CLINICAL MANAGEMENT extra

Systemic Antibiotic Treatment of Skin, Skin Structure, and Soft Tissue Infections in the Outpatient Setting

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This continuing educational activity will expire for physicians on March 31, 2013.

PURPOSE:

To enhance the learner's competence with knowledge of systemic antibiotic treatment of skin, skin structure, and soft tissue infections in the outpatient setting.

TARGET AUDIENCE:

This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

OBJECTIVES:

After participating in this educational activity, the participant should be better able to:

1. Use information about skin and soft tissue infection pathogens to appropriately identify infections.

2. Apply recommended infection treatment modalities to patient care.

ABSTRACT

The unnecessary use of systemic antimicrobial agents can be reduced with more careful consideration when treating patients with skin, skin structure, and deep soft tissue infections. Improved prescribing habits will reduce potential adverse events for patients and help fight against the development of multidrug-resistant bacteria especially in the era of methicillin-resistant *Staphylococcus aureus*.

KEYWORDS: intravenous antibiotics, oral antibiotics, methicillin-resistant *Staphylococcus aureus*, D-test

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INTRODUCTION

Because of the prevalence and continued emergence of multidrug resistant bacteria (MDRB), it has become imperative for healthcare providers to be more thoughtful in their utilization of systemic antibiotics. Perhaps more than any other specialists, wound care providers are in a unique position to more readily *lessen* the unnecessary use of systemic antibiotic agents in patients we treat for skin or soft tissue infections. In many situations, the use of one of the various topical antimicrobial formulations or specialty antimicrobial dressings available to us should preclude a ''knee-jerk'' reaction of randomly prescribing systemic antibiotic therapy until determining that an oral or intravenous systemic agent is indicated.[1]

Although the goal of healthcare providers is to make patients better, automatically prescribing antibiotics without proper consideration may actually do more harm than good. By the time the author had completed her internal medicine residency, she learned that the quick approach was not necessarily the right decision in most situations. Today, the author first asks not *which*, but rather *should* a systemic antibiotic be prescribed.

Notwithstanding the fact that the number of available useful systemic antibiotic options is limited, the consequences of inappropriate systemic antimicrobial use reach beyond the decision itself. Adverse effects and complications can and do occur when these agents are used and misused. Neuropathies, pancytopenias, gastrointestinal and neurological disturbances, and other soft tissue complications are among the risks associated with many commonly prescribed antibiotic agents.[2] From an epidemiological perspective, bacteria that survive exposure to an antibiotic can develop resistance mechanisms that may be spread to other classes of bacteria, thereby pushing clinicians farther down the road of increasing numbers of MDRB.[3] Therefore, providers must give due diligence to the considerations of the following: (1) Is a systemic antimicrobial agent indicated? (2) What is the most likely pathogen(s) that should be targeted? (3) Which route of delivery and for what length of time should antibiotics be prescribed? (Usually the length of time for intravenous therapy is 3 to 7 days, depending on the patient's response, but it remains a clinical decision.) (4) Do the benefits to the patient outweigh the risks associated with a particular agent?[4] When these points are considered in light of the variables unique to the patient, he/she will likely be successful in completing his/her treatment plan. Consequently, the clinician will help impede the further development of antimicrobial resistance.

This article will help clinicians to better understand the implications of methicillin-resistant *Staphylococcus aureus* (MRSA) and prescribe antimicrobial agents more effectively and with more specificity.

DISCUSSION

When clinicians assess a patient with a localized, well-defined abscess, carbuncle, or furuncle, their first thought should be, ''Is there a reason not to drain this?'' In other words, is it safe to open the area and evacuate it? Although the clinician may not automatically suspect that the lesion could be caused by MRSA, every first-year surgery intern should know that the treatment of an abscess is incision and drainage (I&D). A fact that may not be fully appreciated, however, is that many of the abscesses frequently encountered are due to organisms with the genetic capability to inhibit the patient's white blood cells' function. The end result of this situation is that the germ prevents the host's immune system from forming pus within the abscess.[5]

Because of this, patients commonly undergo an unintentionally inadequate initial I&D. The hallmark finding of this kind of abscess will be the absence of a purulent explosion upon scalpel penetration through the skin. Mistakenly, the clinician may assume that the abscess has not matured. When this situation occurs, a more extensive local procedure is indicated and should be completed before considering whether or not to add systemic antibiotic therapy. Failure to completely evacuate the affected tissue can lead to unintentional adverse outcomes for the patient.

Methicillin-resistant *S aureus* is responsible for about 68% to 70% of all skin infections in the United States. Based on population estimates in 2010, according to the Centers for Disease Control and Prevention (CDC), this equals approximately 94,360 cases that progressed to *invasive* MRSA infections. In addition, according to the CDC, MRSA was associated with 18,650 deaths.[6] Determining who is at risk for progression of disease is not without limitations as MRSA typically follows a 30%/30%/30% rule in regard to colonization

only/colonization and disease/evidence of disease only, in respect to the aforementioned percentages.[7] Invasive disease due to MRSA can include endocarditis, necrotizing pneumonia, and disseminated invasive osteomyelitis.[8] The Infectious Diseases Society of America (IDSA) has also recently added MRSA infection to its list of sexually transmitted diseases.[9] Further classification of MRSA infections is based on its overall sensitivity patterns. Generally, community-acquired MRSA (CA-MRSA) refers to a MRSA infection that demonstrates preserved sensitivities to antibiotic classes other than those administered intravenously.[4] Methicillin-resistant *S aureus* infections that are resistant to almost every oral option available and are sensitive only to those delivered intravenously are noted to be hospital acquired.[3]

Several conditions have a strong association (odds ratio [OR]) with MRSA infection and therefore should lower the threshold of consideration of MRSA as a pathogen.[7] These conditions include patients having had any antibiotics within the last month (OR, 2.4); history of an abscess (OR, 1.8); reported spider bite (OR, 2.8); history of MRSA infection (OR, 3.3); close contact with another person with MRSA (OR, 3.4); snorting or smoking illicit drugs (OR, 2.9); and incarceration within the last 12 months (OR, 2.8).[10]

Ideally, antibiotic prescriptions should be dispensed with a specific microbial target in mind and based on a culture and sensitivity profile. However, in reality, that often is not practical—because of not only cost consideration, but also the fact that even 1 dose of systemic therapy can make culture results falsely negative. Furthermore, most importantly, if the clinician waits for a completed culture report to prescribe therapy or not, that could postpone for 48 hours the prescribing of what could be a lifesaving antibiotic. Because of this window of time, the clinician may utilize the information obtained from a Gram stain, thereby guiding one's decision regarding antibiotic use without too much delay. Most on-site laboratories can provide this information in only a few minutes. Keep in mind that not all laboratories automatically perform Gram staining from received culture samples, so it is important to order one. Notwithstanding the subjective nature of Gram staining and the fact that it reflects a snapshot of 1 point in time, it may offer information that allows the clinician to intervene earlier on the patient's behalf. This should always be done if the clinician is especially suspecting MRSA as a pathogen, due to factors other than the patient's clinical presentation. Of the usual skin pathogens, gram-positive cocci (GPCs) can be only *Staphylococcus* or *Streptococcus* species. The former usually appear in clusters; the latter in chains. Gram-positive cocci in clusters may be MRSA, methicillin-sensitive *S aureus* (MSSA), or one of many other *Staphylococcus* species collectively referred to as ''staph epis,'' which also can be methicillin-susceptible *Staphylococcus epidermidis* (MSSE) or methicillin-resistant *S epidermidis* (MRSE).[3]

Knowing early on whether a Gram stain is positive for GPCs in clusters allows the clinician to make decisions that may preclude other subsequent unnecessary events, such as hospital admission or progression to an even more serious infection. For example, after undergoing an I&D, a patient calls to report new or progressing symptoms that may alert the clinician to the progression of what was initially observed as a localized process. A positive Gram stain may help clinicians decide to add empiric MRSA-targeted systemic therapy or make other changes to the patient's plan of care. Thus, although a negative Gram stain report could be falsely misleading and not particularly helpful from a clinical decision-making standpoint, a report that shows the presence of GPCs in clusters that was from a culture obtained from an adequately evacuated site can be very helpful. At a minimum, it indicates that there were still organisms present in the source of the culture. If empiric systemic therapy was added, de-escalation or stopping therapy can proceed after the sensitivity report is finalized. Or, if no growth is reported on the final culture, following a positive Gram stain, the clinician's judgment and the patient's status can guide the decision regarding whether additional therapy is needed. This situation can occur, not uncommonly, when there are insufficient numbers of bacteria present on the culture swab to sustain growth of a colony to the threshold of 10^5 organisms once it was transferred to the agar plate.[3]

If the number of organisms to support growth of a colony on an agar plate is sufficient, the final report (antibiogram) will provide the clinician with the relative effectiveness of a panel of antibiotics against the organism. If the antibiogram provided by the laboratory lists only ''S'' or ''R'' (sensitive or resistant, respectively), it is imperative to call the laboratory and request the specific minimal inhibitory concentration (MIC) for the drug therapy that is being considered. This information will be available, but sometimes not automatically provided on the report that the provider receives.

Deciding which systemic antimicrobial agent to prescribe is more straightforward than the determination of whether to prescribe one. This is true for a number of reasons. First, there are only a few classes of antibiotics that are useful and practical in the outpatient setting. Second, depending on the patient's medication allergies, the clinician may have even fewer options from which to choose.

As long as the patient is not systemically ill, does not have other comorbidities that would support adding empiric systemic antimicrobials, is able to notify the clinician of any deterioration

or progression to a more serious illness, and has had an appropriate I&D if needed, then a primary antimicrobial dressing should provide sufficient local antibiotic therapy.[11]

PATIENT SELECTION

At the risk of being redundant, when deciding about empiric systemic antibiotic therapy, the decision of what to prescribe should be based on the patient's risk of having MRSA, the MRSA sensitivity patterns in the patient's community, and variables unique to the patient. Most importantly, the established treatment plan should be one that is based on factors unique to the patient and one to which the patient will be able to adhere. For example, can the patient afford his/her portion of the expense after insurance benefits, or has he/she exhausted such benefits, or not met his/her potentially exorbitant deductible for pharmaceuticals? Or, will the patient be able to take the drug on an empty stomach? And, finally, is the patient taking any other medications that would contraindicate taking the prescribed therapy?

Despite these conditions, clinicians still may not be completely sure whether to empirically prescribe systemic antibiotics. Hence, reconsideration of the following may be helpful: A patient's request for an antibiotic is not a sufficient reason to prescribe one. What is the clinician seeing, feeling, or smelling that suggests the need for an antibiotic? Is what the clinician is seeing, feeling, or smelling congruent with what the patient is reporting or hoping that the clinician will or will not see? Has the patient been previously treated with antibiotics for the same condition, yet not had an adequate I&D? Does the patient physically appear ill? Are the patient's vital signs within reference ranges? Is the patient hypotensive, slightly tachycardic, or slightly febrile? Does the patient have any comorbidities that cause him/her to be otherwise immunosuppressed and therefore mask the usual signs of illness? Are there subtle findings that suggest other health issues need to be further explored?

Both intravenous and oral systemic antibiotics can have complicated dosing schedules, but some agents have daily or twice-daily dosing regimens that may improve patient adherence. In certain circumstances, hospital-based outpatient antimicrobial infusion clinics can provide improved patient outcomes through increased adherence and fewer unnecessary inpatient admissions.[12] Such a program can also have positive effects on a hospital system's revenue cycle management through favorable cost/reimbursement profiles.[13]

ANTIMICROBIAL AGENT OPTIONS

The following section is a nonexhaustive, but focused, review of oral and intravenous systemic antimicrobial agents that have favorable dosing regimens and are useful when treating skin and soft tissue infections in the outpatient setting (Table 1).

β-lactams

Antibiotics that belong to this class are further divided into the cephalosporin and penicillin families. They all contain a unique chemical foundational structure called the β-lactam ring through which they exert their mechanisms of action. β-lactams are bactericidal and are frequently utilized in the management of skin and skin structure infections. They are noteworthy for their in vitro activity against non-MRSA strains of many staphylococci and streptococci species. Several oral β-lactam antibiotics are specifically recommended by the IDSA for skin and soft tissue infections.[9] These include, but are not limited to, dicloxacillin, cephalexin, and amoxicillin. The latter is technically an aminopenicillin and can be prescribed alone or in combination with a β-lactamase inhibitor (clavulanate). Clavulanate provides additional coverage against Gram-positive, Gram-negative, and select anaerobic organisms that produce the β-lactamase enzyme that causes resistance to amoxicillin alone. Amoxicillin's major role is in the treatment of β-hemolytic streptococcus, not an uncommon cause of skin and soft tissue infections. However, amoxicillin, or any other oral β-lactam antibiotic, should never be used for the treatment of any *Staphylococci* species found to be methicillin resistant. This is because that resistance includes any antibiotics that contain the β-lactam ring as its structural core.

In the situation when empiric therapy was begun against MRSA and the causative organism has been confirmed to be a methicillin-sensitive organism, de-escalation of treatment to an antistaphylococcal β-lactam is considered the standard of care and should be made, barring any patient allergies that would otherwise preclude a change in therapy.[2] The recommended adult dose of amoxicillin-clavulanate is 500 mg orally (PO) 3 times a day (TID) or 875 mg twice a day (BID) taken with food.[7] An adjustment in dose is required for renal dysfunction. The most common adverse effects are gastrointestinal. Diarrhea can occur with amoxicillin alone but is

Table 1.
ORAL SYSTEMIC ANTIMICROBIAL AGENT CLASSES

β-lactams
Sulfa-based
Lincosamides
Quinolones
Tetracyclines
Oxazolidinones

substantially increased with the addition of clavulanate. Dicloxacillin is an oral penicillin that does not require dose adjustment for renal insufficiency, and like augmentin, diarrhea is a common adverse effect. It is important to be reminded of the fact that oral penicillins often have erratic to poor absorption, and are *not* effective for any methicillin-resistant organisms. It is usually dosed as an every-6-hour oral therapy with a dose range of 125 to 500 mg per dose.[7]

Cephalexin is a first-generation cephalosporin that has excellent activity against β-hemolytic streptococci and methicillin-sensitive *Staphylococcus* species. The recommended adult dose is 500 mg PO 4 times a day (QID) and does require adjustment of the dose in patients who have renal dysfunction.[7] Cephalexin may be a good option for patients allergic to penicillins, although should not be used in patients with a history of life-threatening allergy because there is a potential for cross-reactivity.[9] Adverse effects are similar to penicillins and include gastrointestinal distress, such as diarrhea and pseudomembranous colitis. Of the third-generation oral cephalosporins, cefpodoxime is the only one with good activity against methicillin-sensitive staphylococci. It is usually dosed as 400 mg BID for 7 to 14 days in patients with normal renal function.[7]

If cost is not prohibitive, antibiotics that are taken once or twice daily may promote increased patient adherence. However, if patients can adhere to a plan of care that involves taking a medication every 6 hours, there should be no difference in efficacy.

Sulfonamide-Folate Antagonist

Trimethoprim and sulfamethoxazole independently are antimicrobial agents, each with bacteriostatic properties. In combination, they become bactericidal. Trimethoprim-sulfamethoxazole (TMP-SMX) has excellent activity against CA-MRSA but offers no coverage for β-hemolytic streptococci, which are also causes of skin or wound infections.[2] Trimethoprim-sulfamethoxazole is an ideal bridge to oral therapy from intravenous or intramuscular ceftriaxone because the spectrum of coverage is equivalent. Dosing is based on the trimethoprim component (80 or 160 mg), and available dosages are single strength or double strength (80 mg/400 mg or 160 mg/800 mg, respectively). Trimethoprim-sulfamethoxazole has a very wide dosing range from 1 single-strength tablet daily to 2 double-strength tablets TID. Dosage should be based on the patient's renal function and the microbial target. Patients who are allergic to TMP-SMX usually are allergic to the sulfamethoxazole component; therefore, trimethoprim alone may be an option for your patient.[9]

Of all the oral antibiotics most commonly used in the outpatient setting, a frequent adverse effect of skin rash has been reported with TMP-SMX use. Although rare, a much more serious, life-threatening complication involving the skin is toxic epidermal necrolysis or Stevens-Johnson syndrome, which has also been associated with TMP-SMX. This may begin as small blisters that can form anywhere. Squamous cell epithelium is found. Other more serious adverse effects of TMP-SMX include: bone marrow suppression resulting in anemia, neutropenia, thrombocytopenia, and agranulocytosis. This is due to the fact that its mechanism of microbial cell kill is also affected onto the host's cells, thereby preventing maturation of normal cell lines. The degree to which this occurs is directly proportional to the dose used. Other significant adverse effects include hyperkalemia, particularly if the patient is on a spironolactone or an angiotensin-converting enzyme inhibitor, and increased activity of various other drugs, such as oral sulfonylureas, warfarin, and phenytoin. Rifampin decreases the levels of TMP-SMX.[7]

Patients should also be warned about enhanced risk of photosensitivity and possible development of an impressive drug fever.[7] A fact that is not widely appreciated is that some men of African or Indian descent can have a deficiency of the enzyme G6PD (glucose-phosphate-dehydrogenase). In G6PD-deficient patients, depending on their level of deficiency, a hemolytic anemia can develop under the pressure of TMP-SMX, which can become quite significant.[9] The anemia corrects with cessation of the drug. Therefore, weekly to biweekly complete blood count with differential and a basic metabolic panel should be obtained during the patient's therapy with TMP-SMX.

Lincosamide

The most commonly used agent in this class is clindamycin, which is a bactericidal agent with intracellular activity. It binds to the 50S ribosomal subunit and causes early protein chain termination, thereby causing interruption of the bacteria's replication processes.[3] One of the most important facts to know with regard to dosing is that this drug does *not* have equivalent dosing by intravenous and oral routes. Typically, intravenous doses can range from 600 to 900 mg every 6 to 8 hours. Oral dosages range from 150 to 450 mg every 6 to 8 hours.[2]

As with any oral antibiotic, development of diarrhea due to *Clostridium difficile* colitis is a real possibility. The author tries to use a different agent if an antibiogram confirms other options. When clindamycin is prescribed, the author recommends doing so at lower dosages and for shorter periods, especially in older adults. A unique favorable characteristic of clindamycin is its antitoxin property, which can be very beneficial in severe cases of cellulitis because of a toxin-producing *Staphylococcus* or

Streptococcus species.[4] In this clinical situation, the patient's skin may appear particularly involved and exhibit a fire-engine red discoloration and feel hot and edematous. In this situation, the author suggests adding 48 hours of clindamycin to the patient's primary oral or intravenous antibiotic. As soon as the toxin is neutralized, the erythema resolves very rapidly and allows better determination of the patient's response to the primary therapy.

A laboratory test related to clindamycin is known as a D-test. It is usually performed on isolates of MRSA that have been reported as erythromycin (EES) resistant and clindamycin sensitive. Results of the D-test are either positive or negative.[10] *S aureus* isolates which are resistant to erythromycin (EES), may harbor a gene that portends resistance to clindamycin despite the isolate being reported as sensitive to clindamycin. A positive D-test confirms the presence of this hidden genetic resistance potential and warns the provider not to use clindamycin against a particular isolate. Exposure of the isolate to clindamycin in this case will cause the resistance to be unmasked and the patient will be ineffectively treated if using clindamycin.[8] For example, an antibiogram report shows that MRSA is EES resistant and clindamycin sensitive, and the D-test is positive. This means that for the identified isolate, clindamycin resistance *will* develop under the pressure of clindamycin use. Therefore, some other appropriate antibiotic must be chosen if the patient requires antimicrobial therapy. A D-test that is negative for an organism that has EES resistance and clindamycin sensitivity tells the provider that the organism does not carry the unmasked gene for clindamycin resistance. Therefore, using clindamycin would be an effective option based on sensitivities alone.

Lastly, although clindamycin offers great anaerobic coverage, it misses about 15% of non-*aureus Staphylococcus* species. Hence, closer follow-up may be warranted, and a change of therapy may be indicated in patients who do not turn around within 48 hours of initiation of therapy.

Quinolones

Ciprofloxacin, levofloxacin, and moxifloxacin are well-known members of this class of antibiotics. Although these drugs have favorable outpatient dosing intervals, these are not Gram-positive drugs. Therefore, these *should not* be routinely prescribed for common skin, skin structure, or soft tissue infections unless patient allergies restrict therapy choices, or in the rare case of when a Gram-negative organism is found by culture to be the pathogenic target.[4]

The widespread misuse of the quinolones as a whole has led to significantly increased resistance and loss of efficacy to this class against numerous Gram-positive and Gram-negative organisms. Risks associated with their use include alterations of mental status in older adults, lowered seizure threshold, QT-interval prolongation, worsened photosensitivity, and development of Achilles tendon rupture. Unintentional patient nonadherence frequently occurs, as well, because of inappropriate dosing routine.

Tetracyclines

Tetracyclines that are effective in treating skin and skin structure infections include doxycycline and minocycline. They are considered bacteriostatic antibiotics because of their mechanism of action, which involves slowing bacterial protein synthesis.[7] Doxycycline and minocycline both have activity against CA-MRSA, thus like clindamycin and TMP-SMX, they are an effective treatment for skin and soft tissue infections due to CA-MRSA.[2] The recommended usual adult dose for doxycycline and minocycline is 100 mg PO BID, but it has a much larger range, up to 500 mg QID in some cases. Both agents are recommended in the IDSA MRSA guidelines for treatment of skin and soft tissue infections in the outpatient setting.[12] Tetracyclines are not recommended in patients younger than 8 years because of the potential for decreased bone growth and tooth enamel discoloration. In addition, tetracyclines are pregnancy category D. Other important adverse effects to note include photosensitivity, gastrointestinal upset, and, rarely, Stevens-Johnson syndrome. Key patient counseling points include instructions to use sunscreen when outdoors and to avoid milk, dairy, or divalent cation containing vitamin supplements within 2 hours of administration.[7]

Although not as widely used, minocycline is superior to other tetracyclines in its reliability to fight against MRSA/MSSA. Minocycline is one of only a few oral agents that have efficacy against vancomycin-resistant *Enterococcus* (VRE).[4]

Oxazolidinone

Linezolid is the only member of this class and is the newest of the aforementioned oral agents to treat skin and skin structure infections. Also a bacteriostatic antibiotic, linezolid interrupts protein synthesis. Like clindamycin, linezolid has some in vitro data on staphylococcal toxin inhibition. Linezolid has activity against not only CA-MRSA, but also nosocomial strains of MRSA, vancomycin-insensitive *S aureus*, and vancomycin-resistant *S aureus*. In addition, linezolid has activity against β-hemolytic streptococci. Thus, it is an appropriate agent for the treatment of nonpurulent cellulitis.[2] The recommended adult dose for both intravenous and oral administration is 600 mg every 12 hours, as linezolid is 100% bioavailable. Because linezolid is still a branded product, therapy with this drug is more expensive compared with

alternative oral agents. The IDSA MRSA guidelines recommend linezolid for the treatment of both skin and soft tissue infections and osteomyelitis.[10] Dosage adjustment is not warranted in renal impairment other than to administer the drug after hemodialysis. Because linezolid has weak monoamine oxidase inhibitor (MAOI) properties, it is contraindicated to administer it with MAOIs, selective serotonin reuptake inhibitors, tricyclic antidepressants, meperidine, triptans, and buspirone because of the risk of serotonin syndrome. In addition, linezolid should not be administered with sympathomimetic agents unless the patient's blood pressure is monitored.

Adverse effects include rash, gastrointestinal upset, and headache. More serious adverse effects include myelosuppression, peripheral neuropathy, blindness, and lactic acidosis. (Refer to the manufacturer's patient information insert.) These adverse effects may be long term or irreversible and are more likely to occur with treatment longer than 2 weeks; therefore, patients should be routinely monitored, especially if drug therapy lasts longer than 7 to 10 days. Many insurance plans require preauthorization, and copays may be cost-prohibitive for the patient.

Intravenous Systemic Antimicrobial Outpatient Therapy

Patient selection for outpatient antibiotic infusion therapy depends on insurance coverage, social issues, and patient support system. However, the main factor that portends success of systemic intravenous therapy in the outpatient setting is the frequency of administration. Although a single, once-daily dosing regimen is preferred over one that requires multiple dosing times in 1 day, an antibiotic that is dosed multiple times a day is acceptable if it can be delivered through a device which, once connected to a PICC or peripheral Hep-Lock, delivers subsequent doses at the appropriate intervals for the dosing cycle of that antibiotic.[12]

Ertapenem

Ertapenem is a member of the carbapenem group of the larger β-lactam class of antibiotics (along with cephalosporins and penicillins). Carbapenems are administered only intravenously and offer increased coverage against Gram-negative pathogens, as compared with other β-lactams. Members of this class include imipenem, meropenem, and doripenem. Ertapenem is the only member of this class that is given once daily. Of the carbapenems, ertapenem is an ideal choice for outpatient use because it can be administered over 30 minutes and does not require a central line. Ertapenem has activity against Gram-positive, Gram-negative, and anaerobic pathogens. Notable Gram-positive coverage includes streptococci and MSSA. Gram-negative coverage is not useful against Gram-negative organisms that produce extended-spectrum β-lactamase resistance. Ertapenem has excellent *anaerobic* coverage against *Bacteroides fragilis*. However, it has *no* coverage for MRSA or some Gram-negative pathogens (*Pseudomonas aeruginosa* and *Acinetobacter baumannii*). Ertapenem is ideal for mixed-type infections and is the drug of choice for diabetic foot infection empiric therapy.[2] If MRSA coverage is desired, another agent should be added to adequately cover this pathogen. Contraindications to the use of ertapenem include anaphylactic reaction to β-lactam antibiotics because of cross-reactivity within the class. Another precaution includes coadministration with valproic acid or its derivatives. Carbapenems can decrease drug levels and potentially increase the risk for seizures. A rare but serious adverse effect of ertapenem and the carbapenem class is seizures; therefore, caution should be exercised when using ertapenem in patients with a predisposed risk of seizures. Other adverse effects include injection-site reactions and gastrointestinal upset, most notably diarrhea. The recommended adult dose is 1 g intravenously daily and should be decreased to 500 mg intravenously daily for patients with renal dysfunction (creatinine clearance [CrCl] <30 mL/min) to avoid supratherapeutic drug levels.

Glycopeptides

Vancomycin is the only glycopeptide used in the United States. For nearly 40 years, vancomycin has generally been considered the criterion standard for the treatment of MRSA infections.[9] Lately, however, its efficacy is questionable with the emergence of a microbiologic event referred to as ''heteroresistance,'' which involves clones of bacteria within a colony that are less sensitive to vancomycin than others within the colony. This can slow the bactericidal effect of vancomycin.[3] Typically, vancomycin has activity against Gram-positive pathogens, such as *Streptococcus*, *Staphylococcus* (including MRSA), and *Enterococcus* (excluding VRE), which are commonly involved in skin and soft tissue infections. Nevertheless, compared with β-lactams, vancomycin has inferior activity against MSSA.[10] Therefore, when a methicillin-sensitive organism is identified as a pathogen, therapy should be switched to a β-lactam agent if there are no other contraindications.[12] According to the American Society of Health-System Pharmacists, IDSA, and the Society of Infectious Disease Pharmacists, the recommended adult dose ranges from 15 to 20 mg/kg per day (actual body weight) every 8 to 12 hours, not to exceed 2 g per dose. In all cases, trough levels should be equal to or greater than 10 μg/mL to prevent the emergence of resistance. Per the guidelines, most patients

with skin and skin structure infections who are not obese and have adequate renal function should achieve adequate drug exposure with 1 g administered intravenously every 12 hours. Trough monitoring should be initiated for all other patient types, including patients with severe infections. If osteomyelitis is involved, the goal trough should be between 15 and 20 μg/mL. Trough concentrations should be obtained at a steady state, which is prior to the fourth or fifth dose, and doses should be adjusted accordingly. Because monitoring of serum drug levels is necessary in many cases, as well as the potential for dosing 2 to 3 times daily, vancomycin may not be the ideal antimicrobial for the outpatient setting.[12] Although the nephrotoxicity risk of vancomycin has been low historically, recent cases have demonstrated an increased risk. With these findings, trough levels should be monitored not only for efficacy, but also for toxicity in addition to renal function on at least a weekly basis. In addition, vancomycin should be administered via a PICC line as it is technically a vesicant and can cause severe subcutaneous injury.

Cephalosporins

Cephalosporins, as noted earlier, are a type of β-lactam because of their core chemical structure. There are several drugs in this class that may be used as the preferred therapy for methicillin-sensitive *Staphylococcus* species. In contrast, these agents are not effective for methicillin-resistant organisms. They do have a risk of cross-reactivity with penicillin-allergic patients and are easily changed from intravenous to oral therapies. They do not all have the same dosing intervals, but those with longer dosing intervals are ideal for use in the home or outpatient setting. Ceftriaxone is a frequently used, once-daily drug. Its dose range is 1 to 2 g intravenous piggyback daily, and it requires renal dosing adjustment for patients with altered renal function. Ceftriaxone can be given via peripheral Hep-Lock over a 30-minute period or administered intramuscularly in divided doses. As a third-generation cephalosporin, it offers extended Gram-negative coverage.

Synthetic Vancomycin Derivative (Lipoglycopeptide)

Televancin is not available as an oral antibiotic and is dosed at 10 mg/kg per day and is administered over 1 hour. Televancin requires dose reduction for renal insufficiency, can cause disturbances in taste and QTc interval prolongation, and is also related to red man syndrome. Because of the QT interval prolongation, it should be avoided in anyone taking medications known to likewise prolong the QT interval; examples include clarithromycin and moxifloxacin. Most problematic are the animal data that suggest an association with fetal harm. Serum pregnancy tests are recommended prior to the first dose when prescribing for any childbearing-age woman.

Lipopeptides

Daptomycin is a cyclic lipopeptide that is Food and Drug Administration approved for the treatment of complicated skin and skin structure infections. Daptomycin has coverage against predominant Gram-positive pathogens such as MRSA, MSSA, *Streptococcus*, and *Enterococcus* (including VRE). Because of its unique mechanism of action that disrupts the bacterial cell membrane, daptomycin is rapidly bactericidal but does not result in cell lysis (see manufacturer's package insert). The recommended adult dose of daptomycin is 4 to 6 mg/kg (actual body weight) intravenously once daily for skin and soft tissue infections. In addition, daptomycin requires dosage adjustment in renal dysfunction (CrCl <30 mL/min); the same dosage is recommended every 48 hours. Because it is dosed once daily or less often in patients who have renal insufficiency, it can be given over a 2-minute intravenous push via a Hep-Lock rather than a central line. It is an ideal antibiotic to be given in the outpatient setting. Development of resistance to daptomycin has been reported and associated with widely invasive infections and prior use of vancomycin.

Common adverse effects of daptomycin include gastrointestinal upset and creatine phosphokinase (CPK) elevations. Because of the potential risk of rhabdomyolysis, patients should be observed for symptoms of muscle pain or weakness and have their CPK drawn at baseline and weekly. Caution is advised for patients concomitantly on statin drugs because the combination could increase this risk.

SUMMARY

When treating skin and soft tissue infections, it is important to remember that antibiotics only treat infections due to bacteria. Therefore, be sure to consider other infectious etiologies prior to automatically prescribing an antibiotic. Once the decision to prescribe an antibiotic has been made, the selection of which agent to use should be indivdualized to enhance outcomes and patient adherence. Frequent monitoring of the patient's response to therapy is ideal as there may be an opportunity to stop therapy earlier than planned based on the patient's resolution of infection. In addition, if a change in therapy is needed due to inappropriate response, this can be addressed in a more timely fashion. Implementing these thought processes will lessen inappropriate antibiotic use and help preserve the efficacy of the limited antibiotic choices currently available.

PRACTICE PEARLS

- A patient's request is not a valid reason for antimicrobial prescribing.
- Because MRSA and MRSE are common causes of skin and soft tissue infections, broad initial therapy may be better for the patient. De-escalation of therapy is more easily done than escalation of therapy in progressing infections.
- The treatment of an abscess is always drainage; systemic antibiotics may or may not be indicated as additional therapy.
- Topical antimicrobial agents are available for open infected wounds and provide 100% drug delivery at the target site, which prevents patients' exposure to systemic adverse effects of oral or parenteral antibiotics.
- Unnecessary antibiotic prescribing leads to development of multidrug-resistant bacteria.
- Become familiar with the resistance patterns in your practice community.
- Quinolones
  - Are not indicated for the treatment of skin infections due to Gram-positive bacteria
  - Do cause tendon rupture
  - Do have an untoward effect with many cardiac drugs
- When prescribing linezolid, monitor blood counts and be aware of the potential for development of peripheral neuropathy, which is irreversible.

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