CHAPTER 16

Common Antibiotics, Allergies, and Alternatives

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INTRODUCTION

An allergy is simply an unpleasant hypersensitivity of the immune system. Most allergies are benign and can be contained when detected early; however, a few could be debilitating and may even lead to death. Most common causes of allergic reactions include food, latex, pollen, dust, insect stings, and most importantly medications. Certain medications are well known to cause allergies such as antibiotics, anticoagulants, opioids, and diabetic agents (1). Approximately 4 per 1,000 emergency department visits in 2013-2014 were for adverse drug reactions, of which approximately 27.3% resulted in hospitalization (1). Another study reviewing International Classification of Disease, 9th edition, Clinical Modification codes during a 6 year period for identification of allergic drug reactions found 27% of the emergency department visits were for allergic drug reactions (2).

Hives and rash after taking a particular medication are common symptoms of an allergy. However, the most life-threatening condition of any allergy is called anaphylaxis shock, which affects multiple body organs (2). Epinephrine is the first line treatment for an anaphylaxis reaction (3). It is important for the podiatric physician to realize that a true allergy occurs when the immune system recognizes a harmless substance as a foreign body, thereby triggering an immune response (4). A common immune reaction is the production of immunoglobulin E (IgE) that is specific to the particular drug called an allergen (3). The onset and symptoms of a drug allergy can be divided into 2 categories: Immediate reaction (from seconds to hours), which is IgE mediated, and delayed response (from hours to days or weeks), which is T cell dependent (4).

PENICILLIN/BETA-LACTAMASE

Arguably the most common drug allergy is penicillin (5). Penicillin and its derivatives are commonly the first line drugs for common bacterial infection, and surgical prophylaxis. They are also very affordable. All the drugs in the penicillin family contain the compound beta-lactamase, which is a known culprit for true penicillin allergy (5). Beta-lactam antibiotics include penicillins, cephalosporins, carbepenems, and monobactams (6). Beta-lactam is a cyclic amide with a 4-membered ring that inhibits cell wall synthesis in bacteria. It is very difficult for physicians to determine ahead of time which patients will develop an allergic reaction to beta-lactamase. An allergic reaction can happen within seconds or minutes of taking a medication although some may take hours, days or even weeks (6). It is a bigger challenge to determine the source of allergy when a reaction develops after completing the dose of medications or when the patient is taking multiple medications at once. Many people in the health care field will argue that a true penicillin allergy is rare. Hives, rash, and anaphylaxis are common allergic reactions to penicillin (5). Patients with a penicillin allergy are routinely not prescribed any medication in the beta-lactamase family. This is unfortunate because beta-lactamase penicillins and cephalosporins have excellent coverage against many penicillin sensitive organisms (7). Physicians tend to avoid cephalosporins in patients with penicillin allergy even though the cross-reactivity between cephalosporins and penicillin is low (8,9). It is even lower between carbapenems and penicillins (10). It is not uncommon to hear a patient say they had an allergic reaction as a child without knowing the exact reaction. The old adage “better safe than sorry” applies here. This has unintended consequences because the practitioner is forced to use other stronger broad-spectrum antibiotics, which over the years, has led to the development of methicillin resistant Staphylococcus aureus (MRSA) (11).

Skin sensitivity testing for penicillin allergies can help confirm a true allergy in patients with the presence of IgE mediated hypersensitivity (10), however no commercial skin test reagent is available. Testing is beneficial to patients because cephalosporins and penicillin derivatives such as augmentin are cheaper compared to other medications and thus help control health care cost (12). A common alternative for those with a true penicillin allergy is clindamycin. Clindamycin is the most commonly used prophylaxis in preoperative patients who have a penicillin allergy (13). Other alternatives depend on the organism and area of the body. Commonly used alternatives are vancomycin, sulfamethoxazole/trimethoprim (Bactrim), doxycycline, clindamycin, linezolid, synercid, and levofloxacín (14-16).
SULFA DRUGS

Sulfa drugs are any drugs containing sulfonamides. They are derivatives of para-amino benzoic acid (17). There are many groups of drugs that contain sulfa. Examples include antibiotics (sulfamethoxazole/trimethoprim), diuretics for high-blood pressure (hydrochlorothiazide, furosemide), sulfonylureas for reducing blood sugar in diabetes mellitus (glyburide), and dapsone for leprosy (18). Other drugs containing sulfa include burn creams and eye drops. Drugs containing sulfa were one of the earliest drugs used against bacterial infections. Antibiotic derivatives of sulfa drugs include septrin, gantanol, and bactrim. Bactrim is the most common drug used in patients with MRSA diabetic foot infection (19). Today, it is a commonly prescribed prophylactic drug for patients living with HIV/AIDS. These patients should be monitored because a retrospective cohort study showed that sulfamethoxazole/trimethoprim could cause reversible hyperkalemia in HIV patients (20). Trimethoprim works by inhibiting dihydrofolate reductase while sulfamethoxazole inhibits dihydropteroate synthase (21). Together they inhibit the production of folic acid in bacterial cells thereby making it bactericidal. Bactrim has excellent coverage for gram-positive cocci (Staphylococcus aureus and Streptococcus agalactiae, not active against Enterococcus), and gram-negative rods (Escherichia coli, not active against Pseudomonas spp or Anaerobes) (21).

It should be noted that nausea, diarrhea, vomiting, and rash are common side effects of sulfa drugs (21) and these should not be mistaken for an allergic reaction. Other adverse drug reactions include cytopenia and hepatotoxicity (22). A true allergic reaction to sulfa drugs occurs when the sulfonamide molecule is metabolized by the body, and the molecule binds to proteins in the human body thereby producing large molecules (23). This large molecule serves as an allergen that triggers the body’s immune response leading to rash, hives, and swelling of the mucous membrane and lips with difficulty breathing. In severe cases, patients can have an anaphylactic reaction which could be life threatening (23). A common misconception is mistaking a sulfa allergy for a sulfite allergy. These two are mutually exclusive, and patients must be educated. Sulfonamides and sulfa are chemically different, and both can cause an allergic reaction independently. Sulfite is found naturally in wine and used as a preservative in some foods (processed foods) (23). Alternatives to sulfa drugs for gram-positive coverage is augmentin in patients without history of MRSA; clindamycin, levofloxacin, or doxycycline should be utilized in patients with an active MRSA infection or history of MRSA.

VANCOMYCIN

Vancomycin is a glycopeptide produced by Streptococcus orientalis (24). It is bactericidal, and it works by inhibiting cell wall synthesis in bacteria. It has excellent gram-positive coverage (24). Vancomycin is widely used as the first-choice drug in the treatment of MRSA (25). It is also the drug of choice for patients with penicillin allergies or patients that have failed treatment with penicillins or cephalosporins. Vancomycin is widely used intravenously however oral vancomycin is available and used for the treatment of Clostridium difficile (c diff) (26). A known adverse reaction from vancomycin is red man syndrome (RMS) (25), with an incidence between 3.7 and 47% (27). This occurs when vancomycin is rapidly infused or administered over a short period of time (25). RMS does not involve any antibodies but rather a histamine release. This causes pruritis, erythema, and flushing usually affecting the face and neck (27). Treatment involves steroids and antihistamines (27). Histamine receptor blocker can help reduce the occurrence of RMS (25). The upper body is more likely to be affected than the lower body (24). RMS can be reduced by slow infusion of vancomycin over several hours (27). Other side effects of vancomycin include muscle spasms, dyspnea, and hypotension (24). Peaks and troughs are routinely ordered for vancomycin and the trough value is used to measure toxicity (28). Increased vancomycin use and higher trough concentration can lead to nephrotoxicity (28,29). It must be noted that other antibiotics such as ciprofloxacin, amphotericin B, and rifampin can also lead to RMS (25). Although rare, a true allergy to vancomycin can initially present as RMS and then progress to anaphylaxis (30). Therefore, it is important for health care professionals to recognize it early and treat it accordingly. Alternative treatments for MRSA in patients with a vancomycin allergy include bactrim, doxycycline, linezolid, daptomycin, tigecycline, and synercid.

CLINDAMYCIN

Clindamycin is an antibiotic with gram-positive and anaerobic coverage, which is also sensitive to MRSA with good bone and joint coverage (31). Clindamycin is produced by the bacterium Streptomyces lincolnensis (32) and it is available in both oral and parenteral forms. Clindamycin is the drug of choice for surgical prophylaxis in patients with a penicillin allergy. It works by stopping the translocation of ribosomes, thereby inhibiting protein synthesis (32) and making it bacteriostatic (32). Clindamycin also has an antitoxin effect against strains of staphylococcus and streptococcus that produce toxins; this mechanism is not clearly understood.
CLINICALLY IMPORTANT ANTERIOR growers in adults, as well as those in children younger than 18 years, including cartilage damage and osteonecrosis.

BRUISES are rarely seen in children younger than 18 years, as well as those in children younger than 18 years, including cartilage damage and osteonecrosis.

ANTIBIOTICS are used to treat infections caused by bacteria and fungi, as well as those in children younger than 18 years, including cartilage damage and osteonecrosis.

METRONIDAZOLE

Metronidazole, widely known as flagyl, is an imidazole with exceptional anaerobic coverage (46). It is available in both oral and parenteral forms (47). Anaerobes are unicellular or multicellular organisms that thrive in environments with little or no oxygen. Examples include bacteroides spp, clostridia spp, peptococcus spp, and peptostreptococcus spp. Metronidazole works by inhibiting the DNA of bacteria cells by disrupting nucleic acid synthesis (47). It is important to note that metronidazole functions in a partially reduced state, which only happens in anaerobic cells. Anaerobic organisms can cause gas gangrene in diabetic foot infections, which are seen on radiographs as diffuse soft-tissue emphysema. Gas gangrene is a surgical emergency and immediate incision and drainage is required. Metronidazole is a remarkable drug used to cover anaerobes in diabetic foot infection (47). It is also used to treat diarrhea associated with Clostridium difficile (46). A known side effect when using metronidazole is a disulfiram-like reaction when taken with alcohol. Patients should be advised to avoid alcohol when taking any medication especially metronidazole (47). Other side effects include nausea, headache, loss of appetite, metallic taste, and stomach upset (48). To prevent stomach upset, patients should be advised to take the medication with food or a glass of milk. Neurotoxicity secondary to metronidazole has been reported in a few case reports (48-50). A true allergic reaction to metronidazole is rare. Alternatives to metronidazole are clindamycin, linezolid, synercid, cefoxitin, and cefmetazol.

TETRACYCLINE

Tetracyclines are broad spectrum antibiotics active against gram-positive and gram-negative organisms. It was originally made from the bacteria Streptomyces (51), and works by binding reversibly to the 30s subunit of ribosomes thereby inhibiting protein synthesis (52). Consequently, it has a bacteriostatic effect. Tetracyclines are sensitive to atypical pathogens such as treponema spp, rickettsia spp, borrelia spp, borrelia burgdorferi, vibrio cholera, and mycoplasma pneumonia. The two most common derivatives of tetracycline are doxycycline and minocycline (53). However, a newer generation of tetracycline is tigecycline, which is indicated for severe soft tissue and bone infections (54,55). Doxycycline is routinely prescribed to patients with diabetic foot infections that are resistant to penicillin.
Known side effects to tetracycline include vomiting, diarrhea, rash, black hairy tongue, and sore throat. Other notable side effects include tooth discoloration in children (56, 57). Tetracycline is contraindicated in pregnant women because it can cross the placenta and be toxic to fetal tissues (57). Reversible Fanconi syndrome has been associated in patients who take outdated medication (58). A true allergy to tetracycline is rare but allergic reaction can include rash, skin lesions, and itching (59). Alternatives to tetracycline include penicillin (if sensitive), bacitracin, vancomycin, and ciprofloxacin.

Important factors to consider when deciding alternatives to antibiotics, is to look at the sensitivity report and also the history of susceptibility or resistance of the patient. Alternatives to a medication should only be prescribed for well-defined indications.

REFERENCES


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