You Asked for It! CE

Patient Safety
The Risk of Treatment:
Antibiotic-Induced Adverse Events

UCONN

AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- Describe mechanisms of action that cause antibiotic induced adverse effects
- Analyze risks and sequelae to determine adverse event or causative medication
- Recommend appropriate treatment for antibiotic induced adverse effect
- Discuss counseling points for outpatient antibiotic use

After completing the continuing education activity, pharmacy technicians will be able to

- List adverse effects induced by antibiotics
- Recognize patients at risk of adverse effects
- Recall medications used to treat adverse effects
- Identify when to refer patient to pharmacist for recommendation or referral

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the post-test with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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TARGET AUDIENCE: Pharmacists and pharmacy technicians who work with patients who need antibiotic treatment in any setting .

ABSTRACT: When a patient is diagnosed with an infection, an antibiotic is usually the first line of treatment to cure the ailment. Antibiotics are effective treatments when patients have validated infections. Most often, treatment with antibiotics is benign. Typically, it does not pose a risk to patients, but antibiotics are associated with several risks to consider before initiating treatment. Risks of antibiotic use range from mild adverse effects of gastrointestinal upset and mild rash to life-threatening allergy development, toxic megacolon, and death. Recognizing and understanding the risks associated with antibiotic use is crucial in preventing severe patient complications.

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FACULTY DISCLOSURE: Dr. Provisor has no financial relationships with an ineligible company.

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INTRODUCTION

An injury or response that results in any harm to a patient after medication administration is an adverse drug reaction (ADR). Every medication can potentially cause ADRs, but antibiotics are notorious for causing several individual and class-wide type reactions. A 2017 study (N = 1488) showed that 20% of all inpatients who receive antibiotics will develop an ADR within 24 hours of therapy. That risk increases by 3% every ten days of therapy.[1] Education and recognition of ADRs from antibiotics are essential components in the campaign against antibiotic resistance. The Centers for Disease Control and Prevention (CDC) developed the Core Elements of Antibiotic Stewardship to optimize antibiotic use by decreasing unnecessary antibiotic prescribing and helping fight antibiotic resistance in differ-

ent practice settings. One Core Element is education directed at prescribers, nurses, pharmacists, and patients about the adverse reactions associated with antibiotic use.[2]

Antibiotic Resistance

One of the most noxious antibiotic-induced ADRs is the development of antibiotic resistance. Antibiotic resistance is a global health threat to the world population and affects food security.[3] Antibiotic resistance develops when a bacteria is no longer susceptible to a previously effective antibiotic, which can stem from unnecessary antibiotic use.[1] A 2011 study that surveyed American acute care hospitals found that almost half of all inpatients will receive at least one day of antibiotic therapy.[4] A separate U.S. study found that one-third of all antibiotic treatment days are inappropriate.[5]

Antibiotic resistance kills at least 1.27 million people worldwide every year.[6] The United States (U.S.) has reported more than 2.8 million antimicrobial-resistance infections yearly, with 35,000 deaths.[7] Antimicrobial resistance can affect anyone at any age, at all different types of healthcare facilities, and in veterinary and agricultural industries.[6] Antibiotic resistance prevents patients from using first or second-line therapy for indicated infections, making patients more susceptible to severe ADRs.

Antibiotic Allergies

Allergic reactions reportedly account for 20% of adverse drug events and are seen in about 8% of the population.[8] Antibiotics are the most common medication reported as an allergy.[9] Elderly and female patients are more likely to report antibiotic allergies.[9,10] Typically, antibiotic allergic reactions present as mild rash and hives but approximately 3% of the population's health records documented past anaphylaxis.[11]

In the 1960s, Robert Coombs and Philip Gell established a classification system for hypersensitivity reactions. Coombs is most notable for developing the Coombs test that detects anti-Rh antibodies on red blood cells in 1945.[12] Their classification system has four presentations of hypersensitivity reactions involving different immune mediators that develop into various manifestations. **Table 1** summarizes the Coombs classification.

Table 1 - Classification of Allergic Reactions[13-15]

Type	Description	Mechanism	Timing	Clinical features
I	IgE-mediated, immediate-type hypersensitivity	IgE serves to protect and eliminate parasitic infections. IgE antibodies form after exposure to allergens, such as food, drugs, or other environmental elements. Re-exposure triggers an immediate hypersensitivity reaction.	Minutes to hours after exposure	• Anaphylaxis • Angioedema • Bronchospasm • Hives • Hypotension • Asthma • Allergic rhinitis
II	Antibody-dependent Cytotoxicity	The drug binds to the surface of the cell. Antibodies then bind to the cell surface and are targeted for clearance by macrophages. Usually involves IgG or IgM	Appear 5-8 days after exposure but can take longer	• Hemolytic anemia • Thrombocytopenia • Neutropenia
III	Immune complex disease	Soluble drug in bloodstream forms a complex with IgG or IgM. The immune complexes can activate complement and then deposits in various tissue like small blood vessels, joints, and renal glomeruli	One or more weeks to develop after drug exposure	• Serum sickness • Arthralgias • Acute glomerulonephritis • Vasculitis
IV	Cell-mediated hypersensitivity	Stimulation of T cells	At least 48-72 hours, but can take days to weeks following exposure	• Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN) • Drug rash with eosinophilia and systemic symptoms (DRESS) • Contact dermatitis

Antibiotic allergy reporting is essential to prevent patients from severe adverse effects, but it also comes with a risk. Prescribers overuse and overprescribe antibiotics. Overprescribing of antibiotics is associated with a higher incidence of new antibiotic allergies.[9] In countries with low antibiotic usage, antibiotic allergies are less prevalent.[9] Antibiotic overprescribing is especially notorious at urgent care facilities. A study showed that in patients presenting to urgent care for upper respiratory infections, healthcare providers prescribed antibiotics approximately twice as much as in emergency departments and nearly three times as much in primary care.[16] This is concerning; nationwide, there are more than 10,000 urgent care facilities, and that number is growing.[16]

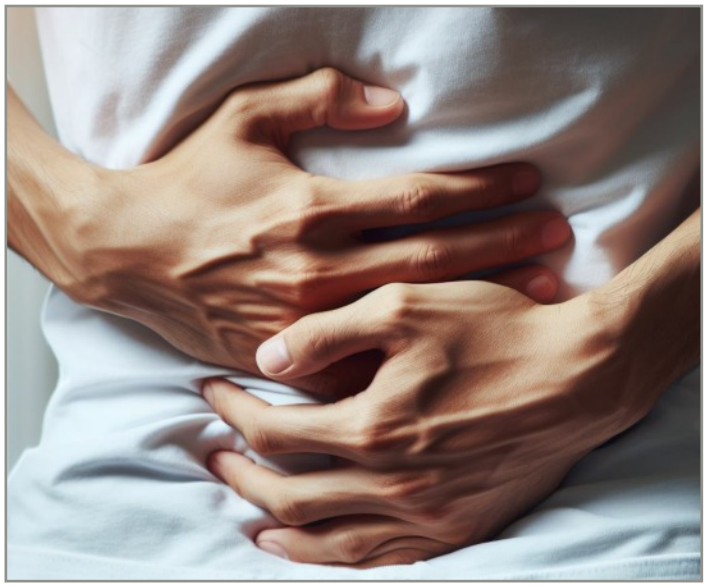
Inaccurate allergy documentation is another concern with antibiotic allergy reporting. Five percent to 15% of patients have documented penicillin allergies; however up to 90% of those patients can safely receive a penicillin antibiotic.[17,18] Antibiotic allergies prevent patients from receiving first-line therapy, which can increase health care costs, and increase the risk of treatment failures and adverse events.[17] A study from 2003 showed that patients labeled with a penicillin allergy had a 63% greater cost for antibiotics than patients without a penicillin allergy.[19]

PAUSE AND PONDER: What are some individual antibiotics that make up penicillins and cephalosporins?

The best treatment for allergies is prevention. Before initiating any new antibiotic, the prescriber should obtain an allergy history. Pharmacists must review patients' profiles for allergies to beta-lactams and consider cross-reactivity. There is about a 2% risk of cross-sensitivity between penicillins and cephalosporins.[17] Treatment for allergies depends on the type of reaction. Type I reactions are usually a medical emergency, and patients need immediate care. Antibiotic rechallenge is appropriate for patients with mild reactions like gastrointestinal distress or mild itching or rashes but should not occur for any patient who develops a severe reaction, like anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, or hemolytic anemia.[10] Reactions that occur need documentation with sufficient detail, including medication used and time to reaction.[17]

Antibiotic-Associated Diarrhea

A frequent adverse event associated with antibiotic use is diarrhea, defined as three or more loose stools in 24 hours.[20-22] Antibiotic-associated diarrhea reportedly occurs in 5% to 30% of patients while receiving or up to two months after receiving treatment.[23] Antibiotic-associated diarrhea's clinical presentation can range from mild diarrhea to pseudomembranous colitis.[23,24] Essentially all antibiotics can cause diarrhea, especially those that cover anaerobic microorganisms (organisms that grow without oxygen) like amoxicillin/clavulante, cephalosporins, and clindamycin.[21-23]



Antibiotic-associated diarrhea can occur from multiple mechanisms. First, antibiotics disrupt normal microflora, allowing overgrowth of microorganisms known to cause diarrhea.[23] *Clostridium difficile (C. diff)*, which will be discussed later, is the most common of those pathogens. Other pathogens are *Salmonella, C. perfringens* type A, *Staphylococcus aureus, and Candida albicans.*[20,24] Antibiotics can directly affect the intestinal mucosa, independent of any antibiotic activity. For example, erythromycin stimulates a receptor that increases contractions in the stomach and small intestines, and clavulanate can activate small bowel motility.[20,24] Last, antibiotics can decrease normal fecal flora that breakdown carbohydrates and bile acids in the colon. The increase of carbohydrates and bile acid causes an influx of water into the colon, causing osmotic diarrhea.[20,24]

Treatment of antibiotic-associated diarrhea depends on its severity. Mild to moderate disease treatment should focus on rehydration, discontinuation of the provoking antibiotic, or changing to a lower-risk antibiotic like quinolones, sulfamethoxazole/trimethoprim, or aminoglycosides, if appropriate.[22,23] Clinicians should order *C. diff* testing in patients with severe or persistent disease or any microbes mentioned above.[23]

Probiotics are an alternative method to decrease antibiotic-associated diarrhea, but mixed evidence surrounds their use. A 2021 meta-analysis reviewed 82 randomized controlled trials and found a statistically significant association between probiotic administration and the reduction of antibiotic-associated diarrhea.[25] The results are difficult to translate to a specific recommendation as the meta-analysis included many randomized controlled trials that did not document the exact probiotics used. In addition, the study excluded antibiotics that are more likely to cause diarrhea and specific subsets of patients like geriatrics.[25] Probiotic use is low risk for most patients, but immunocompromised patients should use caution when consider-

ing therapy.[26,27] Probiotics are associated with rare secondary bacterial and fungal infections; it is more prevalent in immunocompromised patients.[28-30] The most ideal way to prevent antibiotic-associated diarrhea is to limit antibiotic use.[23]

C. diff is a spore-forming bacteria that produces two separate exotoxins, A and B, that cause mucosal damage and inflammation.[22,23] Patients with *C. diff* infection (CDI) account for 10% to 25% of antibiotic-associated diarrhea cases, but CDI causes the majority of pseudomembranous colitis associated with antibiotic therapy.[23,24] Patients with CDI typically present with fever, lower abdominal pain, and cramping. CDI stool usually contains visible mucous and is foul-smelling.[22] Significant risk factors include age older than 65, hospitalization, proton pump inhibitor use, and previous diagnosis of CDI.[22,24] Patients older than 60 have a much greater risk of developing CDI than patients aged 10 to 20 years.[24,31] Prescribers should consider *C. diff* testing after a patient has three or more unformed new or unexplained stools in 24 hours.[12]

Multiple diagnostic criteria confirm CDI. Lab results from CDI patients show elevated white blood cell count, decreased albumin, and fecal leukocytes.[24] Imaging with a CT scan can show inflammation and thickening of the colon, but it is not specific to CDI.[24] The Gold Standard testing for CDI is to test for toxins A and B with polymerase chain reaction (PCR) tests, but patients need to have unformed stool (bowel movement that is watery or soft) for this test. Patients with solid-formed stools do not have diarrhea and therefore do not have CDI, so testing is not warranted. Enzyme immunoassay (EIA) is another option that produces results much faster than the PCR test but has much lower sensitivity.[22,32]

Providers should start treatment for *C. diff* after a positive test or before positive testing if a strong clinical suspicion exists.[24,32] Clinical guidelines do not recommend routine testing of *C. diff* in asymptomatic patients as *C. diff* colonization frequently occurs, especially in hospitalized patients and residents of long-term care facilities.[32] Severity of disease, initial or recurrent occurrence, and other risk factors determine treatment. Disease severity can be non-severe, severe, or fulminant. In severe illness, the patient will have leukocytosis with a white blood cell count (WBC) of at least 15,000 cells/mL and a serum creatinine (Scr) level higher than 1.5 mg/dL. In non-severe disease, WBC and Scr levels are less than that of severe. Fulminant severity presents with hypotension or shock, ileus (an obstruction of the intestines), or megacolon (abnormal widening of the colon that is not caused by an obstruction).[12] Vancomycin and metronidazole have been the mainstay of treatment for more than 30 years until the development of newer medications. Fidaxomicin and bezlotuxumab are newer agents recently added to the Infectious Disease Society of America (IDSA) guidelines for CDI treatment.[33] Refer to 2021 IDSA guidelines for specific treatment recommendations.

Antibiotic-Induced Kidney Injury

Medications cause an estimated 20% to 40% of cases of acute kidney injury, with that estimation reaching almost 60% in the elderly population.[34,35] Antibiotics are a well-known cause of medication-induced renal dysfunction. Antimicrobials cause kidney dysfunction through tubular injury, severe tubular necrosis with cellular death, intratubular obstruction from crystal formation, and other mechanisms.[34] The direct cause is increased drug concentration, decreased excretion, and genetic differences predisposing some individuals to increased cell death or mitochondrial injury after exposure to certain antibiotics. In addition, patients with underlying kidney disease, acid-base disorders, and dehydration are at a greater risk of crystal formation with antibiotics that are insoluble in urine.[34,36] Most classes of antibiotics have varying degrees of risk for the development of renal dysfunction, but it is most commonly associated with aminoglycosides, beta-lactams, and vancomycin.[34,37]

Renal dysfunction will develop in 10% to 25% of patients on aminoglycosides.[34,38] Symptoms of renal dysfunction develop five to seven days after initiation of therapy and will take up to 20 days for complete recovery after discontinuation of the aminoglycoside.[34,38] The risk for AKI increases in patients with longer therapy durations, exposure to concomitant nephrotoxins, and other comorbidities like chronic kidney disease.[38] Patients on aminoglycosides most commonly develop renal toxicity in the proximal tubule. Gentamicin has the highest potential to cause nephrotoxicity, followed by tobramycin and amikacin. Clinical practice has moved away from using neomycin systemically as it has an increased risk of causing nephrotoxicity, neurotoxicity, and ototoxicity.[34]

Beta-lactams have a high risk of causing renal dysfunction, with carbapenems causing more renal toxicity than penicillins or

cephalosporins.[34] Beta-lactams cause a wide range of renal toxicity, including acute glomerulonephritis, acute tubular necrosis, and acute interstitial nephritis.[34,39] Prolonged infusions of beta-lactams possess a similar risk of AKI compared to intermittent infusions.[39]

Vancomycin's incidence of nephrotoxicity is between 5% and 43%.[38,37,40] Vancomycin nephrotoxicity was initially associated with manufacturing impurities, but new manufacturing methods have eliminated this cause.[41-43] Onset occurs four to eight days after initiation of vancomycin and improves after discontinuation.[34,43] The overall pathophysiology of vancomycin-induced AKI is poorly understood as several mechanisms most likely contribute. Most patients who develop AKI on vancomycin do not undergo renal biopsies, and it is commonly prescribed with other nephrotoxic agents, which hinders a conclusive diagnosis.[34,38,43] Patients with pre-existing kidney disease, severe illness, a combination of nephrotoxic agents, obesity, and daily cumulative doses greater than four grams are at a higher risk of AKI.[34,41,44] Adjusting the vancomycin dose based on weight, levels, and renal function can help decrease the risk of kidney injury.[34] Pharmacists monitor vancomycin levels as trough and peaks which are low and high measurements of the actual medication in the patient.

Evidence of the risk of nephrotoxicity from the combination of vancomycin and piperacillin/tazobactam (VPT) has been conflicting. Previous evidence has shown VPT to carry a two to three-fold higher risk than vancomycin alone, but this is unclear due to piperacillin/tazobactam being a pseudo-nephrotoxin.[42,45] Prescribing information states that piperacillin/tazobactam can increase serum creatinine causing a pseudo-nephrotoxicity.[46] Most studies that reported increased risk of nephrotoxicity used increased creatinine as an indicator of acute kidney injury (AKI). [45,47] A 2022 study looked at levels of cystatin C (a biomarker used to test kidney function) and found no significant change in its value for patients on VPT. Further, it also showed VPT combination did not lead to higher rates of dialysis or death.[48] A 2023 study looked retrospectively at 35,644 patients receiving either VPT, vancomycin plus meropenem, or vancomycin plus cefepime. This study found that the combination of VPT has a greater risk of AKI, dialysis, and mortality in patients receiving treatment for greater than 48 hours.[49] At this time, available research on the VPT combination's nephrotoxicity is conflicting. Clinicians should exercise caution when using VPT and consider other therapies in patients at high risk of renal dysfunction, especially if the combination will continue for longer durations.

Overall, antibiotics pose a significant risk to renal function, so the clinical team must assess risk factors of age and co-morbid conditions before initiating therapy.[34] A few ways to prevent the development of AKI are[34,38]

- dosages adjusted based on creatinine clearance and glomerular filtration rate (GFR)
- changing the dose based on trough or random levels
- adequate hydration, especially when using agents that form crystals in the urine
- avoiding concomitant nephrotoxins (i.e., NSAIDs, contrast, etc.) and
- regular monitoring of kidney function for long-term antibiotic use or when a patient has known risk factors for developing kidney dysfunction.

Clinicians must always practice good antimicrobial stewardship by prescribing shorter therapy courses to lower nephrotoxic agent exposure to the kidneys.[34]

Sulfamethoxazole/Trimethoprim-Induced Hyperkalemia

The early 1980s through 1990s saw a significant rise worldwide of the human immunodeficiency virus (HIV) which also coincided with the first reported cases of hyperkalemia (high potassium levels) from sulfamethoxazole/trimethoprim (SMX/TMP). The CDC published a report in *Morbidity and Mortality Weekly Report* (MMWR) in June of 1981 describing the incidence of *Pneumocystis carinii* pneumonia (PCP; now known as *Pneumocystis jirovecii*) in five previously healthy young men.[50] This CDC report documents the first known cases of HIV. Before the discovery of HIV, *P. jirovecii* was a disease associated with malnourished and immunocompromised patients. Premature and malnourished infants often contracted *P. jirovecii* during World War II, and patients with hematologic malignancies in later years.[51] Dr. Walter Hughes, known for his research with *P. jirovecii*, first recommended SMX/TMP for prophylaxis in 1977 and then for treatment in 1989.[52-54] Emerging cases of hyperkalemia associated with SMX/TMP usage increased significantly at the start of the HIV epidemic as P. jirovecii treatment requires high doses and HIV patients are prone to the development of hyperkalemia.[55,56]

Table 2. Alternate Causes of Increased Risk of Hyperkalemia [57,60,62]	
Disease States	**Medications**
• Renal insufficiency • AIDS patients • Diabetes Mellitus • Congestive Heart Failure • Metabolic Acidosis • Congenital Adrenal Hyperplasia • Hypoaldosteronisim & Pseudohypoaldosteronism	• NSAIDs • ACEs/ARBs • Direct Renin Inhibitors • Bet-blockers • Heparin • Digoxin • Cyclosporine and tacrolimus • Pentamidine • Potassium sparing diuretics

SMX/TMP causes hyperkalemia because trimethoprim is structurally similar to the potassium-sparing diuretics amiloride and triamterene.[55,57] Trimethoprim blocks channels that excrete potassium into the urine, causing a potential 40% reduction of urinary potassium excretion.[58,59] Inhibition of urinary potassium excretion also decreases potassium in the urine.[55,58] Hyperkalemia will subside after discontinuation of trimethoprim.[58]

Although SMX/TMP-induced hyperkalemia is low risk for most outpatients, it is essential to recognize risk factors and drug interactions because hyperkalemia is a medical emergency if untreated.[60] Trimethoprim is excreted in the kidneys and will accumulate during acute and chronic kidney disease, which can increase the risk of hyperkalemia.[61] Chronic kidney disease increases potassium levels, making it the most critical factor to consider when assessing risk for hyperkalemia.[57,62] Age greater than 65 and dose of greater than 20 mg/kg of trimethoprim for longer than a week also increases risk.[57,58]

Risk assessment should include a review of any disease states or concomitant medications that could cause hyperkalemia (see **Table 2**). Studies have examined spironolactone's effect when taken concurrently with SMX/TMP. A 2011 Canadian study examined patients receiving spironolactone and SMX/TMP prescriptions over 18 years. The study found that elderly patients treated with both medications had a 12-fold increased risk of hospital admission.[63] A 2015 Canadian study over 17 years looked at 206,319 patients to find an association between sudden death for patients taking spironolactone and antibiotics. Patients taking SMX/TMP were twice as likely to suffer from sudden death when compared to amoxicillin.[59]

Prevention of hyperkalemia from SMX/TMP should include decreasing the dose in patients with impaired renal function. SMX/TMP is contraindicated in patients with severe hepatic damage and severe renal disease if the patient does not have monitoring of renal function and electrolytes.[57,61] If hyperkalemia develops, prescribers should discontinue SMX/TMP and treat hyperkalemia following guideline recommendations.[58]

Daptomycin-Induced Eosinophilic Pneumonia

The FDA approved daptomycin, a lipopeptide antibiotic, in 2003. Providers use it to treat complicated infections due to methicillin-resistant staph and vancomycin-resistant enterococci. Daptomycin has been an effective treatment alternative for patients who cannot use vancomycin due to intolerance or drug resistance.[64] Daptomycin's approved labeling lists eosinophilic pneumonia and myopathies as severe adverse events.

Eosinophilic pneumonia (EP) is a rare respiratory illness that can present with severe dyspnea, hypoxemia, and respiratory failure.[65-67] It is caused by eosinophil accumulation in the lungs as an acute or chronic process. Acute EP symptoms last less than one month and typically less than one week, while chronic presentation can take an average of five months before diagnosis.[68] Patients with acute EP present with a varying range in the presentation of symptoms. Some patients may have very mild symptoms and require no treatment, while some studies have shown much more severe manifestations, with more than 50% of patients requiring mechanical ventilation.[68,69] Patients typically present with a dry cough, chest pain, and fever.[68]

EP develops when alveolar macrophages detect an antigen, which initiates an inflammatory process, eventually producing eosinophils and their subsequent migration to the lungs. Eosinophils are white blood cells that provide an essential defense against helminth parasites (worms). Reactions will develop in humans to presumably benign agents that incite a release of eosinophils.[70] In daptomycin-induced eosinophilic pneumonia, daptomycin is the inciting agent.

Accumulating eosinophils in the lungs or any tissue can cause significant damage.[71] Eosinophils release toxic granule products like major basic protein and eosinophil peroxidase that can damage epithelial cells and nerves. They also release cytokines like transforming growth factors (TGF)-alpha and beta, which are associated with tissue remodeling and fibrosis.[71] Alveolar macrophages, pulmonary endothelial cells, and airway smooth muscle cells also produce eotaxin, a potent chemoattractant of eosinophils.[65,72]

EP's primary causes are idiopathic.[68,72] Secondary reasons for EP are drugs or toxins and less commonly, parasitic or fungal infections.[68,72] The most frequently cited medications causing EP are daptomycin, mesalamine, sulfasalazine, and minocycline.[68] Daptomycin-induced EP was initially reported in 2007 after the drug's approval.[65] Its pathophysiology is poorly understood. One proposed mechanism is that daptomycin may bind to human surfactant and accumulate in the alveolar space causing injury to the epithelium and subsequent eosinophil migration to the damaged tissue.[65,66,73] The second proposed mechanism is that daptomycin interacts with surfactant resulting in abnormal lipids. This contact induces an allergic reaction causing the release of several inflammatory markers and eventually shifts eosinophils into the respiratory tissue at least one week after the start of daptomycin therapy.[65,66,73]

The Food and Drug Administration (FDA) has issued guidance for the diagnosis of daptomycin-induced EP with all of the following sequelae confirming a diagnosis of EP[74]:

- Concurrent exposure to daptomycin
- Fever
- Dyspnea with increasing oxygen demands requiring mechanical ventilation
- New infiltrates on chest X-ray or CT
- Bronchoalveolar lavage (BAL) with >25% eosinophils
- Clinical improvement with daptomycin withdrawal

Risk factors have not been well established for daptomycin-induced EP. A 2016 study that reviewed 43 cases in systematic literature found that most patients were male (83%) and elderly (mean age of 65 years old). The same study found that dose or duration was not a risk factor.[66] A 2020 review looked specifically for risk with daptomycin and EP and found no association with age and sex. It also did not find an increased risk with high treatment doses. The study found, however, that around 30% of patients had diabetes or renal impairment.[75]

Discontinuation of daptomycin should occur after a probable or definitive diagnosis of daptomycin-induced EP. Patients can experience respiratory failure from EP and may require oxygen supplementation or mechanical ventilation. Treatment can include a steroid taper starting with methylprednisolone and converting to prednisone over two to six weeks if appropriate.[65,66]

Daptomycin-Induced Myopathy

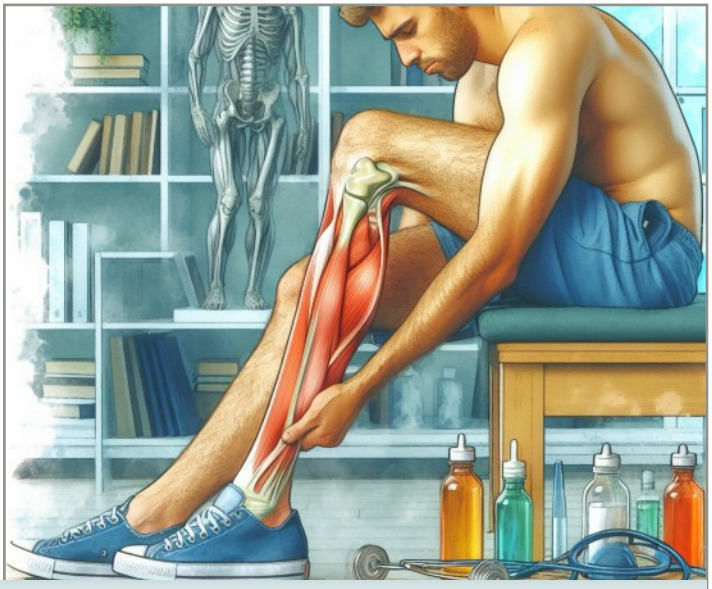
Skeletal muscle effects are a rare but serious adverse event associated with daptomycin use. This adverse event presents as muscle weakness and pain, typically preceded by creatine phosphokinase (CPK) elevations.[76] In clinical trials, up to 6.7% of patients had elevated CPK levels, and daptomycin-associated myopathy occurred in 2% to 14% of patients.[77,78] During early clinical trials in the 1990s, researchers used 12-hour dosing intervals, but adverse skeletal muscle effects prohibited the trials from continuing.[79] Trials eventually restarted when once-daily dosing in dogs showed a lower incidence of CPK elevations.[80] Dosing frequency has a more direct relationship on skeletal muscle than peak plasma concentrations, making once daily daptomycin safer to administer than twice daily.[80]

Skeletal muscle releases CPK from cells after various circumstances, including infections, intramuscular injections, and intense physical activity.[81] The effect of daptomycin on skeletal muscle is thought to be from the drug's mechanism of action. Daptomycin works by breaking down the cell wall of bacteria, creating an opening, and causing a release of intracellular ions. In skeletal muscle, daptomycin also opens the cell wall and causes a release of intracellular CPK.[82] Less frequent administration of daptomycin decreases the likelihood of CPK release as it allows skeletal muscle cells more time to repair.[82]

Patients on concurrent statin therapy or who are obese (BMI >30) are at an increased risk of developing myopathies.[78] Daptomycin-induced myopathy is more likely to be seen with elevated daptomycin trough levels, but testing trough levels is expensive. Monitoring recommendations include weekly CPK levels to prevent skeletal muscle adverse events. More frequent monitoring should occur in patients with risk factors.[64,76] Holding statins when appropriate can help prevent adverse events during daptomycin administration.[78] Adverse skeletal muscle effects are reversible upon discontinuation of daptomycin.[76] Clinicians should discontinue daptomycin when CPK levels are more than 2000 U/L in asymptomatic patients or patients with CPK levels greater than 1000 U/L in symptomatic patients with no other reasoning for myopathies.[64]

QT Prolongation

Medications are the most common cause of QT prolongation.[83] Medications can block specific outward potassium channels (IKr channels) in the heart, leading to QT prolongation. The slowing of outward potassium increases the plateau phase of the action potential, and electrocardiograms show a longer QT interval.[84] When potassium remains in the heart, the heart is kept at a



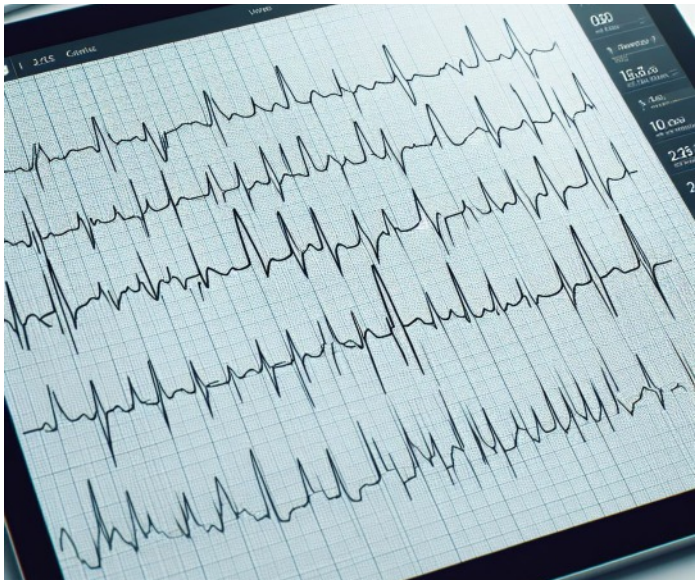
positive charge that can prolong the repolarization phase. During this time, an ectopic beat generated by the heart can lead to Torsades de Pointe (TdP), a very dangerous and sometimes fatal arrhythmia.[85] Antibiotics like fluoroquinolones (FQ) and macrolides block IKr channels and can cause QT prolongation, which can potentially cause harm in patients with risk factors.

Macrolides and FQs are the most widely prescribed drugs in the inpatient and outpatient setting.[83] Levofloxacin and erythromycin have been cited most frequently for prescriptions in critical care and outpatient settings that cause QT prolongation.[86,87] A 2003 study found that a single dose of FQ administered to healthy patients can significantly prolong the QT interval when compared to placebo. The study demonstrated that moxifloxacin caused the most notable change, followed by levofloxacin and ciprofloxacin.[88] Ciprofloxacin and levofloxacin have more case reports of TdP than other fluoroquinolones but have a lower risk of QT prolongation. Their widespread use plays a more significant role in the incidence of TdP than their actual risk of developing QT prolongation.[83]

A study reviewed the FDA Adverse Event Reporting System for patients who developed TdP. One-half of reports included macrolide use with no other concurrent QT-prolonging medications.[89] Of all the reports, 53% involved erythromycin use, while clarithromycin and azithromycin were 36% and 11%, respectively; further, in all of the reports that included erythromycin, 49% used intravenous (IV) erythromycin.[89] Of note, IV erythromycin use accounts for much less than other dosage forms with ointment at 66.1% of all prescriptions in 2020, oral dosages at 29.8% and all other forms including IV at 4.1%.[90]

PAUSE AND PONDER: What medications can indirectly affect QT?

The risk of QT prolongation with antibiotics is difficult to assess as several factors can influence risk. Potassium channel blockade is concentration dependent; anything that increases the medication's concentration will increase risk of QT prolongation.[83] Examples are rapid intravenous administration and impaired clearance through inhibition of hepatic metabolism.[83,91] Another important risk factor to consider is female sex, especially elderly females.[83,84,91,92] Female patients have consistently developed prolonged QT at a rate much higher than males and are more commonly prescribed medications that prolong the QT interval than males.[87] Older patients are more at risk for QT prolongation but are also more likely to have structural heart disease, drug interactions, and decreased drug clearance.[93] Risk assessments for QT prolongation should consider structural heart disease, subclinical long QT syndrome or genetic abnormalities, electrolyte abnormalities like hypokalemia and hypomagnesium, and patients with a family history of sudden death.[83,91,92] Pharmacists need to review concurrent medications for drug interactions that cause direct QT prolongation



and medications that can affect QT indirectly, like diuretics, which can lead to electrolyte abnormalities.[92]

For inpatients, baseline and subsequent electrocardiogram monitoring is an option for patients at high risk for QT prolongation, but it is too expensive to perform on every patient.[92] Counseling for outpatients should include warning signs of arrhythmias like palpitations and near-syncope or syncope and other conditions that can affect potassium levels, like gastroenteritis or the addition of a diuretic.[92] A risk assessment for QT prolongation is imperative for every patient started on a fluoroquinolone or macrolide.

Tendinopathy with Fluoroquinolones

In 1995, the FDA warned about the possibility of tendon rupture with fluoroquinolones.[94] Since then, several studies have looked at the risk of tendinopathies with FQ and found that they are associated with a two to four times increased risk of acute tendinopathy and tendon rupture. The risk is highest in the first month after drug exposure.[94,95] The Achilles tendon is most commonly involved as it is a weight-bearing tendon and more susceptible to injury, but any can occur in any tendon.[95-97]

The mechanism of action of tendinopathy from fluoroquinolones needs to be better understood and may be multifactorial. One proposed mechanism is that fluoroquinolones increase substances known to cause tendons' breakdown. In a study, matrix metalloproteinase (MMPs) increased after exposure to ciprofloxacin. MMPs cause collagen breakdown, which makes up 70% of tendons.[98] Another proposed mechanism is chelation. A study looked at connective tissue of magnesium-deficient dogs and found that the tissue had a similar damaged appearance to tissue treated with FQs. The study hypothesized that because FQs chelate with cations like magnesium, its effect on joints is similar to magnesium deficiency.[99]

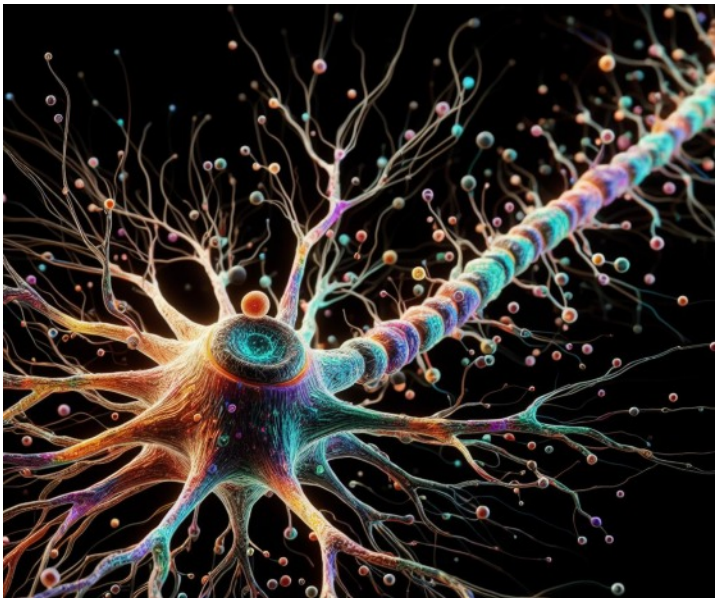
Patients are at a higher risk of developing tendinopathies with FQs if they are older than 60 years, transplant recipients, or on concurrent corticosteroid therapy.[94] Prescribers should avoid concurrent use of steroids and FQ as the risk of tendon rupture increases by 14-fold.[94] Treatment recommendations are discontinuing the offending agent and using supportive therapy like analgesia and physical therapy.[95] Approximately 90% of patients recover without surgery in one month, but 10% develop long-term adverse effects like difficulty walking, decreased mobility, and pain.[96]

Cefepime-Induced Neurotoxicity

Cefepime is a 4th generation cephalosporin available since 1997.[100] The package insert for cefepime warns against neurotoxicity, but it is a potential adverse effect with all beta-lactam antibiotics.[101] Beta-lactams cause neurotoxicity because they antagonize the gamma-aminobutyric acid (GABA) receptor to varying degrees.[102] Beta-lactams all have an affinity for GABA receptors because they are all structurally similar to GABA.[103,104] Cephalosporins, including cefepime, competitively inhibit the GABA receptor by binding directly to the receptor.[105,106]

Cefepime-induced neurotoxicity (CIN) typically presents as encephalopathy, somnolence, agitation, confusion, and disorientation, while aphasia and hallucinations are less common.[107-109] Patients occasionally will develop convulsions or non-convulsive status epilepticus.[110]

The most significant risk factor for CIN is renal dysfunction.[100,104,108] When a patient with poor renal function receives cefepime, a higher concentration of unbound medication stays within the cerebrospinal fluid, causing symptoms when it enters the central nervous system.[108] A study of 42 patients with CIN found that 93% of patients with neurotoxicity had abnormal renal function, and 76% of the studied patients had their cefepime dose adjusted appropriately.[102] A study has shown that CIN occurred despite dose reductions and even in dosages of 500 mg daily in patients with ESRD.[111]



In addition to renal dysfunction, several other risk factors for CIN need review. Overdose or use of excessive dosages puts patients at risk for CIN, and it is much more likely to be seen in patients without appropriate dose adjustments.[108,109] Drug monitoring sometimes includes measurement of the medication in the blood called a peak (highest) and trough (lowest) levels. A study has associated CIN with high trough levels. The study showed neurotoxicity did not occur at troughs of less than 7.7 mg/L, while it always manifested at troughs at or eceeding 38.1 mg/L. The study's author has suggested a trough of 7.5mg/L as a potential target.[112] Patients 65 and older are at risk because of pharmacokinetic changes.[100,113] Although age is a significant risk factor, CIN will occur in 25% of patients younger than 65.[100] Last, patients with underlying brain diseases like cerebrovascular accident, Korsakoff's syndrome, small-vessel disease, Alzheimer's disease, benign brain tumor, malignancy, or previous seizures are at risk for CIN.[108,114]

Prescribers should discontinue cefepime in patients who develop suspected CIN.[100,108] It typically takes two to three days to resolve symptoms.[100,108] Providers can initiate dialysis in patients experiencing severe symptoms as it can rapidly decrease the concentration of cefepime.[114] Medications that stimulate the GABA receptor, like benzodiazepines or barbiturates, are more effective than phenytoin in patients who develop seizures.[104] Last, switching antibiotics can sometimes resolve symptoms, but symptom prolongation can occur with other beta-lactams like piperacillin and meropenem. Consider alternative antibiotic classes in appropriate patients.[108]

Linezolid-Induced Thrombocytopenia

Linezolid belongs to a class of medications called oxazolidinones. The discovery and investigation of oxazolidinones occurred in the late 1980s, but development did not continue due to severe adverse events in animals.[115] In the 1990s, scientists from the Pharmaca Corporation derived linezolid from the oxazolidinones class, and the FDA approved its use in April 2000 after clinical safety testing.[116] Linezolid has a considerable advantage for treating severe gram-positive infections as it is available intravenous (IV) but also has 100% oral bioavailability.[117] Another advantage of linezolid is it's relatively safe to use, with only 0.4% of patients experiencing severe adverse effects in phase 3 trials.[115] Several case reports of adults experiencing varying types of myelosuppression, like anemia or pancytopenia, emerged following linezolid's clinical approval, but thrombocytopenia (low platelets) is the most prevalent.[115]

Linezolid-induced thrombocytopenia (TP) takes approximately seven to 14 days before onset.[115,118] Reports of TP differ depending on geographical location or definition used.[118-120] TP typically takes around 14 days to develop because the platelet

has a seven to ten day life cycle.[115] Although studies have proposed several mechanisms, a definitive cause has yet to be established.[120]

Patients with the following risk factors need monitoring for the development of thrombocytopenia[115,118,121,120]:

- Prolonged treatment course greater than 14 days
- Underlying disease with a predisposition to hematologic abnormalities
- Renal dysfunction, CrCl less than 30 ml/min, and dialysis. Linezolid is not primarily cleared renally but metabolized into two compounds. These compounds are renally eliminated and can accumulate in patients with renal dysfunction and may play a role in the development of thrombocytopenia
- Chronic liver failure
- History of vancomycin use
- Low baseline platelet level of less than 200
- Low body weight–Linezolid dosing does not change for adults nor require renal or hepatic impairment adjustment. When body weight decreases and total mg/kg of linezolid increases, the risk of thrombocytopenia increases. A study found that daily mg/kg doses between 22-27 (body weight between 55-70 kg) had a 48% chance of developing thrombocytopenia versus 72% in dosages greater than 27 mg/kg (body weight less than or equal to 45kg).

Discontinuation of linezolid should occur for patients who develop thrombocytopenia or any myeloid cell abnormality while on therapy.[115] Myelosuppression is reversible after discontinuation of linezolid. Patients actively receiving therapy should have weekly monitoring of complete blood count and renal function monitoring.[121] Monitoring is essential in patients receiving treatment for longer than 14 days, have pre-existing myelosuppression, take concurrent medications that cause myelosuppression, or have received prior antibiotic therapy from a chronic infection.[117]

Reporting ADRs

Identifying ADRs as they occur is vital to comprehensive patient care, but reporting ADRs is equally essential. The FDA established MedWatch in 1993 as a tool for healthcare providers and consumers to voluntarily report ADRs. ADRs can be reported through MedWatch or directly to drug manufacturers, who then are required to report ADRs to the FDA. The FDA uses the reported ADRs to make up the Adverse Event Reporting System (AERS), a postmarketing surveillance database. The information entered into AERS helps identify trends that are useful in determining causes and preventing prospective events.[122,123]

PAUSE AND PONDER: Why is it important to include so much information when reporting ADRs?

The FDA defines a serious Adverse Drug Event (ADE) as fatal, life-threatening, incites hospitalization or prolongation of existing admission, causes significant disability, or congenital disability or anomaly to the patient.[124] The FDA asks healthcare providers and manufacturers to report all serious ADEs. Healthcare providers, including pharmacists, should also report any non-serious unexpected ADEs. These reports are helpful, even if the reaction is not directly related to the drug, as the reports may help discover unidentified ADEs. Healthcare providers should submit as much information as possible that is relevant to the ADE.[122] **Table 3** (next page) includes essential information to include in ADE reporting.

Image by Freepik

Table 3. Key-Inclusions for High-Quality ADE Report[125]

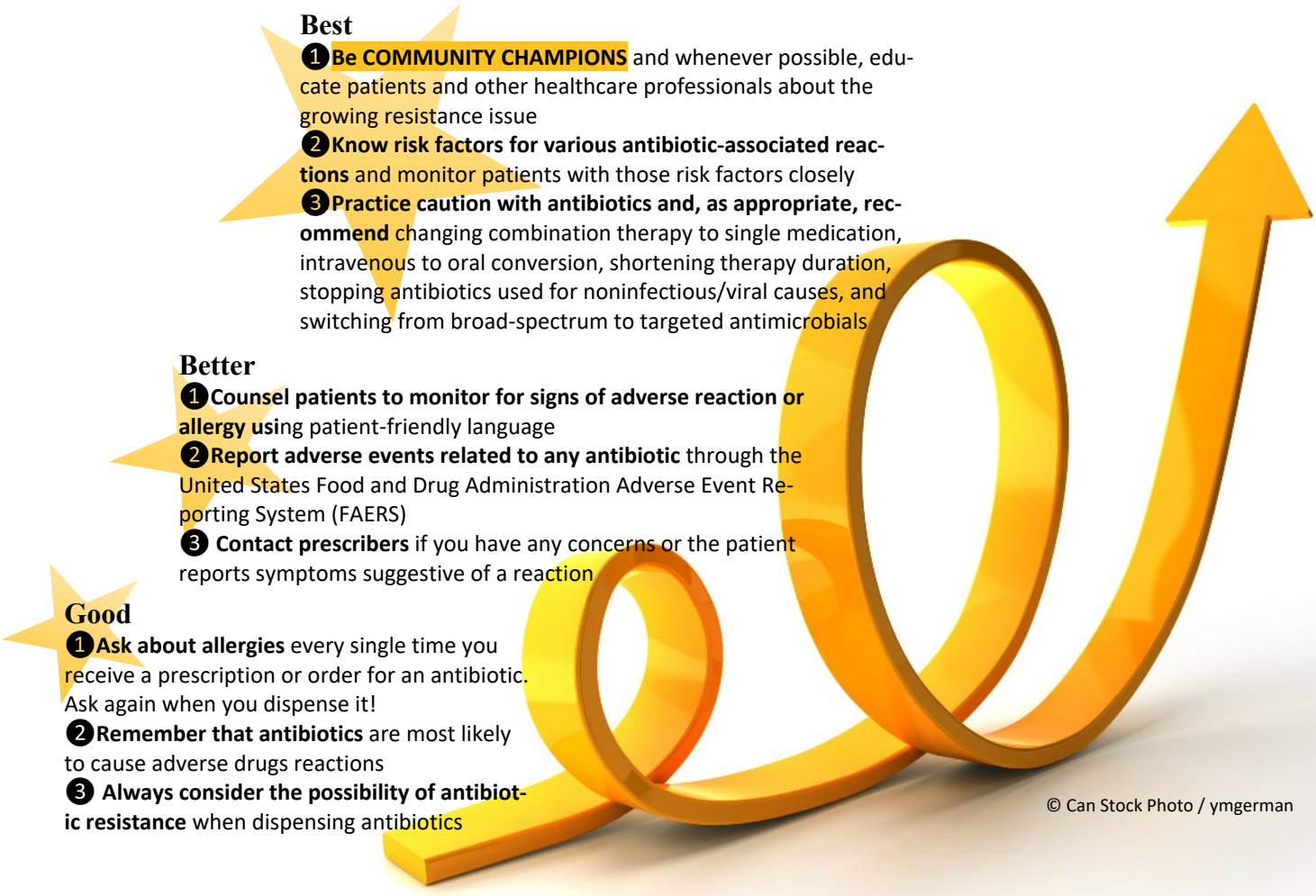
- Clear description of event or outcome, include time to onset of signs and symptoms;
- Suspected and concurrent medications details: dose, lot number, schedule, dates, duration (Include non-prescription medications, dietary supplements, and any recently discontinued medications);
- Patient characteristics, including demographics (e.g., age, sex, race), baseline medical condition prior to treatment, co-morbid conditions, medication allergies, relevant family history, other risk factors;
- Documentation of diagnosis, including methods of making diagnosis;
- Clinical course of event and outcome (e.g., death, hospitalization, treatment);
- Relevant objective information (e.g., laboratory data) at baseline, during therapy, and after therapy;
- Response to discontinuation of therapy and re-initiation if available;
- Any other relevant information.

Conclusion

This continuing education activity discusses only a fraction of commonly experienced adverse drug reactions associated with antibiotics. It is not an exhaustive list, but it provides valuable guidance for healthcare providers for antibiotics with established reactions and serves as a reminder to report any serious or atypical reactions that may occur while using new antibiotics.

Antibiotic-associated adverse drug reactions are a significant concern in healthcare. These reactions occur when antibiotics lead to unintended harmful effects, such as allergic reactions, organ damage, or antibiotic resistance. Inappropriate use or overuse of antibiotics increases risk of adverse reactions. Decreased renal and hepatic function, elderly patients, and drug interactions are common risks of developing ADRs in antibiotics. Recognizing risks and following recommended monitoring can help prevent ADRs from occurring. Anyone directly involved in direct patient care should report suspected ADRs and educate patients on the impact of these events to ensure the safe and effective use of antibiotics.

Figure 1. Key Points to Remember when Dispensing Antibiotics



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