CHAPTER **39**

ANTIBIOTIC UPDATE

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INTRODUCTION

In recent years, antibiotic resistant bacteria have become a world-wide epidemic. Serious skin and soft tissue infections (SSTIs) precipitated by multi-drug resistant organisms are even more common. The inappropriate administration of antibiotics is an important factor in the occurrence of these resistant pathogens. Published rates of incorrect antibiotic use range from 41 to 91%. A 9-month prospective observational study of 539 admitted patients assessed the adequacy of empirical and adjusted antibiotic therapies in a Swiss University hospital. Of the patients studied, empirical antibiotic therapy was inadequate 22% of the time. Initial therapy was adjusted for 168 patients. The newly adjusted regimen was inadequate 27% of the time. The study sheds light on the need for interventions aimed at streamlining antibiotic therapy.

Many complicated and uncomplicated SSTIs are the result of diabetic complications arising from the insensate foot. Sensory, autonomic and motor neuropathies are additive factors, which increase a patient's risk for diabetic ulceration and infection. The diabetic ulceration is usually a repeat offender, often leading to infection and antibiotic coverage.

The Infectious Disease Society of America (IDSA) provides a focused guideline for treating all diabetic patients who have a suspected foot infection. Wound infections should be diagnosed clinically per local signs and symptoms. Wounds absent of purulence and inflammatory signs are uninfected. Mild wound infections possess 2 or more signs of inflammation with ≤2-cm of cellulitis extending from the ulcer. Moderate level wounds team with complications such as lymphangitic streaking, deep abscess, and cellulitis extending ≥2-cm from the ulcer base. Last, severe diabetic SSTIs present with systemic toxicity or metabolic instability. The IDSA guidelines are one of several tools used as a framework for the focused antibiotic recommendations provided in this review. It is not the intention of this update to minimize the importance of culture and sensitivity data. The intention is only to make the clinician more informed and confident with his or her own future preculture antibiotic recommendations.

ANTIBIOTIC DEFENSE FOR MILD SSTI

Diabetic foot, skin, and soft tissue infections increasingly are a common and costly problem. Pedal infections account for the largest number of diabetes-related hospital inpatient days. Foot infections cause severe morbidity and are the most common cause of pedal nontraumatic amputations. Beginning with uncomplicated or mild SSTIs, Staphylococcus aureus or Group B Streptococci are the most common offending organisms. The dilemma in such patients is whether oral antibiotics are sufficient for tissue penetration or if parental antibiotics via hospital admission are required.

Nevertheless non-limb threatening foot infections can be treated with oral antimicrobial therapy without hospitalization. However, as with parental antibiotics, oral antibiotic therapy for mild infections encourages resistance, incurs financial cost, and may cause drug-related adverse effects. Therefore, a focused approach to prescribing these antibiotics is imperative. Although less active against beta-hemolytic streptococci than staphylococcus aureus, Dicloxacillin (500-mg every six hours) is effective against uncomplicated cellulitis. Clindamycin (300-mg every six hours) is another alternative with effective coverage against beta-hemolytic streptococci and staphylococcus aureus infections. A less expensive approach would be Cephalexin (500-mg every six hours.)

However, a study by Madaras-Kelly et al reported a 27% failure rate of Cephalexin verses comparator antibiotics, thus the regimen is not endorsed per this review.

ANTIBIOTIC DEFENSE FOR MODERATE SSTIs

Frequently, SSTIs present clinically that blur the lines between mild and moderately-complicated. Clinicians must decide if these skin and soft tissue infections require parental antibiotics or if outpatient oral therapy is sufficient. Several inpatient parental regimens afford the clinician the potency of intravenious (IV) antibiotics while remaining focused in coverage. Penicillin G continues to effectively cover streptococcal SSTIs while Naficillin (2 g IV every four hours) is equally affective for staphylococcus

aureus infections. Also Cefazolin (1 to 2 g IV every eight hours) for uncomplicated cellulitis is recommended. More extensive coverage for the moderate level wound or skin and soft tissue infection is provided by Clindamycin (600-mg given IV every eight hours.) Clindamycin is unique in that it suppresses toxin production, thus improving clinical response.

ANTIBIOTIC DEFENSE FOR SEVERE SSTIs

The incidence of complicated or severe skin and soft tissue infections has increased recently as a result of factors such as aging of the general population and increase in the number of critically-ill patients. Virtually all complicated SSTI will require parental antibiotics initially. Definitive therapy of course should be based on both culture results and susceptibility data. The complicated SSTI presents additive challenges of providing extended coverage for gram-negative organisms and or antibiotic resistant pathogens such as methicillin resistant staphylococcus aureus (MRSA).

Currently, flouroquinolones and cephalosporins are among the more frequently-administered antibiotics for treatment of complicated SSTIs. Yet, rising resistance rates have compromised this approach according to a study by Lee et al. The study compared the probability of achieving bactericidal levels for commonly used antibiotics. They concluded that due to increasing resistance rates, third-generation cephalosporins, flouroquinolones, and ertapenem should be avoided for empiric treatment of complicated SSTIs. They found impressive rates of bactericidal capabilities with Cefepime (2 g every 12 hours), Imipenem and Meropenem (500 mg to 1 g every 6 hours) and Zosyn (3.375 g every 6 hours) in the absence of MRSA. Cefepime performed optimally against E. coli, enterobacter, klebsiella, and MSSA. Imipenem and Meropenem were the only antibiotics attaining at least 90% CFR (cumulative fraction of response) against all bacterial populations. Ertapenem was competitive with the other carbapenems against all pathogens except p.aeruginosa, which had a CFR of 28.5%. Piperacillin-Tazobactam regimens were effective against s. aureus, e.coli, and klebsiella. As an aside, with all populations including p. aeruginosa, the 3.375 g every 6 hour regimen reached higher CFR values than the 4.5 g every 8 hours regimen.

Methicillin was introduced to the market in 1959. By the early 1960s MRSA infections were presenting. MRSA is defined as s. aureus with a MIC to oxacillin ≥4 microgram/ml. MRSA infections are defined as either hospital- or community-acquired. Hospital-acquired MRSA is identified when there is a history of hospitalization, a history of surgery, residence in a long term care facility within one year of MRSA diagnosis, previous history of MRSA, and patients that acquired a positive culture after 48 hours of hospital admission. Cases not associated with the aforementioned findings are classified as community-acquired.

Vancomycin remains the first line antibiotic for most institutions for treatment of MRSA infections. However, the reliance on Vancomycin as the go-to drug has led to the emergence of Vancomycin resistant strains of s. aureus. Clinical investigation of this problem has led to the development of new therapeutic options for methicillin-resistant complicated SSTIs. Linezolid is a compound that exhibits inhibitory activity against a broad range of gram-positive bacteria including but not limited to MRSA. In a phase III trial Stevens et al compared Vancomycin and Linezolid and found that Linezolid was comparable with Vancomycin in the treatment of SSTIs caused by MRSA. Also it was found that the length of hospital stay was 5 days shorter for the Linezolid group than the Vancomycin group.

In addition, a study by Li et al focusing on length of hospital stay found that when compared with Vancomycin, Linezolid can significantly reduce the length of hospital stay of patients with complex SSTIs secondary to MRSA. The recommended treatment regimen is 600 mg IV/PO every 12 hours.

In 2003 Daptomycin was approved by the Food and Drug Administration (FDA) for treatment of SSTIs. Daptomycin exerts its bactericidal effect through the depolarization of the bacterial cell membrane. This mode of action is unique thus making cross-resistance between Daptomycin and other antibiotics classes unlikely. In a prospective, randomized study of 517 patients, success rates were comparable for Daptomycin compared with Vancomycin. Recommended therapy is 4 mg/kg q 24 hours.

Quinupristin/Dalfopristin is a semisynthetic combination antibiotic. The drug possesses a broad gram-positive spectrum of activity including MRSA. Although bactericidal against most gram-positive species, the activity against MRSA strains is bacteriostatic. Nevertheless Quinupristin/Dalfopristin (7.5 mg/kg every 12 hours) is considered a treatment option for SSTIs complicated by MRSA in patients failing alternative therapy. Notably Linezolid, Daptomycin, and Quinupristin/Dalfopristin have coverage against Vancomycin resistant s. aureus.

Tigecycline is a new drug receiving FDA approval for complicated SSTIs. Grosse et al compared Tigecycline with Vancomycin/Aztreonam and found no significant difference in the clinical cure rates (86.5 versus 88.6%, respectively).

Investigation drugs on the horizon for treatment of MRSA infections to note include Lysostaphin, Telavancin,

Oritavancin, and Dalvabancin. Lysostaphin is a peptidase that disrupts glycine-glycine bonds in the staphylococcal cell wall. Telavancin inhibits transglycosylase activity and is a highly bactericidal antibiotic. Oritavancin, a semisynthetic glycopeptide has a similar mechanism of action as Telavancin. Oritavancin has a spectrum of activity similar to Vancomycin, and exhibits potent activity against Vancomycin resistant s. aureus. Dalvabancin is a semisynthetic glycopeptide active against a wide variety of gram positive bacteria. MIC results of Dalvabancin are lower than several comparable MRSA antibiotics such as Linezolid and Vancomycin. Dalvabancin also is more rapidly bactericidal than Vancomycin. Long half-life and once weekly dosing are additional advantages to its already imposing efficacy.

ANTIBIOTIC DEFENSE FOLLOWING WATER EXPOSURE

Skin and soft tissue infections often arise from the diabetic insensate foot as previously discussed. Nevertheless, a complete history and physical is imperative because SSTIs may result from sources other than diabetes. Trauma leading to soft tissue infection may be caused by objects, living or inanimate, in an aquatic environment. Microorganisms most closely associated with water-born infection include Aeromonas, Vibrio vulnificus, Edwardsiella tarda, Erysipelothrix rhusiopathiae, and Mycobacterium marinum. The acronym AVEEM will be used to associate the organisms.

As with most SSTIs culture and sensitivity data is optimal. In the absence of culture and sensitivity data, coverage should be directed at the most likely organisms. It is recommended that coverage be directed towards staphylococcus, beta-hemolytic streptococci and the AVEEM organism. Therefore, gram-positive coverage plus Metronidazole (500-mg every 6 hours) is suggested if exposed to sewage-contaminated water. If exposed to sea water when the SSTI occurred add Doxycycline (100-mg every12 hours) for activity against Vibrio. Most isolates of Edwarsiella tarda are susceptible to Aminoglycosides, Flouroquinolones, and Bactrim. A number of different regimens have been used for Mycobacterium marinum. Bactrim dosed at 160-mg/800-mg every 12 hours or Minocycline 100-mg every 12 hours orally is an effective regimen. Also combination therapy with Rifampin (600-mg) plus Ethambutol (15 mg/kg daily) is recommended.

Aeromonas infections have been isolated from various aquatic environments such as fresh water or polluted waters. Aeromonas isolates are often resistant to Penicillin, Ampicillin, Ticarcillin, and are susceptible to third-generation cephalosporins, aminoglycosides, and the flouroquinolones. Lastly, in vitro Imipenem and PCN are the most active antibiotics against Erysipelotrix.

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