Complications of Antibiotic Therapy

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KEYWORDS

• Antibiotics • Side effects • Drug interactions • Drug-induced lupus

KEY POINTS

- Macrolides and quinolones are associated with QT prolongation.
- Amoxicillin/clavulanate is probably the most common antibiotic to cause drug-induced liver disease.
- Trimethoprim/sulfamethoxazole is associated with many important side effects including agranulocytosis, hemolytic anemia, hyperkalemia, and the highest risk for cutaneous allergy. It also is the cause of severe drug interactions with warfarin and methotrexate.
- Quinolones have several unique side effects including tendonitis and tendon rupture, as well as retinal detatchment. Quinolones are also an important cause of delirium and hallucinations in elderly patients.

INTRODUCTION

Antibiotics can be life-saving, and help in treating many infectious diseases. Antibiotics also pose the risk of predisposing patients to superinfections, and can have serious direct toxicities and side effects. Antibiotics are also common causes of drug interactions that can cause other prescribed medications to increase to dangerously high levels, creating severe problems. Knowing the risk of drug interactions and understanding direct toxicities of antibiotics help physicians make wise choices in their use by allowing an appropriate assessment of risk versus benefit and making selections that are less risky for patients.

ANTIBIOTIC COMPLICATIONS BY SYSTEM

Hematologic

There are many potential hematologic complications of antibiotic therapy. Perhaps the best known are immune hemolytic anemia (IHA), the most common offenders being

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cefotetan, ceftriaxone, piperacillin, and, less commonly, other β-lactamase inhibitors.[1] In cases of drug-induced IHA, a history of previous exposure to the drug is common, the time course of development of the anemia is helpful in making the diagnosis, and treatment is primarily withdrawal of the drug. That said, it is often difficult to differentiate between a drug-induced IHA and an idiopathic autoimmune hemolytic anemia, direct antiglobulin testing being positive in both cases.

Antibiotics can also result in anemia by other mechanisms. Sulfonamides, nitrofurantoin, and dapsone can precipitate a hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency is the most common erythrocyte enzyme deficiency, and can be caused by various mutations on the X chromosome. It is particularly common among people of African descent. Because of the high frequency of the mutation coupled with the common use of trimethoprim/sulfamethoxazole (TMP/SMX) and dapsone in patients with human immunodeficiency virus (HIV) disease, many physicians providing care to HIV-positive patients will screen for this mutation. Aplastic anemia is a well-known potential adverse effect of chloramphenicol, now rarely used, but it can also occur with sulfonamides, albeit with a much lower frequency.[2] Isoniazid can cause an isolated/pure red cell aplasia.

Isolated thrombocytopenia is also a known potential side effect of antimicrobial therapy. Agents implicated include linezolid and TMP/SMX; less commonly reported are piperacillin and vancomycin.[3] Patients requiring prolonged treatment with linezolid (>2 weeks) should be monitored for development of thrombocytopenia and, though less common, anemia.

Another hematologic side effect seen in long-term antibiotic therapy is agranulocytosis. Historically this was a concern with prolonged nafcillin therapy; now that there are agents with more favorable dosing schedules, this medication is rarely used for a prolonged period. Other agents associated with this very rare but concerning complication include dapsone, TMP/SMX, β-lactams, and erythromycin.[4–6]

Cardiac

Multiple antibiotics are associated with QT prolongation and, in turn, an increased risk of sudden cardiac death attributed to torsades de pointes. It should be noted that the risk in the general population is low. For example, in a recent study assessing risk of sudden cardiac death in patients on azithromycin there were 47 additional cardiovascular deaths per 1 million antibiotic courses[7]; however, both drug-drug interactions and patient factors such as baseline cardiovascular disease/risk factors can increase the risk further.

Antimicrobials associated with QT prolongation include macrolides and quinolones, antifungal azole agents, and pentamidine. The macrolides clarithromycin and erythromycin have historically been reported to be the antibiotics most highly associated with torsades de pointes, although recent publications have also implicated azithromycin.[7,8] This class of antibiotics likely increases risk based on 2 mechanisms, a direct effect of potassium channels and inhibition of cytochrome P450 enzymes leading to increased levels of other QT-prolonging medications, the latter less so with azithromycin. Quinolones are another class of very commonly prescribed antibiotics associated with QT prolongation. Cardiac fatalities have led to the withdrawal of some quinolones (most notably gatifloxacin) from the market. These medications primarily appear to result in QT prolongation owing to effects on potassium channels, and less so because of drug-drug interactions. Risk of QT prolongation is highest with moxifloxacin.[9]

When prescribing antibiotics that carry an increased risk of QT prolongation, it is important to be mindful of additional risk factors that may amplify this otherwise small risk. Such factors include: (1) drug-drug interactions, for example prescription of

erythromycin and diltiazem, which results in elevated erythromycin levels; (2) additive effect of being on multiple QT-prolonging medications, other common culprits being methadone and antipsychotic agents; and (3) patient factors resulting in an increased inherent cardiac risk, including cardiomyopathy, electrolyte abnormalities, or renal failure leading to increased drug levels.

Respiratory

Overall pulmonary complications of antibiotic therapy are rare. Nitrofurantoin is an antibiotic used for treatment of both acute cystitis and prevention of recurrent cystitis. It can rarely be associated with pulmonary toxicity, occurring in less than 1% of patients on nitrofurantoin. The most common pulmonary reaction is an acute pulmonary toxicity, likely a hypersensitivity reaction. Within a month of starting therapy, patients present with systemic manifestations, including fever and rash, and pulmonary symptoms, including cough and dyspnea. Evaluation will frequently reveal eosinophilia and bilateral infiltrates on chest radiography.[10] Patients typically recover quickly with discontinuation of the drug, and should not be rechallenged with this medication in the future. Less common is a chronic nitrofurantoin pulmonary toxicity, which presents insidiously with cough and dyspnea in patients on chronic, daily nitrofurantoin, sometimes years after starting therapy. Laboratory evaluation may reveal a positive antinuclear antibody (ANA) test, and lung computed tomography will reveal a pattern consistent with pulmonary fibrosis, bilateral ground-glass opacifications, and contraction bronchiectasis. The mainstay of treatment is withdrawal of the drug. Fibrosis may be irreversible, although there are reports of slow improvement.[10] The role of corticosteroids is debated.

An even less commonly reported complication of long-term nitrofurantoin use is immune-mediated concomitant pulmonary and liver disease. It is recommended that patients with chronic pulmonary toxicity be screened for concomitant liver disease.

Gastrointestinal

Patients treated with antibiotics frequently develop diarrhea and although *Clostridium difficile* is obviously of great concern, the majority of cases will not be attributable to this infection. In general, antibiotic-associated diarrhea may occur in 10% to 25% of patients treated with amoxicillin-clavulanate, 15% to 20% of patients treated with cefixime, 5% to 10% of those treated with amoxicillin, and 2% to 5% of patients treated with other cephalosporins, fluoroquinolones, macrolides, and tetracycline.[11] Although it is difficult to clinically differentiate between *C difficile* infection and non–*C difficile* antibiotic-associated diarrhea, characteristics of non–*C difficile* diarrhea may include patient history of antibiotic-associated diarrhea, more moderate severity of diarrhea, and an otherwise benign physical examination, for example a normal abdominal examination and normal vital signs.

Judicious use of antibiotics is likely the best form of prevention, although clearly at times antibiotic use cannot be avoided. There is limited evidence that use of probiotics may be beneficial in the prevention of antibiotic-associated diarrhea, although studies have used a variety of probiotic preparations including bacteria and yeast. At present, both the optimal probiotic formulation and the correct dosing remain unclear.[12]

Nausea is a symptom frequently encountered in practice for which it is often difficult to identify a specific cause, although it should be noted that there are some antibiotics for which this is a very common side effect, including erythromycin (25%), metronidazole (12%), TMP/SMX (>10%), fluoroquinolones (2%–8%), and, to a lesser extent, amino-penicillins (eg, amoxicillin) and third-generation and fourth-generation

cephalosporins.[13] The temporal relationship of the side effect (nausea) with initiation of antibiotic therapy will often be the best hint that this is the origin.

A less common gastrointestinal side effect of antibiotic therapy is pill esophagitis, associated primarily with doxycycline. Symptoms include substernal chest pain and odynophagia.[14] This side effect can be prevented by having the patient take the medication with a full glass of water and avoid lying down for at least 30 minutes after taking the medication.

Hepatobiliary

Several antibiotics have notable liver toxicities. As discussed elsewhere in this article, nitrofurantoin and minocycline have reported hepatic toxicities. Other agents known to cause drug-induced liver injury (DILI) are amoxicillin/clavulanic acid, sulfonamides, macrolides, and quinolones, in addition to several antituberculosis agents, most notably isoniazid. Amoxicillin/clavulanate may be the most common antibiotic implicated in DILI, and the risk seems to be increased in older patients. DILI remains a rare side effect; overall, the estimated frequency reported in studies is low, for example, 1.7 per 10,000 treatment courses.[15] Estimates regarding the frequency of liver injury for sulfonamides are also somewhat low; the frequency in cases resulting in hospitalization has been estimated to be 4.8 per million patients treated.[16] Ceftriaxone can cause biliary sludge and can trigger acalculous cholecystitis; this is much more common with prolonged courses of the drug, such as in the treatment of endocarditis or osteomyelitis.

Renal

Antibiotics can be nephrotoxic by way of several mechanisms. In the inpatient setting antibiotics such as intravenous aminoglycosides, amphotericin, colistin, and vancomycin can result in kidney injury. In the case of vancomycin it remains debatable as to what degree the nephrotoxicity is due to the medication itself rather than patient factors that independently increase the risk of acute kidney injury, such as hypotension.[17] It should also be noted that the risk is higher when vancomycin is dosed to maintain high trough levels; again this is fraught with confounders, given these are typically sicker patients overall.

Allergic interstitial nephritis (AIN) is a hypersensitivity reaction rather than a direct nephrotoxic side effect of a drug. In keeping with this, AIN is most commonly seen with the antibiotics most commonly associated with hypersensitivity reactions, such as β-lactams and sulfonamides; other agents implicated include quinolones, most commonly ciprofloxacin, erythromycin, vancomycin, and minocycline. In addition to renal manifestations, patients may present with systemic symptoms such as fever and rash, which is most common with the β-lactam antibiotics and sulfonamides. The classic laboratory finding of eosinophiluria is in fact not as good a screening test as is commonly believed; the sensitivity is likely only 67%, although the specificity is 87%.[18] Definitive diagnosis is made by kidney biopsy. Treatment involves withdrawal of the offending agent. It is unclear whether corticosteroid therapy is of benefit.

Electrolyte Abnormalities

Hyperkalemia is a common side effect of TMP/SMX therapy. Because of direct effects of the medication on the distal renal tubules, serum potassium is increased in approximately 20% of patients. These interactions are of well-documented clinical significance. Studies have found that patients on renin-angiotensin blocking antihypertensives who are prescribed TMP/SMX have a 7-fold increased risk of hospitalization for hyperkalemia compared with patients on the same antihypertensives prescribed amoxicillin.[19] Similarly, risk of hospitalization for hyperkalemia was

increased 12-fold in patients on chronic spironolactone prescribed TMP/SMX in comparison with amoxicillin.[20] For this reason, caution should be exercised when prescribing this antibiotic to patients with a predisposition to hyperkalemia resulting from renal disease or other medications such as spironolactone, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Elderly patients are at greatest risk for this complication.

Aminoglycosides are rarely used in outpatient practice, but are well known for their nephrotoxic side effects. An aminoglycoside occasionally used in the outpatient setting of management of drug-resistant tuberculosis infection is capreomycin, given by intramuscular injection. This agent is associated with frequent hypokalemia.[21]

Hypokalemia is also associated with penicillin and antistaphylococcal penicillins such as nafcillin and dicloxacillin, although the clinical implications of this in outpatient practice are negligible. This side effect has been reported in the setting of large-dose parenteral therapy.[22]

Genitourinary

Vulvovaginal candidiasis is a common complication of antibiotic therapy. Studies indicate that up to one-quarter of women treated with a short course of oral antibiotics develops symptomatic vulvovaginal candidiasis.[23,24] Median onset in one of the larger studies was 5 days, based on enrollment criteria that would be 5 to 7 days after starting antibiotic therapy.[24] Women with a history or vulvovaginal candidiasis after antibiotic treatment were, not surprisingly, at higher risk of developing this complication again. Women frequently use probiotics in various oral and vaginal preparations to prevent this complication, although there are no strong data to support this.[25,26]

Rheumatologic

Drug-induced lupus is characterized by development of symptoms of idiopathic systemic lupus erythematosus (SLE) in the setting of exposure to a medication and with resolution of the symptoms with discontinuation of the medication. Several antibiotics are associated with drug-induced lupus, most notably minocycline, with an estimated incidence of 5 cases per 10,000 prescriptions.[27] Other antibiotics associated with drug-induced lupus are isoniazid and nitrofurantoin. In the case of minocycline, patients are frequently young women; otherwise, drug-induced lupus tends to occur in older patients with equal frequency in both genders, quite unlike idiopathic SLE. This complication typically occurs after patients have been on the offending drug for a prolonged period; longer duration of therapy and higher cumulative dose of the medication are both risk factors in its development.

Minocycline-induced lupus typically presents with arthralgias, myalgias, fatigue, and fever, and is unique in its association with hepatic manifestations. Less commonly, it is associated with cutaneous manifestations and rarely with pleuritis or pericarditis. Patients will typically have elevated inflammatory markers, namely erythrocyte sedimentation rate and, again somewhat unique to minocycline-induced lupus, an elevated C-reactive protein and transaminitis. A positive ANA test is typical, though not required to make the diagnosis of drug-induced lupus. Although antihistone antibody is present in more than 90% of cases overall, it is only present in the minority of the minocycline-associated cases.[27] Other laboratory findings commonly found in minocycline-induced lupus is a positive perinuclear antineutrophil cytoplasmic antibody, present in 67% to 100% of patients, and anti-Smith antibodies, present in approximately 40% of patients.[27]

Dermatologic

The most common dermatologic adverse reaction associated with antibiotic therapy is a drug-induced exanthem, a "drug rash." The classic description is a maculopapular eruption, particularly prominent on the trunk, symmetric in distribution overall. Unlike viral exanthems, these drug-induced rashes are typically pruritic. The most common antibiotics implicated are penicillins including aminopenicillins (eg, amoxicillin), antistaphylococcal penicillins (eg, dicloxacillin), and the antipseudomonal penicillins (eg, piperacillin), in addition to sulfonamides (eg, TMP/SMX). The rash typically starts within 7 to 14 days of initiation of therapy. A population at particularly high risk of developing adverse cutaneous reactions to antibiotics is patients with HIV disease; up to 40% of HIV-positive patients on TMP/SMX will develop a cutaneous adverse reaction.[28] Management, in all patient populations, involves removal of the offending agents. If needed, oral antihistamines and topical steroids can be prescribed for associated pruritus.

Should a patient with a drug rash have significant systemic symptoms, such as fever and abdominal pain, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) should be considered. This rare, poorly understood, but life-threatening drug reaction has mortality rates of up to 10%.[29] A recent review found antibiotics implicated to include minocycline, dapsone, vancomycin, and sulfonamides, although nonantibiotic pharmacologic agents such as allopurinol and anticonvulsants are more common causes.[29] Presentation is typically 2 to 6 weeks after drug therapy is initiated, symptoms typically including a diffuse morbilliform rash, hypereosinophilia, lymphadenopathy, and, frequently, hepatitis, although other organ systems can also be affected. Management includes withdrawal of the offending agent. Patients are also frequently treated with corticosteroids, although treatment recommendations remain an area of active investigation.

Another important life-threatening dermatologic complication of antibiotic therapy is Steve Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), conditions of similar pathophysiology, differing mainly according to the extent of skin involvement. SJS is defined as involving less than 10% and TEN greater than 30% of body surface area, with an overlap syndrome in patients falling between these two levels. Mortality is high, at 5% for SJS and 30% for TEN. Patients are typically relatively young, 20 to 40 years old.[30] These are rare diseases most commonly caused by medications; antibiotics implicated include sulfonamides and β-lactams. These conditions are thought to represent hypersensitivity reactions. A typical patient will frequently develop systemic symptoms such as fever and malaise, even before onset of a painful blistering rash. Nikolsky's sign (lateral pressure resulting in shearing of the skin) is present, though not pathognomonic. Treatment involves removal of the offending agent and supportive care, with patients often requiring intensive care in settings such as a burn unit.

Penicillins and TMP/SMX are the most common antibiotics associated with drug-induced urticaria, another hypersensitivity reaction. These hives manifest quickly, within minutes to hours, and can be life-threatening if associated with angioedema or anaphylaxis. Should patients have a history of life-threatening penicillin hypersensitivity reactions, caution is advised when prescribing cephalosporins, as approximately 10% will have cross-reactivity, which in the case of a life-threatening reaction would rarely outweigh the benefit.[31] Although structurally similar to cephalosporins and penicillins, cross-reactivity with carbapenems (imipenem and meropenem) and monobactams (aztreoman) does not occur; therefore, these antibiotics can be safely used in patients with a history of hypersensitivity reactions to penicillin.[6]

Fixed drug eruptions are likely underdiagnosed cutaneous drug reactions, which present as well-demarcated erythematous patches with a predilection for the face,

lips, genitalia, or buttocks. On the first exposure they typically occur 1 to 2 weeks after the antibiotic is started; subsequent exposures will result in the eruption occurring within days, in the same location. Antibiotics implicated include sulfonamides (TMP/SMX), tetracyclines, metronidazole, ampicillin, and dapsone.[28] Use of the offending agent should be avoided in the future.

Photosensitivity is common and is associated with many antibiotic agents, including doxycycline and ciprofloxacin. Doxycycline is one of the most common offenders, studies reporting rates of up to 20%.[32] This figure is of particular interest because doxycycline is frequently prescribed for malaria prophylaxis to patients traveling to sunny locations. Use of sunscreen should be advised.

Neurologic

Peripheral neuropathy can be a manifestation of toxicity to several antibiotic agents including isoniazid, metronidazole, and nitrofurantoin. In the case of isoniazid, typically used to treat latent tuberculosis, peripheral neuropathy can be prevented by concomitant administration of vitamin B_6, pyridoxine. Metronidazole-associated and nitrofurantoin-associated neuropathy is seen in patients on long-term therapy; in ambulatory medicine nitrofurantoin is often used daily for prevention of urinary tract infections, and patients with recurrent *C difficile* infection may receive multiple courses of metronidazole. These patients need to be monitored for signs or symptoms of neurotoxicity and, if noted, the medication should be discontinued. Metronidazole-induced peripheral neuropathy is predominantly a sensory neuropathy that usually improves once therapy is stopped. It is more common with longer courses of therapy. Metronidazole has also been rarely a cause of reversible optic neuritis and cerebellar disease.

Ciprofloxacin and imipenem are both known to carry an increased risk of seizure in patients predisposed to seizure, such as patients with a history of seizures, or at risk of accumulating high levels of the drug in their system, such as those with renal failure.[33] In neither case is this clearly a class effect; neither fluoroquinolones such as levofloxacin nor carbapenems such as meropenem seem to carry a significant risk.

Delirium is frequently multifactorial and common in the setting of infection, therefore teasing out if antibiotics are deliriogenic can be challenging. However, fluoroquinolones, ciprofloxacin more so than levofloxacin, have frequently been implicated in drug-induced delirium[34,35]; this does not preclude their use in the elderly, although this is something providers should be aware of.

Drug Fever

Parenteral therapy with β-lactams (penicillins and cephalosporins) is associated with drug-induced fever, as is therapy with several other antibiotics including sulfonamides. Diagnosis requires that infectious causes are ruled out. Laboratory abnormalities frequently noted in the case of drug fever include mild transaminitis, possibly eosinophilia; clinically patients are often noted to appear well and not to have the expected tachycardia associated with fever.[6] Regarding the discussion on drug-induced lupus, fever can be an adverse effect associated with minocycline use. Fever is also seen in other drug-related syndromes such as DRESS and serotonin syndrome, which can be a complication of therapy with serotonin-specific reuptake inhibitors (SSRIs), alone or in combination with other medication, notably the antibiotic linezolid.

ANTIBIOTIC COMPLICATIONS BY CLASS/AGENT

Fluoroquinolones

Quinolone antibiotics are associated with tendinopathy, in particular Achilles tendonitis and tendon rupture. Overall the rates of these complications are low, 3.2 cases per 1000 patient-years for tendonitis,[36] and even less frequent for tendon rupture, but there are likely some groups at higher risk for whom quinolones must be used with caution. It appears that the risk of tendonitis is higher in patients older than 60 years and those also on corticosteroids,[36] and there may also be an increased risk in patients with renal failure.

An additional rare adverse effect of quinolones is retinal detachment. Given the high rates of vision loss with this complication, this is a potential complication that providers should be aware of. It is estimated that the absolute increase in risk of retinal detachment in patients on fluoroquinolones is 4 per 10,000 person-years,[37] although it is difficult to be precise in the quantification of this risk given its rarity. Based on available evidence, it is unknown if any one fluoroquinolone is more likely to causes this side effect than others, and also unknown if there are specific patient groups at higher risk. This uncommon side effect should not preclude use of the antibiotic, but it is yet another reminder that antibiotics must always be used judiciously, assuring that the potential risks do not outweigh the benefits. In addition, should a patient on a fluoroquinolone develop symptoms that could be consistent with retinal detachment, such as new "floaters," they should be referred quickly to an ophthalmologist for evaluation.

Linezolid

Serotonin syndrome is a potentially life-threatening condition that results from toxic elevations of serotonin in the central nervous system. Symptoms include neuromuscular hyperactivity such as clonus and rigidity, autonomic hyperactivity such as tachycardia, hyperthermia, and hypertension, and changes in mental status such as agitated delirium. Development can result from use of an SSRI in combination with another medication that alters serotonin metabolism, such as the well-known drug interaction between antidepressant monoamine oxidase (MAO) inhibitors and SSRIs. Perhaps less widely known is that linezolid is a weak MAO inhibitor, and there have been many cases of serotonin syndrome in the setting of concomitant linezolid and SSRI therapy.[38] This combination is also therefore contraindicated, and it is not adequate to simply stop the SSRI on initiation of linezolid therapy; there needs to be an adequate washout period for the SSRI to be completely inactive in the patient's body, which may take several weeks. Should a patient develop serotonin syndrome, treatment involves discontinuation of all serotonergic medications, and use of benzodiazepines as needed for agitation. Cyproheptadine, an antihistamine with serotonin receptor–blocking activity, can be considered, although it should be noted that this is not an indication for use of this agent that is approved by the Food and Drug Administration.

IMPORTANT DRUG-DRUG INTERACTIONS

There are thousands of potential drug-drug interactions involving antibiotic agents. This section is not intended to be comprehensive, but rather highlights a few common and important interactions to be aware of.

Warfarin

Warfarin, an oral anticoagulant prescribed in the setting of atrial fibrillation, venous thromboembolism, and mechanical heart valve replacement, and by nature of the

indications more commonly prescribed to older patients, has many known potential drug interactions. Some studies would indicate that prescription for any antibiotic increases the risk of bleeding in stable outpatients on warfarin,[39] but there are several classes of antibiotics that are particularly problematic. Azole antifungals and TMP/SMX have both been consistently shown to increase the International Normalized Ratio (INR) of patients on stable doses of warfarin and to lead to increased hospitalizations for bleeding complications. Studies estimate a 4.5-fold increased risk of hospitalization for bleeding complication in patients on warfarin recently prescribed an azole antifungal, and a 2.7-fold increase in risk for patients prescribed TMP/SMX.[39] Perhaps not as widely known is that there is also an interaction between warfarin and other antibiotics including macrolides, quinolones, and metronidazole. In a study assessing for changes in INR in patients on stable outpatient doses of warfarin, during and immediately after prescription of antibiotics 16% of patients on azithromycin and 19% of patients on levofloxacin had INR elevations to greater than 4, although again the TMP/SMX interaction was clearly more potent, with 44% of patients having an INR increase to greater than 4.[40] In a study assessing for risk of hospitalization for upper gastrointestinal bleeding in elderly patients on warfarin with a prescription for antibiotics to treat urinary tract infections in the 14 days before hospitalization, TMP/SMX and ciprofloxacin were associated with an approximately 4-fold and a 2-fold increase in risk, respectively. Amoxicillin, nitrofurantoin, and norfloxacin were not associated with an increased risk when compared with controls[41]; when appropriate, these may be safer agents to prescribe.

Trimethoprim/Sulfamethoxazole

In addition to interactions with warfarin, there a few additional important drug interactions one must be aware of when prescribing TMP/SMX. As reviewed earlier in this article, TMP/SMX can lead to hyperkalemia, especially in the setting of concomitant prescription of angiotensin receptor blockers and spironolactone. Use of TMP/SMX with methotrexate is associated with a higher risk of bone marrow suppression than with methotrexate alone, even at low methotrexate doses such as 5 mg weekly.[42] TMP/SMX also interacts with sulfonylureas and meglitinides, increasing their potential to cause hypoglycemia. Studies have indicated that the risk of hospitalization for hypoglycemia for patients on sulfonylureas increases 4- to 6-fold following prescription of TMP/SMX.[43] Finally, there is an interaction between TMP/SMX and the commonly prescribed antiepileptic phenytoin, the result of which is increased phenytoin levels and an increased potential for toxicity.

Clarithromycin

Many of the drug interactions seen with TMP/SMX are due to its effects on cytochrome P450 enzymes. Another drug with several important drug interactions owing to its potent inhibition of the cytochrome P450 3A4 isoenzyme is clarithromycin. In ambulatory medicine, clarithromycin is commonly used in *Helicobacter pylori* eradication therapy; other indications include treatment of bacterial respiratory infections and mycobacterial infections. Potentially dangerous and even fatal complications to be aware of include interactions with statins, especially simvastatin and lovastatin, resulting in increased statin levels and an increased risk of rhabdomyolysis. Decreased metabolism of calcium-channel blockers can result in bradycardia and hypotension, and decreased metabolism of digoxin can result in digoxin toxicity. These interactions are all clinically significant; for example, studies indicate that elderly patients hospitalized for digoxin toxicity were 12 times more likely than controls to have been prescribed clarithromycin in the week before their

hospitalization.[44] Clarithromycin has an important and dangerous interaction with colchicine, especially in patients who have renal insufficiency. Multiple case reports of death from this interaction, caused by refractory agranulocytosis and rhabdomyolysis, have surfaced. Azithromycin has the same spectrum of activity as clarithromycin, and because it has far fewer and much less severe drug interactions, it should be used instead of clarithromycin in almost all clinical settings where a macrolide is needed.

Rifampin

Rifampin, frequently used for adjuvant treatment of staphylococcal osteomyelitis and orthopedic hardware infections, is another antibiotic fraught with interactions. Rifampin is an inducer of many cytochrome P450 enzymes, therefore it increases the metabolism of many medications, at times resulting in subtherapeutic drug levels. There are many clinical scenarios in which this becomes important, including patients on immunosuppressant medications such as cyclosporine and tacrolimus; in this case increased doses may be needed, and immunosuppressant levels should be followed to guide this. When coadministered with methadone for the management of heroin addiction, patients may need an increase in their daily methadone dose to avoid going into drug withdrawal. Patients on oral contraceptive agents should be advised to use a second form of birth control if placed on rifampin. Patients on warfarin need close monitoring of their INR and likely an increase in their warfarin dose. Given the large number of potential drug interactions, all patients started on rifampin need a thorough review of their medication lists for potential interactions. Baciewicz and colleagues[45] offer a comprehensive review of this topic.

Oral Contraceptives

Rifampin has a well-established interaction with combined oral contraceptive pills, resulting in a subtherapeutic contraceptive effect and a potential for unintended pregnancy, but it is less clear if other antibiotics have clinically significant interactions with contraceptive pills. It has proved difficult to study this potential interaction, and beyond the previously mentioned interaction with rifampin there is no convincing evidence that antibiotics result in decreased efficacy of contraceptive medications.[46,47] This is a difficult issue to study because the outcome is rare, and there is potential for significant recall bias in the retrospective studies that led to initial concerns regarding this potential interaction[48]; moreover, unfortunately oral contraceptive failure is not uncommon even outside the setting of concomitant antibiotic use. Overall it appears very unlikely that use of antibiotics, other than rifampin, result in decreased efficacy of oral contraceptives.

Metronidazole

Many providers were taught in medical school that there is an interaction between metronidazole and alcohol, a disulfiram-like reaction resulting in nausea and vomiting. As a result, patients are frequently warned to avoid alcohol while taking this medication. However, it is likely that this is a media myth, as there is little evidence that this interaction exists. There has even been a small experiment on human volunteers in which they were treated with metronidazole and then given alcohol, which showed no results of laboratory tests and physical examination, or symptoms, consistent with a disulfiram-like reaction.[49] It is likely that the symptoms that initially raised concern for this interaction simply represent common side effects of metronidazole treatment itself: nausea, headache, and a bitter/metallic taste.

SUMMARY

Antibiotics are powerful agents that have brought about great advances in medicine, but they are not without potential side effects. When given a prescription, patients should be informed not only of the benefits but also the potential risks of therapy. Judicious use is the best form of prevention overall, but there are some patient populations of whom one needs to be particularly mindful when prescribing. Patient groups at risk include the elderly, those with renal dysfunction, patients with significant cardiac disease, and those on multiple medications. Antibiotics particularly fraught with dangerous interactions include TMP/SMX and, less commonly, rifampin and clarithromycin. Patients on warfarin are also at high risk of dangerous alterations in anticoagulant effect, and deserve special attention.

REFERENCES

1. Garratty G. Immune hemolytic anemia associated with drug therapy. Blood Rev 2010;24(4–5):143–50.
2. Young NS. Acquired aplastic anemia. Ann Intern Med 2002;136(7):534–46.
3. Available at: http://www.ouhsc.edu/platelets/ditp.html. last accessed 11/1/2012.
4. van der Klauw MM, Goudsmit R, Halie MR, et al. A population-based case-cohort study of drug-associated agranulocytosis. Arch Intern Med 1999;159(4):369–74.
5. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med 2007;146(9):657–65.
6. Cunha BA. Antibiotic side effects. Med Clin North Am 2001;85(1):149–85.
7. Ray WA, Murray KT, Hall K, et al. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881–90.
8. Bril F, Gonzalez CD, Di Girolamo G. Antimicrobial agents associated with QT interval prolongation. Curr Drug Saf 2010;5(1):85–92.
9. Lapi F, Wilchesky M, Kezouh A, et al. Fluoroquinolones and the risk of serious arrhythmia: a population-based study. Clin Infect Dis 2012;55(11):1457–65.
10. Vahid B, Wildemore BM. Nitrofurantoin pulmonary toxicity: a brief review. Internet J Pulm Med 2006;6(2).
11. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med 2002; 346(5):334–9.
12. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA 2012;307(18):1959–69.
13. Available at: http://webedition.sanfordguide.com.
14. Gröchenig HP, Tilg H, Vogetseder W. Clinical challenges and images in GI. Pill esophagitis. Gastroenterology 2006;131(4):996, 1365.
15. Leitner JM, Graninger W, Thalhammer F. Hepatotoxicity of antibacterials: pathomechanisms and clinical data. Infection 2010;38:3–11.
16. Carson JL, Strom BL, Duff A, et al. Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. Ann Intern Med 1993;119(7 Pt 1):576–83.
17. Wong-Beringer A, Joo J, Tse E, et al. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. Int J Antimicrob Agents 2011; 37(2):95–101.
18. Perazella MA, Markowitz GS. Drug-Induced acute interstitial nephritis. Nat Rev Nephrol 2010;6:461–70.
19. Antoniou T, Gomes T, Juurlink DN, et al. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system. Arch Intern Med 2010;170(10):1045–9.

20. Antoniou T, Gomes T, Mamdani MM, et al. Trimethoprim-sulfamethoxazole induced hyperkalemia in elderly patients receiving spironolactone: nested case-control study. BMJ 2011;343:d5228.
21. Zietse R, Zoutendijk R, Hoorn EJ. Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. Nat Rev Nephrol 2009;5(4):193–202.
22. Mohr JA, Clark RM, Waack TC, et al. Nafcillin-associated hypokalemia. JAMA 1979;242(6):544.
23. Xu J, Schwartw K. Effect of antibiotics on vulvovaginal candidiasis: a MetroNet Study. J Am Board Fam Med 2008;21:261–8.
24. Pirotta MV, Garland SM. Genital candida species detected from women in Melbourne, Australia, before and after treatment with antibiotics. J Clin Microbiol 2006;44:3212–7.
25. Pirotta M, Gunn J, Chondros P, et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomised controlled trial. BMJ 2004; 329(7465):548.
26. Falagas ME, Betsi GI, Athanasiou S. Probiotics for prevention of recurrent vulvovaginal candidiasis: a review. J Antimicrob Chemother 2006;58(2):266–72.
27. Borchers AT, Keen CL, Gershwin ME. Drug-induced lupus. Ann N Y Acad Sci 2007;1108:166–82.
28. Diaz L, Ciurea AM. Cutaneous and systemic adverse reactions to antibiotics. Dermatol Ther 2012;25(1):12–22.
29. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. Am J Med 2011;124(7):588–97.
30. Usatine RP, Sandy N. Dermatologic emergencies. Am Fam Physician 2010;82(7): 773–80.
31. Romano A, Guéant-Rodriguez RM, Viola M, et al. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Ann Intern Med 2004;141(1):16–22.
32. Vassileva SG, Mateev G, Parish LC. Antimicrobial photosensitive reactions. Arch Intern Med 1998;158(18):1993–2000.
33. Agbaht K, Bitik B, Piskinpasa S, et al. Ciprofloxacin-associated seizures in a patient with underlying thyrotoxicosis: case report and literature review. Int J Clin Pharmacol Ther 2009;47(5):303–10.
34. Tomé AM, Filipe A. Quinolones: review of psychiatric and neurological adverse reactions. Drug Saf 2011;34(6):465–88.
35. Catic AG. Identification and management of in-hospital drug-induced delirium in older patients. Drugs Aging 2011;28(9):737–48.
36. Wise BL, Peloquin C, Choi H, et al. Impact of age, sex, obesity and steroid use on quinolone-associated tendon rupture. Am J Med 2012;125:1228.e23–8.
37. Etminan M, Forooghian F, Brophy JM, et al. Oral fluoroquinolones and the risk of retinal detachment. JAMA 2012;307(13):1414–9.
38. Clark DB, Andrus MR, Byrd DC. Drug Interactions between linezolid and selective serotonin reuptake inhibitors: case reports involving sertraline and review of the literature. Pharmacotherapy 2006;26(2):269–76.
39. Baillargeon J, Holmes HM. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. Am J Med 2012;125:183–9.
40. Glasheen JJ, Fugit RV, Prochazka AV. The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. J Gen Intern Med 2005;20:653–6.
41. Fischer HD, Juurlink DN, Mamdani MM, et al. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents. Arch Intern Med 2010;170(7):617–21.

42. Bourre-tessier J, Haraoui B. Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. J Rheumatol 2010;37:1416–21.
43. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. CMAJ 2011;183(16):1851–8.
44. Juurlink DN, Mamdani M, Kopp A, et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003;289:1652–8.
45. Baciewicz AM, Chrisman CR, Finch CK, et al. Update on rifampin, rifabutin, and rifapentine drug interactions. Curr Med Res Opin 2013;29:1–12.
46. Archer JS, Archer DF. Oral contraceptive efficacy and antibiotic interaction: a myth debunked. J Am Acad Dermatol 2002;46:917–23.
47. Toh S, Mitchell AA, Anderka M, et al. Antibiotics and oral contraceptive failure—a case-crossover study. Contraception 2011;83:418–25.
48. Dickinson BD, Altman RD, Nielsen NH, et al. Drug interactions between oral contraceptives and antibiotics. Obstet Gynecol 2001;98:853–60.
49. Visapaa JP, Tillonen JS, Kaihavaara PS, et al. Lack of disulfiram-like reaction with metronidazole and ethanol. Ann Pharmacother 2002;36:971–4.