Treatment of Skin & Soft Tissue Infections

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, February 2021)

EXCLUSIONS

- Exclusions: cellulitis of dental origin, diabetic foot infections, severely immunocompromised patients (e.g. neutropenia, immunosuppressive therapy), surgical site infections, recent history of fresh/salt water exposure, recent hot tub use, or cellulitis associated with fish and seafood processing.

Treatment Criteria and Considerations

- The diagnosis of cellulitis is largely clinical, and the initial treatment is usually empirical. Misdiagnosis is not uncommon, so the clinician should be alert to the possibility of cellulitis "mimics", such as: venous stasis dermatitis, DVT/thrombophlebitis, hematomas, and gout.
- Cellulitis of the extremities is almost always unilateral. "Bilateral cellulitis" is extremely unlikely; first consider an alternate non-infectious diagnosis.
- Evaluate all patients for predisposing features (e.g. tinea pedis, dermatoses, lymphedema, venous stasis, wounds) as the source of cellulitis, especially in the setting of recurrent cellulitis. If possible, treat predisposing factors to prevent recurrent cellulitis.
    - May consider MRSA decolonization in patients with recurrent MRSA infections.
- **Non-pharmacologic interventions (such as elevation and compression of the affected limb, if appropriate) are adjunctive, but essential, components of cellulitis management.**
    - Affected upper extremities should be elevated higher than the shoulder
    - Affected lower extremities should be elevated higher than the hip joint

Assessment of clinical response

- Marking the outline of the erythema and/or daily photographs may assist in the assessment.
- **Assessment of clinical response in the first 48 hours should be limited to improvement of: pain, fever, and the patient's overall condition.**
    - During the first 48 hours, a mild progression of erythema is expected and "acceptable".
- Review and adjust therapy as needed if microbiology results become available

IV to PO Conversion

- **There is no evidence to support that IV therapy is superior to PO therapy in the management of uncomplicated cellulitis*.**
- **There is no evidence to support a minimum duration of IV therapy for the management of uncomplicated cellulitis*.**
- Patients meeting the following suggested criteria can generally have their therapy converted from IV to PO:
    - The patient is afebrile for at least 24 hours
    - Clinical improvement (such as: overall clinical improvement, decreased pain)
    - There are no complicating factors (e.g. deeper tissue involvement, undrained abscess, insufficient perfusion to the affected area)
    - The patient can tolerate oral medications that will achieve adequate tissue levels

Duration of therapy

- In patients with uncomplicated cellulitis* who show improvement after 72 hours of therapy, a duration of therapy of 5 days is just as effective as 10 days. In cellulitis, a relatively small number of bacteria cause a disproportionately large amount of inflammation. Greater than 5 days of therapy is rarely required if the patient responds within the first 72 hours of therapy.
    - Follow-up is essential to re-assure patients (and prescribers) that any residual redness is only due to inflammation.

MRSA

- MRSA is most often associated with PURULENT skin and soft tissue infections. It has been common practice to prescribe anti-MRSA therapy for all cases of mild to moderate cellulitis in patients with a history of MRSA. However, only mild to moderate PURULENT cellulitis requires empiric anti-MRSA therapy, even in the setting of prior MRSA infection. **Empiric coverage of MRSA is NOT required in mild to moderate NON-purulent cellulitis.**
- Risk Factors for MRSA include: History of MRSA infection or colonization, household contact with a MRSA colonized individual, IV drug use, homelessness, incarcerated persons, recent travel to or residing in an MRSA endemic region or community

* Uncomplicated cellulitis: cellulitis WITHOUT periorbital involvement, severe sepsis, extensive bullous skin changes, undrained abscesses, deep tissue involvement, necrotizing fasciitis, or infected prosthetic material.

Treatment of Skin & Soft Tissue Infections

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, February 2021)

NON-purulent cellulitis

- Cellulitis **NOT** associated with purulent collections (i.e. abscesses, folliculitis, furuncles, purulent ecthyma)
- Usual pathogens: *Streptococcus pyogenes* and other beta-hemolytic Streptococci, *S. aureus*

Severity	Empiric Therapy	Duration of Therapy	Comments
Mild (No signs of systemic toxicity)	cephalexin 500 – 1000 mg PO q6h* OR cefadroxil 500 – 1000 mg PO q12h* **If true immediate allergy[1] to a beta-lactam at risk of cross-reactivity with cephalexin or cefadroxil:** cefuroxime 500 mg PO q8-12h* **If severe delayed reaction[2] to a beta-lactam, where their future use is not recommended:** clindamycin 300 – 450 mg PO q6h	5 days	• **Workup:** None required • Empiric MRSA coverage in mild to moderate non-purulent cellulitis is NOT required, even if presence of MRSA risk factors. • Consider adjusting antibiotic dosing for obese patients to ensure adequate tissue concentrations.
Moderate • Signs of systemic toxicity (e.g. fever, leukocytosis), but NOT sepsis OR • Failure of PO therapy[3]	**Preferred PO Therapy:** Same as mild infection **Preferred IV therapy:** ceFAZolin 2g IV q8h* **Alternatives for outpatient IV management:** **[**probenecid 1 g PO, followed 30 - 60 min later by ceFAZolin 2 g IV**]** repeated q24h*,[4] OR ceFAZolin 2 g IV loading dose x1, then 6 g IV via continuous infusion over 24 hours*,[4] **If severe delayed reaction[2] to a beta-lactam, where their future use is not recommended:** clindamycin 900 mg IV q8h	If response to therapy within 72 hours: 5 days If delayed response to therapy: May extend to 7-10 days if needed	• **Workup:** May consider blood culture in patients with signs of systemic toxicity • There is no evidence that IV therapy is superior to oral therapy in the management of uncomplicated cellulitis. Consider oral therapy in patients with only one sign/symptom of systemic toxicity. • Empiric MRSA coverage in mild to moderate non-purulent cellulitis is NOT required, even if presence of MRSA risk factors. • Consider adjusting antibiotic dosing for obese patients to ensure adequate tissue concentrations.

* Dose adjustment required in renal impairment

[1] True, immediate IgE-mediated allergies include, but are not limited to: anaphylaxis, angioedema, hypotension, bronchospasm, stridor, urticaria, and pruritis.

[2] Severe delayed reactions include, but are not limited to: Stevens-Johnson syndrome, toxic epidermal necrolysis, immune hepatitis, DRESS, serum sickness, hemolytic anemia or interstitial nephritis.

[3] During the first 48 hours, a mild progression of erythema is expected and "acceptable". Assessment of clinical response in the first 48 hours should be limited to improvement of: pain, fever, and the patient's overall condition.

[4] Check for availability in your area.

Treatment of Skin & Soft Tissue Infections

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, February 2021)

Purulent cellulitis

- Cellulitis associated with purulent collections (i.e. abscesses, folliculitis, furuncles, purulent ecthyma)
- Usual pathogens: *Staphylococcus aureus* (MSSA +/- MRSA)
- Assess the patient for MRSA Risk Factors: History of MRSA infection or colonization, household contact with a MRSA colonized individual, IV drug use, homelessness, incarcerated persons, recent travel to or residing in an MRSA endemic region or community

Severity	Empiric Therapy	Duration of Therapy	Comments
Mild (No signs of systemic toxicity)	**If no MRSA risk factors** cephalexin 500 – 1000 mg PO q6h* OR cefadroxil 500 – 1000 mg PO q12h* **If true immediate allergy[1] to a beta-lactam at risk of cross-reactivity with cephalexin or cefadroxil:** cefuroxime 500 mg PO q8-12h* **If MRSA risk factors, ADD one of the following:** sulfamethoxazole/trimethoprim 800/160 mg to 1600/320 mg (1 or 2 DS tablets) PO q12h*[,2] OR doxycycline 200 mg PO x 1 dose, then 100 mg PO q12h[2]	5 days	• **Workup:** Drainage and culture of pus • Incision and drainage of purulent collection (when possible) is essential to the management of purulent cellulitis. • Consider adjusting antibiotic dosing for obese patients to ensure adequate tissue concentrations.
Moderate • Signs of systemic toxicity (e.g. fever, leukocytosis), but NOT sepsis OR • Failure of PO therapy[3]	**If no MRSA risk factors** **Preferred PO Therapy:** Same as mild infection **Preferred IV therapy:** ceFAZolin 2g IV q8h* **Alternatives for outpatient IV management:** **[**probenecid 1 g PO, followed 30 - 60 min later by ceFAZolin 2 g IV**]** repeated q24h*[,4] OR ceFAZolin 2 g IV loading dose x1, then 6 g IV via continuous infusion over 24 hours*[,4] **If MRSA risk factors:** **Preferred PO Therapy:** Same as mild infection **Preferred IV therapy:** Vancomycin 25-30 mg/kg IV x 1 dose, then 15 mg/kg IV q8-12h* (target trough 10-15 mg/L)	If response to therapy within 72 hours: 5 days If delayed response to therapy: May extend to 7-10 days if needed	• **Workup:** As above, may also consider blood culture in patients with signs of systemic toxicity • Incision and drainage of purulent collection (when possible) is essential to the management of purulent cellulitis. • There is no evidence that IV therapy is superior to oral therapy in the management of uncomplicated cellulitis. Consider oral therapy in patients with only one sign/symptom of systemic toxicity. • Consider adjusting antibiotic dosing for obese patients to ensure adequate tissue concentrations.

* Dose adjustment required in renal impairment.

[1] True, immediate IgE-mediated allergies include, but are not limited to: anaphylaxis, angioedema, hypotension, bronchospasm, stridor, urticaria, and pruritis.

[2] Poor coverage for beta-hemolytic Streptococci, may consider combining with cephalexin, cefadroxil, or amoxicillin.

[3] During the first 48 hours, a mild progression of erythema is expected and "acceptable". Assessment of clinical response in the first 48 hours should be limited to improvement of: pain, fever, and the patient's overall condition.

[4] Check for availability in your area

Treatment of Skin & Soft Tissue Infections

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, February 2021)

Animal/Human Bites

- Initial management of bite wounds should always include thorough cleaning and irrigation.
- If the bite was from an unknown animal, or if from an unprovoked attack: assess the need for rabies post-exposure prophylaxis.
- Puncture wounds should be carefully examined to identify foreign objects and determine extent of injury to underlying structures.
- Infection rates can be as high as 80% for cat bites, 50% for human bites, and 20% for dog bites.
- Often polymicrobial; common pathogens can include:
  - Cat/Dog bite: *Pasteurella multocida*, *Capnocytophaga* spp, *Streptococcus* spp, *S. aureus*, anaerobes (e.g. *Fusobacterium*)
  - Human bite: *Streptococcus* spp, *Eikenella* spp, *S. aureus*, anaerobes (e.g. *Fusobacterium*)

Severity	Empiric Therapy	Duration of Therapy	Comments
Prophylaxis/ Pre-emptive Therapy (to be started within 12 hours) Indicated if: • Any cat bites • Bone/joint involvement • Puncture wounds • Moderate/severe injury • Injuries to hand, foot, face, or genitals • Edema in affected area • Cirrhosis • Immunocompromised patients (e.g. asplenia)	**Preferred:** Amoxicillin+clavulanate 875+125 mg PO q12h* **If true immediate penicillin allergy[1]:** cefuroxime axetil 500 mg PO q8h* **PLUS** metroNIDAZOLE 500 mg PO q12h OR doxycycline 200 mg PO x 1 dose, then 100 mg PO q12h **+/-** metroNIDAZOLE 500 mg PO q12h	3-5 days	• **Workup:** In infected wounds, consider blood cultures, pus/wound cultures • If immunizations are not up to date, consider tetanus vaccination. • HIV and hepatitis B&C are rarely transmitted by human bites. • Prolonged duration of therapy would be required in the setting of complications, such as: osteomyelitis, septic arthritis, tenosynovitis. • Consider adjusting antibiotic dosing for obese patients to ensure adequate tissue concentrations.
Mild to moderate infection	**Preferred:** Amoxicillin+clavulanate 875+125 mg PO q12h* **If true immediate penicillin allergy[1]:** cefuroxime axetil 500 mg PO q8h* **PLUS** metroNIDAZOLE 500 mg PO q12h OR doxycycline 200 mg PO x 1 dose, then 100 mg PO q12h **+/-** metroNIDAZOLE 500 mg PO q12h **If signs of systemic toxicity (but not sepsis):** cefuroxime 1.5 g IV q8h* **PLUS** metroNIDAZOLE 500 mg PO q12h	7-10 days	

* Dose adjustment required in renal impairment

[1] True, immediate IgE-mediated allergies include, but are not limited to: anaphylaxis, angioedema, hypotension, bronchospasm, stridor, urticaria, and pruritis.

Treatment of Skin & Soft Tissue Infections

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, February 2021)

Severe Skin and Soft Tissue Infections

- If any of the following are present, consider the possibility of a necrotizing infection, such as necrotizing fasciitis:
  - Deep severe pain disproportionate to what would be expected from skin findings
  - Rapid progression, particularly along fascial planes
  - Presence of gas in soft tissues
  - Areas of anaesthesia in the affected skin
  - Hemodynamic instability
  - Pronounced induration (hard/wooden feel of the subcutaneous tissue)
  - Multi-organ failure
  - Violaceous bullae
- Surgical debridement is ESSENTIAL in the management of necrotizing soft tissue infections.

Severity	Empiric Therapy	Duration of Therapy	Comments

Patient with sepsis, but is hemodynamically stable
 	
AND
 	
Necrotizing soft tissue infection **NOT** suspected
	Preferred:
	ceFAZolin 2 g IV q8h*
	
	If risk of Gram negative/polymicrobial infection (e.g. bite wounds, cirrhosis, foul smelling wound, groin/rectal involvement):
	piperacillin+tazobactam 3.375 g IV q6h*
	(or meropenem 500 mg IV q6h if true immediate penicillin allergy[1])
	
	If MRSA risk factors, add to one of the above agents:
	Vancomycin 25-30 mg/kg IV x 1 dose, then
	15 mg/kg IV q8-12h* (target trough 10-15 mg/L)
		5-10 days	• **Workup: Blood cultures**
			• **If necrotizing soft tissue infection is suspected: urgent surgical assessment for diagnostic biopsy and/or debridement**
			• Consultation with infectious diseases specialist or medical microbiologist is strongly encouraged
			• Assess the patient for MRSA Risk Factors:
			  ○ History of MRSA infection or colonization
			  ○ Household contact with a MRSA colonized individual
			  ○ IV drug use
			  ○ Homelessness
			  ○ Incarcerated persons
			  ○ Recent travel to or residing in an MRSA endemic region or community
			• Consider adjusting antibiotic dosing for obese patients to ensure adequate tissue concentrations.

Patient is hemodynamically unstable (i.e. septic shock) **AND/OR** Necrotizing soft tissue infection is suspected	**Suspected mono-bacterial infection:** ceFAZolin 2 g IV q8h* **PLUS** clindamycin 900 mg IV q8h[2] **If risk of Gram negative/polymicrobial infection (e.g. bite wounds, cirrhosis, foul smelling wound, groin/rectal involvement):** piperacillin+tazobactam 4.5 g IV q6h* (or meropenem 1-2 g IV q8h* if true immediate penicillin allergy[1]) **PLUS** clindamycin 900 mg IV q8h[2] **If MRSA risk factors, add to one of the above regimens:** Vancomycin 25-30 mg/kg IV x 1 dose, then 15 mg/kg IV q8-12h* (target trough 10-15 mg/L)	Consult with specialists	

* Dose adjustment required in renal impairment

[1] True, immediate IgE-mediated allergies include, but are not limited to: anaphylaxis, angioedema, hypotension, bronchospasm, stridor, urticaria, and pruritis.

[2] The goal of add-on clindamycin is to reduce bacterial toxin production; continue for at least 72 hours, and until the patient is no longer critically ill.

Treatment of Skin & Soft Tissue Infections

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, February 2021)

References:

1. Stevens, D., Bisne, A., Chambers, H., Everett, E., Dellinger, P., Goldstein, E. … Wade, J. (2014). Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clinical Infectious Disease,41 (15, November), 1373-1406
2. Blondel-Hill and Fryters. Bugs & Drugs 2.0. Accessed online 06-2020.
3. Hopkins ABX Guide. Accessed online 06-2020
4. INESSS. Optimal Usage Guide: Cellulitis in Adults. October 2017. Accessed online 06-2020.
5. Bystritsky R & Chambers H. In the Clinic® - Cellulitis and Soft Tissue Infections. Annals of Internal Medicine. 2018. doi:10.7326/AITC201802060
6. SHS+UHN Antimicrobial Stewardship Program. Skin and Skin Structure Infections (SSSIs). Accessed online 06-2020.
7. SHS+UHN Antimicrobial Stewardship Program. Management of Uncomplicated Skin and Skin Structure Infections (Non-Purulent and Purulent). Accessed online 06-2020.
8. Raff A & Kroshinsky D. Cellulitis: A Review. JAMA. 2016;316(3):325-337. doi:10.1001/jama.2016.8825
9. McCreary EK, Heim ME, Schulz LT et al. Top 10 Myths Regarding the Diagnosis and Treatment of Cellulitis. The Journal of Emergency Medicine. 2017; 53 (4): 485–492
10. Public Health Ontario. Evidence Brief: Duration of Antibiotic Treatment for Uncomplicated Cellulitis in Long-Term Care Residents. October 2018.
11. Hepburn MJ, Dooley DP, Skidmore PJ et al. Comparison of Short-Course (5 Days) and Standard (10 Days) Treatment for Uncomplicated Cellulitis. Arch Intern Med. 2004; 164:1669-1674
12. Prokocimer P, De Anda C, Fang E, et al. Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections: The ESTABLISH-1 Randomized Trial. JAMA. 2013;309(6):559-569
13. Moran GJ, Fang E, Corey GR, et al. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 2014;14: 696–705
14. Cranendonk DR, Opmeer BC, Van Agtmael MA, et al. Antibiotic treatment for 6 days versus 12 days in patients with severe cellulitis: a multicentre randomized, double-blind, placebo-controlled, non-inferiority trial. Clinical Microbiology and Infection. 2019; DOI:https://doi.org/10.1016/j.cmi.2019.09.019
15. Daum RS, Miller LG, Immergluck L, et al. A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses. N Engl J Med 2017;376:2545-55. DOI: 10.1056/NEJMoa1607033
16. Conway J & Friedman B. Adjuvant Antibiotic Therapy After Incision and Drainage of Cutaneous Abscesses. Academic Emergency Medicine. 2020; 27: 427–428
17. Lake JG, Miller LG, Fritz SA. Antibiotic Duration, but Not Abscess Size, Impacts Clinical Cure of Limited Skin and Soft Tissue Infection After Incision and Drainage. Clinical Infectious Diseases. 2019; DOI: 10.1093/cid/ciz1129
18. Wang W, Chen W, Liu Y, et al. Antibiotics for uncomplicated skin abscesses: systematic review and network meta-analysis. BMJ Open. 2018; 8: e020991. doi:10.1136/bmjopen-2017-020991
19. Hurley HJ, Knepper BC, Price CS, et al. Avoidable Antibiotic Exposure for Uncomplicated Skin and Soft Tissue Infections in the Ambulatory Care Setting. Am J Med. 2013; 126(12): 1099–1106. doi:10.1016/j.amjmed.2013.08.016
20. Collazos J, de la Fuente B, Garcia A, Goomez H, Menendez C, Enriquez H, et al. (2018) Cellulitis in adult patients: A large, multicenter, observational, prospective study of 606 episodes and analysis of the factors related to the response to treatment. PLoS ONE 13(9): e0204036. https://doi.org/10.1371/journal.pone.0204036
21. Sutton JD, Carico R, Burk M, et al. Inpatient Management of Uncomplicated Skin and Soft Tissue Infections in 34 Veterans Affairs Medical Centers: A Medication Use Evaluation. Open Forum Infectious Diseases. 2020. DOI: 10.1093/ofid/ofz554
22. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess. N Engl J Med. 2016 March 3; 374(9): 823–832. doi:10.1056/NEJMoa1507476
23. Talan DA, Moran GJ, Krishnadasan A, et al. Subgroup Analysis of Antibiotic Treatment for Skin Abscesses. Ann Emerg Med. 2018 January ; 71(1): 21–30. doi:10.1016/j.annemergmed.2017.07.483
24. Ihm C, Sutton JD, Timbrook TT, Spivak ES. Treatment Duration and Associated Outcomes for Skin and Soft Tissue Infections in Patients With Obesity or Heart Failure. Open Forum Infectious Diseases. 2019. DOI: 10.1093/ofid/ofz217
25. Landry DL, Eltonsy S, et al. Continuous cefazolin infusion versus cefazolin plus probenecid for the ambulatory treatment of uncomplicated cellulitis: A retrospective cohort study. Official Journal of the Association of Medical Microbiology and Infectious Disease Canada. 2018. doi:10.3138/jammi.2018-0039
26. AHRQ Safety Program for Improving Antibiotic Use. Best Practices in the Diagnosis and Treatment of Cellulitis and Skin and Soft Tissue Infections. November 2019
27. Aboltins CA, Hutchinson AF, Sinnappu RN, Cresp D et al. Oral versus parenteral antimicrobials for the treatment of cellulitis: a randomized non-inferiority trial. J Antimicrob Chemother 2015; 70: 581 –586. doi:10.1093/jac/dku397