INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Skin & Soft Tissue Infections***
-October 2021-

Background:

The Indian Health Service National Pharmacy and Therapeutics Committee (NPTC) reviewed medications used to treat Skin/Soft Tissue Infections (SSTIs), including infections caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) at the Fall 2021 quarterly meeting. The targeted review represents the first analysis for the NPTC on this topic. Amoxicillin, amoxicillin and clavulanate, cephalexin, clindamycin, doxycycline and penicillin V potassium were all named to the National Core Formulary (NCF) prior to this presentation, from separate NPTC reviews of unrelated health conditions. Following this review, the NPTC voted to **ADD (1) mupirocin and (2) trimethoprim-sulfamethoxazole to the NCF.**

Discussion:

The SSTIs reviewed included impetigo, erysipelas, cellulitis, skin abscesses, and necrotizing fasciitis. The incidence of cellulitis is approximately 200 cases per 100,000 patient-years. Cellulitis is more common in middle-aged and older adults and, in non-tropical regions, it is more common in the warmer months. Erysipelas is most common in younger children and older adults. Skin abscesses may occur in healthy individuals with no predisposing conditions and are most often caused by Methicillin-susceptible *Staphylococcus aureus* (MSSA) or MRSA. In 1962, MRSA was first discovered one year after methicillin was released on the market. A modification of the beta-lactam binding site makes MRSA intrinsically resistant to nearly all beta-lactam antibiotics. Historically, MRSA was considered a healthcare associated pathogen but in the 1990s, the incidence of abscesses caused by MRSA acquired in the community increased. Predisposing factors for SSTIs include skin barrier disruption, skin inflammation, edema, obesity, immunosuppression, and pre-existing skin infections. Risks of MRSA infection include close contact with others with MRSA infection or carriage (most common in patients with diabetes, HIV, on dialysis, or intravenous drug use)[1,2,3].

The Agency for Healthcare Research and Quality (AHRQ) provides recommendations to guide treatment of SSTIs and states there are **4 notable moments for prescribers in antibiotic decision making**. The first moment is determining whether or not antibiotics are needed. Various conditions, known as cellulitis mimics, can be misdiagnosed as cellulitis. Cellulitis mimics include venous stasis dermatitis, lymphedema, peripheral arterial disease, contact dermatitis, deep vein thrombosis, and gout. Once cellulitis is appropriately diagnosed, the second moment is deciding whether or not cultures are needed and determining appropriate empiric therapy. Blood cultures are often unnecessary except in severe infections, immunocompromised patients, or in certain exposures. As *Staphylococcus aureus* and various Streptococci strains are both naturally a part of skin flora, surface cultures are often unreliable and should be avoided if possible. Purulent infections should have the pus cultured if possible. Empiric treatment is determined based on whether the infection is purulent or not, and the severity. Non-purulent SSTIs are frequently caused by Streptococcus, most often by group A variants, whereas purulent infections are most commonly the result of MSSA or MRSA. Where available, rapid polymerase chain reaction technology can be a useful tool to quickly guide therapy by determining whether an infection is caused by MSSA or MRSA. Non-purulent infections caused by Streptococcus can be treated with amoxicillin, cephalexin, clindamycin or penicillin. MSSA infections can be treated with cephalexin or any medication(s) that can treat MRSA (e.g., trimethoprim-sulfamethoxazole [TMP-SMX], doxycycline, clindamycin). Local treatment recommendations should be based on local resistance patterns. Co-prescribing of antibiotics for both Staphylococcus and Streptococcus is unnecessary once it has been determined whether a SSTI is purulent or non-purulent and, as such, the practice is not included in the 2014 Infectious Diseases Society of America (IDSA) SSTI guidelines.

Impetigo is a superficial bacterial infection of the skin which frequently occurs in children in hot, humid environments. Impetigo, caused by Group A *Streptococcus* or also known as *Streptococcus pyogenes*, can cause honey crust lesions. Impetigo caused by MSSA and MRSA can cause bullous impetigo which cause varnish like lesions. Mild impetigo can be treated with topical mupirocin. Severe cases can be treated the same antibiotic options above[4,5,6,7,8].

Many of these medications need to be adjusted for special populations. For pediatric populations, weight based dosing and suspensions/liquids are available for amoxicillin, amoxicillin-clavulanate, cephalexin, clindamycin, penicillin and TMP-SMX. For patients with renal dysfunction, amoxicillin, amoxicillin-clavulanate, cephalexin, penicillin and TMP-SMX require renal adjustment. Doxycycline and clindamycin do not need to be renally adjusted. Recent data has suggested that obese patients with cellulitis could benefit with higher doses of clindamycin or TMP-SMX. In 2017, a published study of 208 patients evaluated whether ≥10 mg/kg/day of clindamycin or ≥5 mg/kg/day of TMP/SMX resulted in better outcomes than <10 mg/kg/day of clindamycin or <5 mg/kg/day of TMP/SMX. It was determined that patients taking the lower doses of either clindamycin or TMP-SMX had higher odds of clinical treatment failure (OR = 2.01, p=0.032). The Sanford Antibiotic Guide recommends clindamycin 450 mg PO TID or TMP-SMX Double Strength, 2 tablets PO BID when used for the treatment of skin abscesses in obese patients with BMI >40[9,10,11].

Since the publication of the IDSA guidelines in 2014, the ideal treatment for mild purulent infections remains in question and continues to be evaluated. In 2017, Daum and colleagues examined whether or not incision and drainage (I&D) with antibiotics (clindamycin or TMP-SMX) or I&D alone had better cure rates for mild purulent infections. In total, 786 participants, including both adults and children, met inclusion criteria. The clindamycin group had 83.1% cure rate, TMP-SMX group had an 81.7%, and the I&D alone group had a cure rate of 68.9%. The difference was found to be statistically significant when compared to I&D alone for both the clindamycin (difference −14.2%; 95% CI: −22.0 to −6.4; p<0.001) and TMP-SMX (difference −12.9%; 95% CI: −20.8 to −5.0; p<0.001). The difference between the TMP-SMX and clindamycin groups was not statistically significant. The authors concluded that I&D with antibiotics has a better cure rate than I&D alone for patients with mild abscesses[12].

Although SSTIs are most often caused by *Staphylococcus aureus* and Streptococcus, other organisms can cause SSTIs in certain circumstances. For example, in addition to Staphylococcus and Streptococcus, other bacteria can cause SSTIs as a result of a bite, non-superficial diabetic foot infections, or secondary to a burn. Clinical providers should consider alternate microbial agents in these circumstances. Also, SSTIs in areas where two different systems meet can have additional organisms which cause infection. For example, orbital cellulitis can be caused by Staphylococcus and Streptococcus (skin) as well as by *Streptococcus pneumoniae* or *Haemophilus influenzae* (respiratory tract). Antibiotic treatment should be selected to eradicate the most likely organisms. In the case of bites, cat, dog, and human bites can all be treated with amoxicillin-clavulanate[13,14,15,16].

The third moment in antibiotic decision making is focused on narrowing, including switching to an oral formulation, or stopping antibiotics when indicated and is primarily intended for patients admitted to the hospital. The fourth moment is for determining the appropriate duration of antibiotic therapy. In the 2014 IDSA guidelines, 5 days of treatment for SSTI is recommended initially but can be extended if infection has not improved. The 2019 SSTI guidelines from the United Kingdom's National Institute for Health and Care Excellence recommend 5-7 days of treatment for most patients. These guidelines acknowledge that some patients may need longer treatment, but that decision to extend the duration of antibiotics should be balanced with the fact that skin may not be completely recovered after the infection has resolved[4,17].

Findings:

Antibiotic treatment for SSTI should be targeted to treat the most likely pathogens given the type, source, and location of the infection. Antibiotics should be given for the shortest duration possible (5-7 days is typically sufficient), while recognizing that skin may take time beyond the treatment of the infection to fully recover. MRSA is intrinsically resistant to nearly all beta-lactams. Local treatment options should be guided by local resistance patterns. As such, the NPTC voted to add mupirocin to the NCF as it is the drug of choice in the treatment of mild impetigo, treating MSSA, MRSA, and Streptococcus. Additionally, trimethoprim-sulfamethoxazole was also added to the NCF as an additional treatment option for MRSA infections.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

1. Spelman D, Baddour LM. Cellulitis and skin abscess: Epidemiology, microbiology, clinical manifestations, and diagnosis. UpToDate. Jul 26, 2021.
2. Lowy FD. Antimicrobial resistance: the example of Staphylococcus aureus. *J Clin Invest*. 2003; 111(9):1265-73.
3. Auwaerter PG. Staphylococcus aureus. Hopkins Antibiotic Guide. Updated 3/5/2019.
4. Agency for Healthcare Research and Quality. Best Practices in the Diagnosis and Treatment of Cellulitis and Skin and Soft Tissue Infections – Acute Care. AHRQ Pub. No. 17(20)-0028-EF. November 2019.
5. Stevens DL, Bisno AL, Chambers HF, et al. Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52.
6. Palavecino EL. Rapid Methods for Detection of MRSA in Clinical Specimens. Methods Mol Bio. 2020: 2069:29-45.
7. Boucher HW. Impetigo. Sanford Antibiotic Guide Web edition. Updated Apr 6, 2021. Subscription required.
8. Auwaerter PG. Impetigo. Hopkins Antibiotic Guide. Updated 9/5/2019.
9. Cox KK, Alexander B, Livorsi DJ, et al. Clinical outcomes in patients hospitalized with cellulitis treated with oral clindamycin and trimethoprim/sulfamethoxazole: The role of weight-based dosing. *J Infect*. 2017;75(6):486-492.
10. Chambers HF. Skin Abscess, Boils, Furuncles. Sanford Antibiotic Guide. Updated Aug 4, 2020. Subscription required.
11. Renal Impairment Dosing. Sanford Antibiotic Guide. Subscription required.
12. Daum RS, Miller LG, Immergluck L, et al. A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses. *NEJM*. 2017;376(26):2545-55.
13. Fabre V, Bartlett JG. Bite Wounds. Johns Hopkins ABX Guide. Updated 2/5/19.
14. Boucher HW. Burns, Infected Wound. Sanford Antibiotic Guide Web edition. Updated Jul 30, 2020. Subscription required.
15. Chambers HF. Diabetic Foot. Sanford Antibiotic Guide Web edition. Updated Aug 4, 2020. Subscription required.
16. Auwaerter PG. Orbital Cellulitis. Johns Hopkins ABX Guide. Updated 6/5/2019.
17. National Institute for Health and Care Excellence. Cellulitis and erysipelas: antimicrobial prescribing. NICE guideline. Published: 27 Sept 2019.