Adverse drug events (ADEs) are unwanted consequences of antimicrobial therapy. Side effects that are evaluated at the hospital formulary level may be one of four types; they can be serious but rare, serious and common, common and not serious, or rare and not serious. Side effects have important implications for each patient, the treating physician, and the institution itself.

Antimicrobial side effects have the potential to harm patients and to put physicians and hospitals at legal risk. Depending on the circumstances, rare but important side effects are tolerated because therapeutic alternatives are limited and the incidence of ADEs is rare.

When assessing antimicrobial side effects, hospital formulary committee members should pay particular attention to ADEs that increase the patient’s length of stay (LOS) in the hospital. Phlebitis, cutaneous drug reactions, drug fevers, transient hematological or chemical laboratory test abnormalities, and hospital-acquired diarrhea that is not associated with *Clostridium difficile* (*C. difficile*) are usually not life-threatening, but they can have important economic implications by increasing LOS for patients.

Some antibiotic side effects are unique to a particular drug class, but most effects are limited to one or two specific agents from different classes. To minimize the potential for adverse side effects, clinicians should know the safety profile of the antibiotics selected for the formulary and for the patient. All other factors being equal, hospital formulary committees should opt for the antibiotic with the best safety profile within the class.1–4

**DRUG FEVER**

Drug fever is the sole manifestation of a hypersensitivity reaction to medications and may be caused by a variety of antimicrobial and non-antimicrobial agents. Certain medications are more likely than others to cause this condition.

Among the agents that are intended to treat noninfectious disorders, some antiseizure medications, diuretics, sulfadiazine and sulfadimethoxine, beta blockers, pain medications, sleep medications, cardiovascular medications, and others are common causes of drug fever. Beta-lactams and sulfonamides are the most frequent causes in the antibiotic drug category.

Although patients might become allergic to any antibiotic, drug fever is rare with the macrolides (e.g., Sumycin®, Parke-Davis, Pfizer), the aminoglycosides, and the monobactams. Because drug fever is unusual with these antibiotics, a diagnosis of drug fever should be suspected as being a result of another agent, usually a non-antimicrobial agent.

Patients have an elevated body temperature with a deficit in pulse temperature. Laboratory abnormalities include mild, transient serum transaminase elevations and an elevated erythrocyte sedimentation rate (ESR) and serum immunoglobulin E (IgE) level. Drug fevers are often accompanied by a leukocytosis with a left shift, with eosinophils present in the peripheral smear. Eosinophilia occurs but is less common than the presence of eosinophils in the peripheral smear.

Recognizing a medication-induced drug fever has important pharmacoeconomic implications. Drug fever increases LOS in the hospital and increases the need for multiple laboratory tests with their associated costs, and usually one or more consultants must be called upon for a correct diagnosis of the disorder.4,5

**DRUG RASH**

The same drugs that are capable of causing drug fever—both antibiotics and non-antibiotics—may also cause drug rash. Hypersensitivity reactions tend to be stereotyped; thus, patients with drug fever tend to continue to have it and do not progress to experiencing anaphylaxis or a drug rash. In contrast, patients with drug rash almost always have a fever.

The most serious cutaneous ADE caused by allergic drug reactions is erythema multiforme, the most severe manifestation of which is the Stevens–Johnson syndrome, a potentially fatal condition. The sulfonamides are the most common class of drugs associated with erythema multiforme/Stevens–Johnson syndrome. Sulfonamides may be administered as single drugs but are usually prescribed in combination with trimethoprim as trimethoprim–sulfamethoxazole (TMP–SMX) (Bactrim®, Roche; Septra®, Pharmacia & Upjohn). If patients are receiving TMP–SMX and a skin rash develops that is not caused by another drug, the reaction is invariably a result of the SMX component, not the TMP. If these patients require additional treatment, TMP may be prescribed alone without SMX.

Drug fevers and skin rashes caused by TMP are virtually nonexistent. Skin rashes caused by non-antibiotics and antimicrobial agents need to be differentiated from the rashes of contact dermatitis in the hospital setting. Drug rashes are recognized as being associated with a particular medication and should be discontinued as soon as a potential relationship is suspected. Even more than drug fever, drug rash has a greater potential for increasing LOS and for increasing the cost of hospitalization to patients and to the institution.

If the agent causing drug fever is recognized and discontinued, the fever usually subsides within three days. In contrast, patients with drug rash may have a fever for days or weeks until the exanthem eventually disappears. The same clinical presentation, in addition to cutaneous manifestations, occurs with drug rash as with drug fever, except for pruritus. Drug-induced rashes are itchy, in contrast to viral exanthems, excluding smallpox and chickenpox.5–8

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Antimicrobial Side Effects

DIARRHEA

Noninfectious Diarrheas

In hospitalized patients, the source of diarrhea may be infectious or noninfectious. Noninfectious causes may be the result of a drug’s effect on the gastrointestinal tract. Some antibiotics, such as erythromycin (e.g., Ery-Tab®, Abbott), increase gut peristalsis and may cause diarrhea on that basis. Other drugs, such as ceftriaxone sodium (Rocephin®, Roche), cause changes in the fecal flora, which may result in diarrhea.

Non-antibiotic hyperosmolar medications may also cause noninfectious diarrhea. Patients receiving enteral nutrition through nasogastric tubes may experience diarrhea as a result of the solution’s osmolar and chemical composition.

Alternatively, any enteral feeding solution, if given in volumes beyond the patient’s capacity to tolerate it, may result in diarrhea. Antibiotics associated with noninfectious diarrhea include the macrolides, the tetracyclines, the fluoroquinolones, and medications containing high concentrations of clavulanic acid, ampicillin, and ceftriaxone sodium. In general, all antibiotics that induce diarrhea not caused by C. difficile are poorly absorbed, affect gut motility, or alter the intestinal microflora.

Infectious Diarrheas

Virtually all nosocomial (hospital-acquired) diarrheas of infectious origin are related to C. difficile. Diarrhea that is associated with this organism, also known antibiotic-associated diarrhea, may be induced by chemotherapy or antibiotic therapy. The precise mechanism by which antibiotics or chemotherapeutic agents induce toxin production in C. difficile in the normal fecal flora is unclear.

The likelihood of experiencing C. difficile diarrhea during antibiotic therapy is related to the antibiotic agent being used. Antibiotics are not equal in their potential to induce C. difficile diarrhea. Although all antibiotics have the potential to cause it, some antibiotics are associated with C. difficile diarrhea more frequently than others are (e.g., the beta-lactams and clindamycin). Some antibiotics are more likely to cause noninfectious diarrhea than C. difficile diarrhea (ceftriaxone and the macrolides). The use of certain antibiotics (e.g., clindamycin) can result either in noninfectious diarrhea or in C. difficile diarrhea. Some antibiotics, such as metronidazole (Flagyl®, Pharmacia), can cause and can be used to treat C. difficile diarrhea.

C. difficile diarrhea may be caused by oral or parenteral agents. Beta-lactams, with certain notable exceptions, such as the carbapenems, piperacillin/tazobactam (Zosyn®, Lederle), cefepime (Maxipeme®, Elan), are not commonly associated with C. difficile diarrhea. Antibiotics that are capable of causing C. difficile diarrhea may cause C. difficile colitis, or antibiotic-associated colitis.

All other things being equal, hospital formularies should include the antimicrobial agent with the lowest noninfectious or C. difficile potential. Diarrhea has important pharmacoeconomic implications for hospitals and can increase LOS. Physicians must first differentiate infectious from noninfectious diarrheas. Patients with C. difficile are usually treated with oral metronidazole or vancomycin.

Laboratory tests and subspecialty consultations that might involve gastroenterologists and infectious disease specialists also affect the cost of health care. Patients with severe disease and C. difficile colitis may require intensive medical care, surgery, and expensive radiological monitoring and interventions.

For all of these reasons, agents that are not associated with diarrhea are preferred to those that are. Although antibiotic-associated diarrhea can be more costly to treat than the non–antibiotic-associated type, both have important economic implications.

CYTOPENIAS

Various antibiotics exert diverse effects on different elements of the blood. Some agents are known to cause thrombocytopenia (decreased platelets), anemia (decreased red blood cells), or leukopenia (decreased white blood cells). Some agents (e.g., chloramphenicol) may cause pancytopenia (the deficiency of all cellular blood elements). The agents most likely to be associated with leukopenia are beta-lactams, vancomycin, and TMP–SMX. Relatively few agents are associated with pure depression of red blood cell precursors, and chloramphenicol is the classic antimicrobial in this category.

Thrombocytopenia is the most common antibiotic-associated hematological side effect encountered in clinical practice. Commonly associated agents are the beta-lactams, TMP–SMX, vancomycin, and linezolid. Hospital P&T committee members who are investigating antibiotic-associated side effects should remember that non-antibiotics are also common causes of isolated hospital-acquired thrombocytopenia. For example, if a patient has been receiving furosemide (Lasix®, Aventis) and is being treated with cefazolin (e.g., Ancef®, GlaxoSmithKline), it is more likely that the furosemide, rather than the cefazolin, is causing the thrombocytopenia. Some antibiotics, particularly the beta-lactams as a class, may cause combined cytopenias (i.e., thrombocytopenia with leukopenia). The antimicrobials that most often cause thrombocytopenia with leukopenia are the beta-lactams, TMP–SMX, and vancomycin.

The pharmacoeconomic implications of isolated or combined cytopenias caused by antimicrobials are obvious. If such agents are suspected and eventually are recognized as sources of these blood disorders, they are laboratory cost-intensive. As with other antibiotic-induced side effects, the LOS may be prolonged. It may be necessary to consult hematology and infectious disease specialists to determine the causative agent and to recommend alternative therapy. The cost of the antibiotic used to replace the agent causing cytopenia must be added to the expenses of increased LOS, subspecialty consultants, and laboratory tests.

MISCELLANEOUS SIDE EFFECTS

Other antibiotic side effects, fortunately, are relatively uncommon, in contrast to those described earlier. Some antibiotics (e.g., the aminoglycosides) have a nephrotoxic potential, but if once-daily dosing is used, the potential for damage to the kidneys is virtually nil. Hepatotoxic reactions are more common with antibiotic use, compared with nephrotoxic reactions, but these are also relatively rare. Most drugs that cause severe hepatotoxicity reactions are no longer on the market, such as grepafloxacin (Kaxar®, Glaxo Wellcome), or are restricted in usage, such as trovafloxacin mesylate (Trovan®,
Pfizer). Many antibiotics are associated with mild, transient transaminase elevations, which should not be considered true hepatotoxicity. Relatively few antibiotics, including some agents that are used to treat human immunodeficiency virus infection, are associated with pancreatitis.

Only a few agents, such as tetracycline and sparfloxacin (Zagam®, Parke-Davis), cause phototoxicity, which thus limits the use of these antimicrobials. Among the antibiotics, only the aminoglycosides have been shown to cause ototoxicity. Visual disturbances are largely limited to ethambutol and voriconazole (Vfend®, Pfizer). A prolonged corrected QT interval (QTc), which can lead to ventricular arrhythmias, occurs with the macrolides and the quinolones.1–4,15–21

SUMMARY

Most commonly used antimicrobials are very safe. Adverse effects have a significant impact on patients and institutions and may have important cost implications. The most common antibiotic side effects encountered in hospitals are drug fever, drug rash, cytopenia, and diarrhea. Hospital P&T committees should be aware of the side-effect profiles of commonly used antibiotic agents on their formularies and should opt for the drug with the best safety profile in a given class.

REFERENCES