Antibiotic Adverse Reactions and Drug Interactions

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Each year many patients are hospitalized with adverse drug reactions. Life-threatening reactions include arrhythmias, hepatotoxicity, acute renal failure, and antiretroviral therapy–induced lactic acidosis. In addition, during the latter half of the twentieth century 6% to 7% of hospitalized patients experienced a serious adverse drug reaction [1]. Approximately 5% of serious inpatient reactions were fatal, making hospital-related adverse drug reactions responsible for approximately 100,000 deaths in the United States annually. The elderly [2] and HIV-infected patients [3] are at especially high risk of reactions. Many of these reactions result in intensive care unit (ICU) admission.

More than 70% of ICU patients receive antibiotics for therapy or prophylaxis, with much of this use being empiric and over half of the recipients receiving multiple agents [4,5]. The clinical presentation of an adverse drug reaction may be very different in an ICU patient than in a more healthy individual because of both the severity of the ICU patient's illness, which often requires that the patient be heavily sedated and paralyzed, and the multiple therapies that he or she often requires. Therefore, attributing a particular adverse reaction to a specific antibiotic can be extremely difficult, may involve several factors operating in unison, and can tax the minds of the brightest clinicians.

Adverse reactions associated with drug use include allergies, toxicities, and side effects. An **allergy** is a hypersensitivity reaction to a drug. Many

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are IgE-mediated and occur soon after drug administration. Examples of IgE-mediated type 1 hypersensitivity reactions include early-onset urticaria, anaphylaxis, bronchospasm, and angioedema. Non–IgE-mediated reactions include hemolytic anemia, thrombocytopenia, acute interstitial nephritis, serum sickness, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. **Toxicity**, which is generally due to either excessive dosing or impaired drug metabolism, is a consequence of administering a drug in quantities exceeding those capable of being physiologically "managed" by the host. Examples of toxicity caused by excessive dosing include penicillin-related neurotoxicity (eg, twitching, seizures) and the toxicities caused by aminoglycosides. Decreased drug metabolism or clearance may be due to impaired hepatic or renal function. For example, penicillin G neurotoxicity may be precipitated by aminoglycoside-induced renal failure. **Side effects** include adverse reactions that are neither immunologically mediated nor related to toxic levels of the drug. An example is the dyspepsia caused by erythromycin. By affecting drug metabolism, a patient's genotype can predispose him or her to an allergic reaction (eg, abacavir-related hypersensitivity) or to toxicity. For example, isoniazid-related peripheral neuropathy is more likely in a patient who acetylates the drug slowly.

This review describes adverse reactions and important drug interactions involving antibiotics. It concentrates on those agents likely to be used in critical care and is not encyclopedic. Table 1 summarizes and prioritizes the most common antibiotic-related adverse reactions seen in the ICU. This article only briefly discusses antiretroviral drugs and antibiotic dosing; it does not address issues specific to pregnant or pediatric patients.

Adverse reactions

Anaphylaxis

Anaphylaxis is an acute hypersensitivity reaction that can result in immediate urticaria, laryngospasm, bronchospasm, hypotension, and death. In the critical care setting, these reactions may be masked by underlying conditions or other therapies. While anaphylaxis can be precipitated by antigen-antibody complexes, it is usually IgE mediated. The binding of antibiotic epitopes to specific preformed IgE antibodies on the surface of mast cells results in the release of histamine and other mediators that lead to the aforementioned clinical presentations. β-Lactams are more often associated with these reactions than are other antimicrobials. Best data exist for penicillin where the risk of anaphylaxis is about 0.01% [6]. Death occurs in 1 of every 100,000 courses of this agent [7]. Conversely, only 10% to 20% of patients who claim to have an allergy to penicillin are truly allergic as determined by skin testing [8]. Fifty percent of patients with a positive skin test have an immediate reaction when challenged with penicillins [9]. Approximately 4% of patients with a history of penicillin allergy who test positive

Table 1
Frequency and severity of adverse reactions to antibiotics

	Penicillins	Cephalosporins	Monobactams	Carbapenems	Aminoglycosides	Tetracyclines[a]	Chloramphenicol	Rifamycins	Metronidazole	Macrolides/azalide	Clindamycin	Glycopeptides	Streptogramins	Lipopeptides (daptomycin)	Oxazolidinones	Sulfonamides and trimethoprim	Quinolones	Nitrofurantoin	Amphotericins	Triazoles	Echinocandins	Flucytosine	Acyclovir	Ganciclovir
Anaphylaxis	IIIB	IIIB	IB	IIIB	IB	IB	IB	IB	IB	IB	IB	IIB	IB		IB	IIB	IB	IB	IB	IB	IB	IB	IB	IB
Nephrotoxicity	IIB	IIB		IIB	IIIB			IB				IIA				IIA	IIA		IIIB				IIB	
Anemia	IIA	IIA		IIA	IIA		IIB								IIIA	IIB			IIIB					IIIB
Leukopenia	IIB	IIB		IIB		IIIB					IIA	IIA	IIA		IIA	IIB			IIA			IIIB		IIIB
Thrombocytopenia	IIB	IIB		IIB			IIIB	IIB				IIIA			IIIB	IIB			IIA			IIB		IIIB
Coagulopathy (other than thrombocytopenia)	IIB	IIB														IIB								
Dermatological toxicity (excluding phlebitis)	IIIB	IIIB		IIIB	IIA			IIA				IIIA				IIIB	IIA			IIA				
Neurotoxicity	IB			IB	IIIB	IIA			IIA	IIIB					IIB	IB	IIIA			b				
Cardiotoxicity									IB	IIIB	IB						IIB		IB	IIB				
Hepatotoxicity	IIIA	IIA		IIA		IIA	IIA	IIIB	IIA	IIA	IIA	IIA				IIA	IIA	IIB		IIA				
Musculoskeletal toxicity													IIIB	IIIA										
Electrolyte abnormalities	IIB															IB			IIIB	IIA				
Fever	IIIA	IIIA			IIA											IIIA			IIIB					
Diarrhea	IIIB	IIIB	IIB	IIIB		IIB	IIB	IIB		IIB	IIIB	IIB		IIB	IIB	IIB	IIB	IIB						

The relative frequencies at which different antibiotics cause a specific adverse reaction (e.g., anaphylaxis) are rated as I (least frequent), II, or III (most frequent). The severity of the reaction is rated as A (mild or moderate) or B (sometimes severe) based upon published reports and the authors' opinions. Blank cells indicate that reactions are infrequent and usually mild.

[a] Adverse reactions due to tigecycline may be similar to those caused by tetracyclines.

[b] Visual disturbance due to voriconazole is common, but it is unclear if the reaction is due to neurological dysfunction.

Adapted from Granowitz EV, Brown RB. Adverse reactions to antibiotics. In: Cunha BA, editor. Infectious diseases in critical care medicine, 2nd edition. New York: Informa Healthcare USA, Inc; 2007. p. 577, with permission.

to penicillin experience a reaction (only rarely anaphylaxis) when given a cephalosporin [10]. Interestingly, patients with a history of a penicillin-related allergiclike event have a similarly increased risk of a reaction when given a sulfonamide or a cephalosporin [11]. The incidence of carbapenem cross-reactivity with penicillin is controversial with the most recent studies finding a low rate of cross-reactivity [12–15]. Administering aztreonam is safe in patients with a history of anaphylaxis to all β-lactams except ceftazidime [7].

Cardiotoxicity

A survey of intensivists at the authors' institution found that the antibiotic adverse reaction that concerns them the most is Q-T prolongation with ventricular arrhythmia. In patients with susceptible substrate (eg, coronary artery disease), precipitators (eg, drugs or electrolyte disturbances) can cause torsades des pointes and sudden death [16]. Often, Q-T prolongation precedes the drug-induced arrhythmia. However, drug-induced Q-T prolongation does not always result in torsades des pointes nor do medications that can cause torsades always prolong the Q-T interval. Antibiotics that can prolong the Q-T interval include macrolides, some quinolones, azoles, pentamidine, and quinine. A cohort study of patients receiving oral erythromycin found a twofold increased risk of sudden death in patients receiving this macrolide [17]. Clinicians should consider using alternative antibiotics in patients with a baseline Q-Tc interval of greater than 500 ms. If the Q-Tc interval increases by 30 ms to 60 ms or to more than 500 ms, replacing a known offending agent with a different drug should be considered [16].

Myocardial depression, hypotension, and sudden death have been reported with vancomycin use, generally in the setting of rapid administration in the perioperative period [18,19]. Similarly, rapid administration of amphotericin B has been associated with ventricular fibrillation and asystole, especially in patients with renal dysfunction [20]. Amphotericins and pentamidine infusions can precipitate hypotension.

Nephrotoxicity

Acute renal failure is common in ICU patients and is associated with a risk of mortality of greater than 60% [21]. Numerous agents used in the ICU are capable of affecting renal function. Mechanisms include decreased glomerular filtration, acute tubular necrosis, interstitial nephritis, and crystallization of the drug within the tubules. With regard to antibiotics, the aminoglycosides and amphotericins are the prototypical classes associated with acute renal failure; however, other agents including sulfonamides, β-lactams, and acyclovir, have been implicated. As with other antibiotic-associated adverse reactions, the likelihood of nephrotoxicity from antimicrobials is greater in patients with conditions or on medications that independently cause this complication.

Depending upon the criteria used to define acute renal failure, aminoglycoside-induced nephrotoxicity occurs in 7% to more than 25% of patients who receive these drugs [22]. It usually results from tubular epithelial cell damage and presents as acute tubular necrosis. When using a small change in serum creatinine as the criterion for renal dysfunction [22], one study found that gentamicin (26%) is more nephrotoxic than tobramycin (12%) and that nephrotoxicity usually becomes evident between 6 and 10 days after starting the aminoglycoside. However, other investigations have challenged this conclusion [23]. Aminoglycoside-induced acute tubular necrosis is usually nonoliguric and completely reversible. However, occasional patients require temporary dialysis and a rare patient requires chronic dialysis. Factors that contribute to aminoglycoside-induced nephrotoxicity include dose, duration of treatment, use of other tubular toxins [24], and elevated trough aminoglycoside levels [23]. Even patients with peak and trough levels within recommended ranges can develop nephrotoxicity. Meta-analyses have demonstrated that once-a-day dosing of an aminoglycoside in immunocompetent adults with normal renal function is effective for treating infections caused by gram-negative bacilli (employing bacteriologic cure as an end point) and is less toxic than traditional multiple daily dosing [25,26].

Until recently, amphotericin B was the drug of choice for severe fungal infections due to Candida or Aspergillus. This agent is still used for cryptococcal meningitis, an AIDS-associated illness that occasionally requires treatment in an ICU. Amphotericin B can affect the renal tubules, renal blood flow, or glomerular function; renal dysfunction is seen in at least 60% to 80% of patients who receive this drug [27]. However, renal dysfunction is usually transient, and few patients suffer serious long-term renal sequelae. Rarely, irreversible renal failure develops when the agent is used in high doses for prolonged periods [28]. Risk factors for amphotericin B toxicity include abnormal baseline renal function, high daily and total drug dose, and concurrent use of other nephrotoxic agents (eg, aminoglycosides, diuretics) [27,29]. However, some studies have not found that other drugs enhance amphotericin B-induced nephrotoxicity [20]. Reversing sodium depletion and optimizing volume status before infusing the drug can decrease the risk of amphotericin B–induced nephrotoxicity [27,30]. Liposomal preparations of amphotericin B are associated with a lower risk of nephrotoxicity compared with risks when using the parent compound. Nephrotoxicity with azoles and echinocandins is very rare.

β-Lactams, fluoroquinolones, sulfonamides, vancomycin, and rifampin can occasionally cause interstitial nephritis. Methicillin was the first antibiotic shown to be associated with interstitial nephritis [31]; nephritis can also be caused by numerous other β-lactams [32], usually following prolonged or high-dose therapy. Historically, renal failure was believed to be acute in onset and associated with fever, chills, rash, and arthralgias. However, the presentation of antibiotic-induced interstitial nephritis can be variable and it should be suspected in any patient on a potentially offending agent who

develops acute renal dysfunction. Urinary eosinophilia supports the diagnosis, but is present in less than half of the patients. Conclusive documentation of this disease requires renal biopsy. Discontinuation of the offending agent generally reverses the process and permanent sequelae are unusual.

Sulfonamides and acyclovir can crystallize in the renal tubules causing acute renal failure. Sulfonamides can also block tubular secretion of creatinine; this causes the serum creatinine to rise but leaves the glomerular filtration rate unchanged. Patients on rifampin often develop orange-colored urine of no clinical consequence.

Hematological adverse reactions

Anemia

Linezolid [33–35], amphotericin B, chloramphenicol, and ganciclovir cause anemia by suppressing erythropoiesis. Chloramphenicol (infrequently used in the United States) frequently causes a reversible anemia that is more common if circulating drug concentrations exceed the recommended range. In approximately 1 of every 25,000 recipients, chloramphenicol causes an idiosyncratic irreversible aplastic anemia [36]. β-Lactams, nitrofurantoin, and, rarely, aminoglycosides can cause hemolytic anemia. Patients who are glucose 6-phosphate dehydrogenase–deficient are predisposed to sulfonamide- and doxycycline-induced hemolytic anemia.

Leukopenia

Antibiotic-induced leukopenia and agranulocytosis are generally reversible. Anti-infectives that can cause neutropenia or agranulocytosis include trimethoprim-sulfamethoxazole [37,38], most β-lactams [39,40], vancomycin, macrolides, clindamycin, chloramphenicol, flucytosine, and amphotericin B. Severe neutropenia develops in 5% to 15% of recipients of β-lactams [40] and is associated with duration of therapy greater than 10 days, high doses of medication, and severe hepatic dysfunction [41,42]. Likelihood of neutropenia is less than 1% when shorter courses of β-lactams are used in patients with normal liver function [42]. Rarely do patients develop infection as a result of this decrease in functioning leukocytes. Vancomycin-induced neutropenia is uncommon and generally only occurs after more than 2 weeks of intravenous treatment [43]. The etiology appears to be peripheral destruction or sequestration of circulating myelocytes. Prompt reversal of the neutropenia generally occurs after vancomycin is discontinued.

Thrombocytopenia

Antibiotic-related thrombocytopenia may result from either immune-mediated peripheral destruction of platelets or a decrease in the number of megakaryocytes [44]. The oxazolidinone linezolid is the antimicrobial most likely to cause platelet destruction [33–35]. In one study, linezolid-induced thrombocytopenia occurred in 2% of patients receiving 2 weeks or less of

therapy, in 5% of those receiving 2 to 4 weeks of therapy, and in 7% of those receiving more than 4 weeks of drug [34]. Vancomycin can stimulate the production of platelet-reactive antibodies, which can cause thrombocytopenia and severe bleeding [45]. Sulfonamides, rifampin, and, rarely, β-lactams (including penicillin, ampicillin, methicillin, cefazolin, and cefoxitin) have also been reported to induce platelet destruction [40,46]. Prompt recognition and removal of the offending agent is appropriate therapy. Chloramphenicol-induced thrombocytopenia is usually dose related and, if not associated with aplastic anemia, is reversible following discontinuation of the drug.

Coagulation

Malnutrition, renal failure, hepatic failure, malignancy, and medications can all predispose critically ill patients to bleeding. Although many studies have found an association between antibiotics and clinical bleeding [47], in-depth, statistically validated investigations may be necessary to establish causation in complex patients with multiple underlying diseases [48]. Such an approach established a relationship between cefoxitin and bleeding.

Dysfunctional platelet aggregation, an important mechanism by which selected antibiotics may cause bleeding, is mostly noted with penicillins. Among penicillins, it is most likely with penicillin G and advanced-generation penicillins [49]. The problem is dose related, may be exacerbated by renal failure, and is additive to other factors seen in critically ill patients that could, in their own right, be associated with dysfunctional platelet aggregation [49,50]. Dysfunctional platelet aggregation usually stems from a blockade of binding sites on the platelet surface caused by carboxyl groups on the acyl side chain. This blockage results in the inability of platelet agonists, such as adenosine diphosphate, to affect aggregation [49]. This process is best identified by performing a template bleeding time, and is missed if only the international normalized ratio (INR) and partial thromboplastin times are measured. It should be suspected in patients with bleeding not accounted for by abnormalities in INR or partial thromboplastin time, and often presents as diffuse oozing from sites of cutaneous trauma (eg, recent tracheostomy and intravascular catheters).

Probably the most common reason for antibiotic-associated bleeding in the ICU is prolongation of the INR [51]. Historically, antibiotics associated with INR prolongation include cefamandole, moxalactam, cefoperazone, cefmetazole, and cefotetan [52]. All of these products contain an N-methyl-thiotetrazole, which can interfere with hepatic prothrombin synthesis [53]. Antibiotics can also prolong the INR by affecting the normal gastrointestinal flora and thereby impairing vitamin K absorption.

Dermatological adverse reactions

Rashes are common in ICU patients and present as highly variable conditions with implications ranging from innocuous to life-threatening. The

problem is complicated because skin abnormalities in ICU patients can be caused by disease, pressure, and medications. Identifying an offending agent may be difficult because of the large number of medications administered to ICU patients and the difficulties in temporally associating the rash with initiation of any single agent. While virtually any antimicrobial agent may cause a rash, this problem occurs most commonly with β-lactams, sulfonamides, fluoroquinolones, and vancomycin. Factors that should lead the clinician to suspect a serious drug reaction include facial edema, urticaria, mucosal involvement, palpable or extensive purpura, blisters, fever, or lymphadenopathy. The presence of significant eosinophilia is associated with more severe disease. Maculopapular eruptions associated with antibiotics are especially common, usually occurring at least 5 days after starting the offending agent. The rash often becomes generalized and is pruritic. In patients with thrombocytopenia or other coagulopathies, hemorrhage into the skin may modify the appearance of the rash. The pathogenesis of most maculopapular rashes is unknown [7]. Discontinuation of the offending agent is usually the most important strategy. In some instances, the likely offending agent can be continued and the rash will stabilize or disappear. In patients with penicillin-induced mild or moderately severe maculopapular rashes, it is generally safe to use cephalosporins [54]. If the rash is severe or associated with mucosal lesions or exfoliation, the offending agent should almost always be discontinued.

Stevens-Johnson syndrome is erythema multiforme with mucosal involvement. The most commonly implicated antibiotics are the aminopenicillins and sulfonamides. Onset is typically 1 to 3 weeks after starting the offending agent. Clinically, the rash can present as symmetric target lesions, maculopapular and urticarial plaques, or vesicular lesions. The presence of the latter portends severe disease [55]. Stevens-Johnson syndrome can involve mucosae of the eyes, mouth, entire gastrointestinal tract, and the genitourinary tract. Up to 25% of cases may be restricted to the oral mucosa. Constitutional symptoms are usually present. Mortality is up to 5%. Diagnosis can be proven by skin biopsy with immunofluorescent staining. Infections (for which the offending antibiotic may have been prescribed), including pneumococcal, mycoplasmal, and staphylococcal infections, can cause a similar rash. Stevens-Johnson syndrome can evolve into toxic epidermal necrolysis; mortality of this condition is 30% [55]. Sulfonamides are the antibiotics most often associated with toxic epidermal necrolysis. Although the benefits of corticosteroid therapy are unproven, these products are often used for treatment.

"Red man" ("redneck") syndrome is a transient reaction to vancomycin characterized by flushing of the head and neck, typically beginning within an hour of the start of an infusion [56]. Severe cases have been associated with angioedema, hypotension, chest pain, and, rarely, severe cardiac toxicity and death [18]. Incidence may be as high as 47% in patients and is substantially higher in human volunteers [57]. One study documented a dose-related

increase in circulating histamine concentrations that correlated with the severity of the reaction [58]. The problem is more frequently associated with rapid administration (ie, <30 minutes) and with larger doses. Histamine antagonists may abort the syndrome in patients who require vancomycin and who continue to have red man syndrome despite slow administration of the drug [56,59].

A particularly difficult problem in the ICU is differentiating between septic and drug-induced (chemical) phlebitis. Both may be associated with redness, heat, tenderness, and a ''cord'' at the peripheral catheter site. Therapy for the former is removal of the catheter and administration of appropriate antibacterial agents, while the latter is treated with catheter removal and moist heat. Presence of lymphangitic streaking or purulent drainage from the catheter site generally indicates infection. Antibiotics most likely to cause phlebitis include potassium penicillin, cephalosporins, vancomycin, streptogramins, and amphotericin B.

Neurotoxicity

Ototoxicity

Drug-induced ototoxicity in the ICU can result in hearing loss or vestibular dysfunction. The severity of underlying illness of ICU patients and the use of sedatives or paralyzing agents may make it impossible to diagnose these complications. Although routine audiography has been promulgated for some hospitalized patients given potentially ototoxic drugs [60], in practice such testing is not routinely employed. Therefore, the clinician must recognize the circumstances that could result in ototoxicity and take steps to decrease its likelihood.

Erythromycin and azithromycin can cause bilateral hearing loss or labyrinthine dysfunction that is usually reversible within 2 weeks of discontinuing the agent [61,62]. However, permanent hearing loss or vertigo can occur [63]. These complications are dose related and usually occur in the presence of renal or hepatic dysfunction [64]. A prospective study in patients with pneumonia documented sensorineural hearing loss in approximately 25% of patients treated with 4 g of erythromycin daily, while no patients who received lesser doses or control agents developed this condition [61].

Aminoglycosides cause ototoxicity or vestibular dysfunction in 10% to 22% of patients and this ototoxicity or vestibular dysfunction may be permanent [22,65]. Factors associated with aminoglycoside-induced cranial nerve VIII dysfunction include dose, dosing frequency, duration of treatment, advanced age, fever, anemia, baseline creatinine clearance, and concomitant use of other ototoxic agents [65–67]. Cumulative dose is important and clinicians should be wary of administering repeated courses of aminoglycosides.

Use of an early vancomycin preparation was associated with sensorineural hearing loss [68]. It is unknown whether newer vancomycin preparations cause ototoxicity [69].

Other neurotoxicity

Antibiotics can also occasionally cause peripheral nerve or acute central nervous system dysfunction (eg, seizures, abnormal mentation). Most peripheral neuropathies occur with prolonged administration of selected antibiotics (eg, peripheral neuropathy associated with metronidazole), a situation not likely to occur in ICU patients.

Hallucinations, twitching, and seizures can be caused by penicillin, impenem-cilastatin, ciprofloxacin, and, rarely, other β-lactam antibiotics [70,71]. Seizures may be the result of β-lactams interfering with the function of the inhibitory neurotransmitter γ-aminobutyric acid [72]. Intravenous aqueous penicillin G may cause central nervous system toxicity when normal-sized adults are given more than 20 million to 50 million units per day [70]. Patients with abnormal renal function, hyponatremia, or preexisting brain lesions can experience neurotoxicity at lower doses.

The maximum recommended dose of imipenem-cilastatin in adults with normal renal function is 4 g per day. Seizures occur more regularly with this agent than with other β-lactams. Initial human data found the incidence of seizures to be 0.9% to 2.0% [73,74]. Postmarketing assessments place this percentage at 0.1% to 0.15% [74]. Animal studies confirm that neurotoxicity with imipenem-cilastatin may be noted at substantially lower blood levels than with other β-lactams [71]. The authors' practice has been to virtually never employ imipenem-cilastatin in doses of more than 2 g per day unless treating *Pseudomonas aeruginosa* infections. Seizures have not been noted in more than 2 decades of regular use at the authors' institution.

Fluoroquinolone use has been associated with central nervous system adverse effects, including headaches and seizures, in 1% to 2% of recipients [75]. Hallucinations, slurred speech, and confusion have been noted; these generally resolve rapidly once the offending agent is discontinued. The presence of an underlying nervous system disorder may predispose to neurotoxicity.

Neuromuscular blockade has been reported with most aminoglycosides [70]. Clinical presentation is acute paralysis and apnea developing soon after drug administration. Due to this potential toxicity, aminoglycosides should be avoided in patients with myasthenia gravis.

Minocycline can cause vertigo. Trimethoprim-sulfamethoxazole use can precipitate aseptic meningitis. Approximately one third of patients receiving voriconazole experience transient visual changes, usually with the first dose. The mechanism of this reaction is unknown; neurotoxicity or a direct effect on the retina is possible. No irreversible visual sequelae have been described.

Hepatotoxicity

Liver function test abnormalities are common in ICU patients. Sepsis, severe hypoxemia, congestive heart failure, and primary hepatobiliary disease are the usual causes. Abnormalities are generally classified as predominantly hepatitis, cholestasis, or mixed [76,77]. Rifampin commonly causes

hepatitis, which is occasionally severe. Semisynthetic penicillins are frequent causes of hepatotoxicity, especially when combined with clavulanic acid. Cephalosporins, imipenem-cilastatin, tetracyclines, macrolides, sulfonamides, quinolones, clindamycin, chloramphenicol, streptogramins, nitrofurantoin, azoles, and ganciclovir can all cause hepatotoxicity [76]. Prolonged courses of high-dose ceftriaxone can cause both hepatitis and cholestasis by promoting biliary sludge formation.

Musculoskeletal toxicity

Streptogramins can cause severe arthralgias and myalgias. Daptomycin use is associated with elevations in creatinine phosphokinase of uncertain clinical consequence.

Electrolyte and glucose abnormalities

Amphotericin B can cause clinically significant hypokalemia, hypomagnesemia, and renal tubular acidosis. Electrolyte abnormalities must be anticipated with replenishment of the appropriate electrolyte to prevent future problems. Fluconazole can also cause hypokalemia.

Aqueous penicillin G is generally administered as the potassium salt (1.7 mEq K^+/million units of penicillin). With doses of more than 20 million units per day, patients (especially those with renal failure) may develop clinically important hyperkalemia. A sodium preparation of aqueous penicillin G is manufactured and should be employed when the risk of hyperkalemia is significant. Intravenous pentamidine use is associated with potentially life-threatening hyperkalemia. Ticarcillin disodium should be used carefully in patients requiring salt restriction.

Gatifloxacin [78] can cause both hypoglycemia and hyperglyceridemia and should be avoided in patients with diabetes mellitus. Because pentamidine can induce profound hypoglycemia, patients on this medication require frequent monitoring of their blood sugar.

Fever

Best available data suggest that up to one third of hospitalized patients experience fevers [79], which are commonly noninfectious [80,81]. Although nosocomial fever prolongs length of stay, it is not a predictor of mortality [80]. Management of nosocomial fever remains controversial. Most authorities recommend antibiotic restraint in stable patients pending the results of a thorough evaluation for the cause of the fever [82]. However, empiric antibiotics should be started promptly in most patients in whom fever is associated with significant immunosuppression (eg, asplenia, neutropenia) or hemodynamic instability. Numerous medications have been associated with fever; intramuscular administration may also result in temperature rise [83]. Among antibiotics, β-lactams, sulfonamides, and the

amphotericins most commonly cause fever. Sulfonamide-induced fever is especially common in HIV-infected patients. In contrast, fluoroquinolones and aminoglycosides are unusual causes of drug-related fever. In the opinion of the authors, neither the degree nor characteristics of the fever help define its cause. Fever of both infectious and noninfectious etiologies may be high grade, intermittent, or recurrent [84]. Rigors may occasionally be noted with noninfectious causes of fever.

Diagnosis of drug fever is made on the basis of a strong clinical suspicion, excluding other causes, and resolution of the fever following discontinuation of the offending agent. A clinical "pearl" is that the patient frequently appears better than the physician would suspect after seeing the fever curve. The presence of rash or eosinophilia also favors this diagnosis. Resolution of fever after the offending agent is discontinued can take days because it depends upon the rate of the agent's metabolism.

Antibiotic-associated diarrhea and colitis

Since antibiotics first became available, it has been recognized that these products can cause diarrhea. In the ICU, additional causes of diarrhea include nutritional supplementation, other medications, underlying diseases, and ischemic bowel. In addition to being a nuisance, antibiotic-associated diarrhea can result in fluid and electrolyte disturbances, blood loss, pressure wounds, and (when associated with colitis) occasionally bowel perforation and death. Early recognition of antibiotic-associated diarrhea is important because prompt treatment can often minimize morbidity and prevent the rare fatality.

Clostridium difficile is currently the most common identifiable cause of nosocomial diarrhea. However, most cases of antibiotic-associated diarrhea are not caused by this organism. Rates vary dramatically among hospitals and within different areas of the same institution, occurring in some settings in more than 30 patients per 1000 discharges [85]. Although almost all antibiotics have been implicated, the most common causes of *C difficile* diarrhea are cephalosporins, fluoroquinolones, clindamycin, and ampicillin [86]. Antibiotic use changes the colonic flora, allowing the overgrowth of *C difficile*. This organism then causes diarrhea by releasing toxins A and B, which promote epithelial cell apoptosis, inflammation, and secretion of fluid into the colon. Nosocomial acquisition of this organism is the most likely reason for patients to harbor it [87]. Hospital sources of *C difficile* include hands of personnel, inanimate environmental surfaces, and asymptomatic patient carriers. In addition to antibiotic use, risk factors for acquisition include cancer chemotherapy, severity of illness, and duration of hospitalization. The clinical presentation of antibiotic-associated diarrhea and colitis is highly variable, ranging from asymptomatic carriage to septic shock. Secondary bacteremia has been reported [88]. Time of onset of diarrhea is variable, and diarrhea may develop weeks after using an antibiotic. Most commonly,

diarrhea begins within the first week of antibiotic administration. More severe cases are associated with the presence of pseudomembranous colitis. Unusual presentations of this disease include acute abdominal pain (with or without toxic megacolon), fever, or leukocytosis with minimal or no diarrhea [89]. On occasion, the presenting feature may be intestinal perforation or septic shock [90]. In the ICU, patients may have numerous other reasons for diarrhea, abdominal pain, fever, or leukocytosis. Clinical predictors that can help identify patients with *C difficile* colitis include (1) onset of diarrhea more than 6 days after the initiation of antibiotics, (2) hospital stay more than 15 days, (3) fecal leukocytes on microscopy, and (4) the presence of semi-formed (as opposed to watery) stools [91].

In ICU patients with abdominal pain, workup for *C difficile* colitis should ideally be performed before abdominal surgery. Diagnosis can be made by the less sensitive ($\sim$67%) rapid enzyme immunoassay or a more sensitive ($\sim$90%) but slower tissue culture assay [92]. The finding of pseudomembranes on sigmoidoscopy is also diagnostic and can negate the need for exploratory laparotomy. Optimal therapy of *C difficile* diarrhea/colitis depends on severity of disease and the need for ongoing antimicrobial therapy. Antiperistaltic agents should be avoided. If feasible, the offending antibiotic should be discontinued. In mild cases, this may suffice and specific antibiotic therapy for *C difficile* may be unnecessary.

In the opinion of most infectious disease consultants, oral metronidazole has been the agent of choice for most patients requiring treatment. An increasing minority and a recent study suggest using oral vancomycin for primary therapy, especially in seriously ill patients [86,93]. Metronidazole is the only agent that may be efficacious parenterally [94]; vancomycin given intravenously is not secreted into the gut. In especially severe cases, patients can be treated with the combination of high-dose intravenous metronidazole and nasogastric or rectal infusions of vancomycin. Although therapy with other agents, such as intravenous immunoglobulin and stool enemas, has been promulgated, this approach has not been compared directly to other standard regimens.

Antibiotic-resistant superinfections

In the ICU, the use of antibiotics can predispose recipients to colonization and infection with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* species (mostly *E faecium*), multidrug-resistant gram-negative bacilli, and fungi. Detailed discussion of these superinfections is beyond the scope of this article.

Drug interactions

The remainder of this article discusses important potential interactions amongst antibiotics and between antibiotics and other medications.

Antibiotics can either be the precipitant or the object of a drug interaction. Interactions can be beneficial or harmful. This section addresses beneficial interactions before focusing on interactions that can result in adverse events.

Beneficial antibiotic interactions

Several antibiotics are marketed as fixed combinations of two or more antibacterial agents. Trimethoprim-sulfamethoxazole is a combination of two antibacterials that synergistically inhibit microbial growth by blocking bacterial folic acid synthesis. Quinupristin and dalfopristin are streptogramins that act synergistically by binding to different sites on the 50S bacterial ribosome to inhibit protein synthesis. Piperacillin-tazobactam, ticarcillin-clavulanate, amoxicillin-clavulanate, and ampicillin-sulbactam use a β-lactamase inhibitor (tazobactam, clavulanate, or sulbactam) to broaden an antibacterial's activity to include β-lactamase–producing organisms, such as methicillin-sensitive *S aureus* and some gram-negative bacilli. Imipenem is marketed in combination with cilastatin, because the latter drug inhibits the dehydropeptidase in the proximal renal tubule that converts imipenem into nephrotoxic metabolites.

Clinicians often administer multiple antibiotics concurrently, especially in critically ill patients. In patients with polymicrobial infections, multiple antibiotics are sometimes needed to exert activity against multiple pathogens with markedly different antibiotic susceptibility profiles. Combination antibiotic therapy is most commonly used in life-threatening infections to increase the likelihood that "broad spectrum" empiric therapy includes a drug active against the unknown pathogen. Following identification and antibiotic susceptibility testing of the pathogen, empiric antibiotic therapy should be simplified by discontinuing unnecessary antibiotics. This important practice is known as "de-escalation" and reduces the risk of adverse drug reactions and adverse drug interactions.

Antibiotic combinations can also reduce the chance that a pathogen develops resistance to therapy. Antitubercular therapy and highly active antiretroviral therapy are examples of this practice. When it is necessary to discontinue antiretroviral therapy in HIV-infected patients, it is important to obtain expert advice to minimize the chance that the patient's virus becomes resistant to therapy. Because antiretroviral drugs have different half-lives, discontinuing all antiretroviral drugs simultaneously can result in virus developing resistance to the antiretroviral with the longest half-life during the time this drug is the only antiretroviral present in the circulation. When treating HIV, ritonavir can be used to inhibit the cytochrome P450 3A (CYP3A) isoenzyme responsible for oxidizing some drugs and thereby enhancing their excretion by the liver or kidney. Consequently, ritonavir inhibits the metabolism of lopinavir, atazanavir, fos-amprenavir, and other protease inhibitors. As a result, ritonavir boosts the circulating levels

of these drugs, enhances their efficacy, and reduces the risk of developing resistant virus. Probenecid can be used to inhibit renal clearance of penicillins and ertapenem.

The most controversial reason for using nonfixed drug combinations is to exert synergy against a specific pathogen. Gentamicin is commonly used for synergy for endocarditis caused by enterococci, viridans streptococci, and staphylococci [95,96]. When treating infections caused by gram-positive cocci with multiple daily doses of an aminoglycoside, the goal of gentamicin dosing is a peak of 3 μg/ml and trough of less than 1 μg/ml. Using low doses reduces a patient's risk of developing the aminoglycoside-related toxicities described earlier in this article. When treating *S aureus* endocarditis, gentamicin therapy should be limited to 3 to 5 days [97]. A recent meta-analysis of 17 studies found no mortality benefit of combination antimicrobial therapy in gram-negative bacteremia [98]. While there are in vitro [99–101] and animal data [102] demonstrating synergy of aminoglycosides and antipseudomonal β-lactams against *Pseudomonas aeruginosa*, synergy depends on the bacterial strain and specific drugs combinations [103]. Clinical studies of antibiotic synergy in *P aeruginosa* infections do not convincingly support its benefits. For example, a frequently referenced study demonstrating a statistically significant mortality benefit of combination therapy for *P aeruginosa* infections was flawed because many patients in the monotherapy group had pneumonia that was treated with an aminoglycoside, an approach no longer used because aminoglycosides have limited lung penetration [104]. While subgroup analysis in the aforementioned meta-analysis showed a significant mortality benefit of combination therapy for *P aeruginosa* bacteremia, 1 of the 5 studies included in the subgroup was the flawed study just cited. Also, the meta-analysis did not control for untoward outcomes resulting from empiric antibacterial therapy that did not include a drug active against the causative organism [98,104–106].

Harmful antibiotic interactions

Using multiple antibiotics concurrently is harmful if the drugs are antagonistic against the pathogen or if the combination causes toxicity. Combination therapy also increases the risk of superinfection and is more expensive than monotherapy. Numerous papers describe in vitro antagonism between antibacterials [107] and between antifungals [108,109]. Analogous to synergy, antagonism depends on the microbial strain and the drugs tested. Recently, Stevens and colleagues [110] showed that nafcillin induced and enhanced in vitro toxin production by MRSA. The implication of this observation for the treatment of presumed gram-positive infections is potentially very important. Due to increasing incidence of MRSA, intensivists often empirically treat septic patients with a broad-spectrum β-lactam and vancomycin. However, concurrent use of a β-lactam and vancomycin may be antagonistic in a patient with an MRSA infection.

As defined in the introduction, toxicity is a consequence of administering a drug in a quantity exceeding that capable of being physiologically "managed" by the host. Amongst antibiotics, β-lactams cause few toxic drug interactions. Some toxic antibiotic drug interactions are pharmacodynamic in origin, resulting from the administration of multiple drugs with overlapping toxicities. Combining antibiotics and other drugs (eg, amiodarone, haloperidol, diltiazem) that prolong the Q-T interval can lead to torsades des pointes and sudden death [16]. To avoid prescribing multiple medications that prolong the Q-T interval and predispose patients to torsades des pointes, intensivists and pharmacists can consult the Web site of the Arizona Center for Education and Research on Therapeutics (www.torsades.org). Using parenteral aminoglycosides, amphotericin-based compounds, or pentamidine with other nephrotoxic agents, such as radiographic contrast, nonsteroidal anti-inflammatory drugs, cyclosporine, or cisplatinum, increases a patient's risk of developing significant renal dysfunction. Vancomycin use may also predispose a patient to aminoglycoside-induced nephrotoxicity. Administering cephalosporins with N-methylthiotetrazole side chains to patients on anticoagulation increases the likelihood of bleeding. The risk of neuromuscular blockade is increased when an aminoglycoside, clindamycin, or colistin is used concurrently with other neuromuscular blocking agents or with anesthesia [111].

Most drug interactions are predictable, resulting from one drug affecting the pharmacokinetics (absorption, distribution, metabolism, or excretion) of a second agent. These interactions can impair efficacy or precipitate toxicity. The increasing use of computer software to screen for these interactions should greatly reduce these errors. Oral administration of multivalent cations, such as Al^{3+}, Fe^{2+}, and Mg^{2+}, can interfere with the absorption of oral tetracyclines, doxycycline, and fluoroquinolones. Most antacids contain either Al^{3+} or Mg^{2+} and thereby also interfere with the absorption of these antibiotics. Ca^{2+} and Zn^{2+} also interfere with fluoroquinolone absorption. By altering the gut flora responsible for synthesizing vitamin K, some antibiotics (such as nafcillin) impair vitamin K absorption and thereby further prolong the INR in patients on warfarin. Sulfonamides can increase the INR, possibly by displacing warfarin from its binding site on albumin and thereby enhancing its availability. Metronidazole can inhibit warfarin metabolism.

The most notable antibiotic-related pharmacokinetic effects that result in harmful drug interactions are changes in the activity of the cytochrome P450 (CYP) isoenzymes, especially CYP3A [112]. Macrolides, azoles, and some antiretroviral protease inhibitors (as described for ritonavir in the preceding section) are potent inhibitors of CYP3A. Consequently, their administration can result in increased levels of drugs metabolized by CYP3A, such as warfarin, lovastatin and simvastatin, midazolam and triazolam, cyclosporine and tacrolimus, phenytoin, and theophylline. In contrast, rifampin (and rifabutin) is a potent inducer of CYP3A resulting in lower circulating levels

of drugs metabolized by this enzyme family. A reduced therapeutic response has been reported when rifampin is used concurrently with warfarin, midazolam and triazolam, cyclosporine and tacrolimus, theophylline, glucocorticoids, some azoles, antiretroviral protease inhibitors, and others [113]. Because of the potential for serious adverse effects when using drugs that affect CYP, the authors consult the ICU pharmacist before prescribing any antibiotic that inhibits or induces CYP. Alternatively, intensivists can access Micromedex or the relevant Medscape site (www.medscape.com/drugchecker) to identify drug interactions before prescribing a new drug.

P-glycoprotein mediates the transport of some drugs from enterocytes back into the gut lumen and from cells lining the renal tubules into the tubule itself. Rifampin induces and macrolides inhibit the efflux molecule P-glycoprotein. When coadministered with digoxin, a macrolide can cause toxicity by inhibiting its digoxin's excretion.

Serotonin syndrome is due to impaired serotonin metabolism and is characterized by agitation, neuromuscular hyperactivity, fever, hypotension, and even death. Linezolid is a weak inhibitor of monoamine oxidase. Although linezolid itself does not cause serotonin syndrome, combining this drug with other monoamine oxidase inhibitors can result in toxicity. A small percentage ($<5\%$) of patients on selective serotonin re-uptake inhibitors who are given linezolid develop serotonin syndrome [114–117]. If it is necessary to start linezolid in a patient requiring a selective serotonin re-uptake inhibitor, the patient should be watched for signs of serotonin syndrome and the responsible medications promptly discontinued if signs develop.

Proton pump inhibitors can markedly decrease the circulating levels of some protease inhibitors (especially atazanavir) resulting in suboptimal HIV suppression and drug resistance. Dexamethasone, phenytoin, rifampin, tacrolimus, and efavirenz all enhance caspofungin metabolism and their use necessitates administering higher doses of this antifungal.

Summary

Antibiotics are commonly used in the ICU. Adverse effects are regularly encountered and must be anticipated. The multiplicity of medications and underlying conditions in ICU patients affect the presentation and management of adverse reactions. When possible, the intensivist should employ the fewest number of antibiotics necessary, choosing those least likely to interact with other drugs and cause adverse reactions.

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