrigation and debridement of the affected joint.
    - If the patient has preserved range of motion and does not have pain on weightbearing, the process is unlikely to be septic arthritis but could be a septic bursitis. Aspiration of the bursa for culture of the fluid is indicated.
    - If there is evidence of an acute skin and soft tissue infection overlying a prosthetic joint, please be very careful in your assessment as this could represent an infection of the prosthetic joint. Please discuss the patient's presentation with an Orthopedic surgeon or Infectious Diseases physician.
    - There has been a dramatic increase in gonococcal septic arthritis in Manitoba. Patients presenting with acute septic arthritis should be asked about potential risk factors for sexually transmitted infections and where identified, urogenital samples taken for detection of gonorrhea and chlamydia. Note that in females, urine samples are significantly less sensitive than cervical specimens for detection of *Neisseria gonorrhoeae*. Blood cultures and aspiration of the joint are also necessary when *N. gonorrhoeae* is the suspected pathogen.
    - If *S. aureus* is recovered from a joint that has not been previously replaced or manipulated, an echocardiogram should be performed to evaluate for the possibility of endocarditis as the septic arthritis may have arisen from hematologic spread.

    - *Staphylococcus aureus* is a highly metastatic microorganism that can lead to endocarditis and its recovery from blood cultures must not be dismissed as a contaminant. If there are any questions surrounding the recovery of *S. aureus* from the blood culture, please contact an Infectious Diseases physician for further discussion.
- Although septic arthritis is a consideration when a patient presents with a hot, painful, swollen joint with an altered range of motion, there are a number of mimics that must be considered, specifically if the aspirate is sterile on culture and the patient has not received antibiotics prior to the joint aspiration:
    - Acute presentation of a rheumatological disorder
    - Crystalline arthropathy
    - Reactive arthritis

Investigations

Diagnostic Imaging:

- For diagnosis of osteomyelitis in extremities, plain radiographs remain the first choice of investigation.
- Radiolucent foreign bodies such as splinters are best seen on ultrasound examination and radio-opaque foreign bodies such as metallic objects or glass are best seen on radiographs and computed axial tomographic (CT) scans.
- If a soft tissue collection is suspected, ultrasound or contrast-infused CT scans should be the imaging modalities of choice.
- Use of ultrasound is of limited value for the diagnosis of osteomyelitis
- If erosive changes of osteomyelitis are observed on plain radiographs, additional imaging is not required as the diagnosis has been established. The radiographic appearance of osteomyelitis can lag behind the clinical presentation by approximately 10 days. If initial plain radiographs do not demonstrate findings of osteomyelitis, a follow-up plain radiograph performed 1-2 weeks later should be considered, as the follow-up study will invariably demonstrate changes compatible with osteomyelitis (soft tissue swelling, a periosteal reaction, cortical irregularity, and demineralization)
- Please note that if bone is visible or palpable at the base of the wound, osteomyelitis can be presumed and antimicrobial treatment initiated. If a skin and soft tissue infection is not present then specimens can be collected and culture directed antimicrobial therapy initiated once results are available. Empiric antimicrobial therapy should however be started if there is evidence of a concurrent acute skin and or soft tissue infection.
- Magnetic resonance imaging is seldom required and discussions with a radiologist should be undertaken prior to requesting this modality for the diagnosis of infection.
- Nuclear imaging is seldom of benefit in the investigation of soft tissue and bone infections, and should only be entertained after discussion with a radiologist.

Microbiology

- Specimens for culture should be obtained in select cases when results are likely to impact treatment. For acute mild non-purulent cellulitis in otherwise healthy patients without atypical exposures (e.g. water, animal) empiric treatment without culture is reasonable. In otherwise healthy patients with abscess and limited cellulitis, incision and drainage is curative and cultures are not necessary. *Staphylococcus aureus* is a greater consideration in purulent cellulitis. If antibiotic treatment is offered and does not include anti-MRSA therapy, consider culture in order to detect MRSA and adjust treatment accordingly. Specimens should always be obtained from patients with chronic conditions

predisposing to infection (e.g. venous stasis ulcers, peripheral vascular disease, diabetes), moderate to severe cellulitis, or if atypical exposures are identified by history.

- In most cases, aspirates of pus or tissue specimens are preferred over swabs because surface tissues are frequently contaminated with resident bacteria making results from swabs difficult to interpret.
- When culturing an intact abscess or bursa, the fluid should be collected directly by aspiration through the skin or aspirated immediately after incision. Fluids should be submitted for culture in a sterile screw-top container. A swab may be used instead of an aspirate to collect the pus after incision and drainage in uncomplicated infections.
- For acute infections associated with open wounds, exudate and pus should be thoroughly washed off with saline and any necrotic tissue debrided prior to sampling the base of the wound with a swab or collecting a small amount of infected tissue by biopsy.
- For chronic infections including diabetic foot infections, infected pressure ulcers, infected venous stasis ulcers and osteomyelitis, a biopsy of affected living tissue after debridement of necrotic tissue and surface cleansing is the preferred sample. Tissues should be sent to the microbiology laboratory in a sterile screw-top container. A small amount of saline can be added to small biopsies to prevent desiccation. If this is not feasible, necrotic tissue should be debrided and the surface of the ulcer washed thoroughly with saline to remove exudate, and a sample can be taken by rotating a swab 4-5 times at the base of the ulcer until a small amount of bleeding is observed (Levine method) and submitting it for culture.
- If atypical infections are suspected (e.g. mycobacterial, fungal), a tissue biopsy should always be obtained for culture and sent to the appropriate laboratory for testing.
- For suspected septic arthritis with joint effusion, an aspirate of synovial fluid should be submitted for culture. The aspirate should be submitted in a sterile screw-top container. If needed, additional specimens will be required for cell count and crystal analysis (1 specimen) and biochemistry (1 specimen). In patients requiring surgery for septic arthritis or prosthetic joint infections, additional tissue samples should be sent in collaboration with orthopedic surgery.

For healthcare providers using Shared Health microbiology laboratories, additional information on specimen collection can be found in the Shared Health Laboratory Information Manual.

Take Home Points:

1. Local epidemiology and practice environment should guide diagnostic and therapeutic strategies (e.g. in remote and Northern communities where both MRSA and beta-hemolytic streptococci can be present in skin and soft tissue infections, empiric therapy for both pathogens should be considered).
2. Biopsies of tissue (bone, soft tissue) or deep swabs from abscesses are the desired specimens as they are most likely to yield the true pathogen in invasive infections, while superficial swabs are more likely to yield superficial contaminants.
3. When there is doubt about diagnostic or therapeutic strategies, or a patient is not improving on presumably appropriate therapy, please contact a consultant to assist in the patient's care and if necessary, arrange transfer to a centre with more advanced resources.
4. In situations where there is potential infection overlying or involving implanted orthopaedic hardware, please consult with either a specialist in Orthopedics or Infectious Diseases.
5. The plain radiograph should be the first diagnostic imaging modality undertaken, and if evidence of osteomyelitis or septic arthritis is identified additional investigations are not needed unless otherwise directed by a radiologist or the clinical scenario.

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