Adverse Drug Reactions in the Intensive Care Unit

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Contents

Adverse drug reactions (ADRs) are undesirable effects of medications used in normal doses [1]. ADRs can occur during treatment in an intensive care unit (ICU) or result in ICU admissions. A meta-analysis of 4139 studies suggests the incidence of ADRs among hospitalized patients is 17% [2]. Because of underreporting and misdiagnosis, the incidence of ADRs may be much higher and has been reported to be as high as 36% [3]. Critically ill patients are at especially high risk because of medical complexity, numerous high-alert medications, complex and often challenging drug dosing and medication regimens, and opportunity for error related to the distractions of the ICU environment [4]. Table 1 summarizes the ADRs included in this chapter.

ADRs are among the leading causes of death in hospitalized patients [1, 5]. Other serious effects include disability, prolonged hospitalization, and increased healthcare costs. These costs are variable depending on the severity, but each ADR could cost $6000–9000 and increase the length of stay by a median of 8.8 days [4, 6]. One observational study of ICU patients found an incidence of 20.2%, or 80.5 events per 1000 patient days, of which 13% were life threatening and/or fatal [7].

Medical toxicologists can help to decrease healthcare costs and reduce length of stay by assisting with the rapid detection and treatment of ADRs. This benefits both the patient and healthcare system. This chapter will provide a background for identifying ADRs as well as

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Table 1 Adverse drug reactions (*ADRs*) in the ICU chapter overview. ADRs are categorized alphabetically by organ system

Allergic/ hypersensitivity ADRs	Angioedema
	Bronchospasm
	Infusion reactions
	DRESS
Dermatologic ADRs	SJS and TEN
Cardiovascular ADRs	Arrhythmias and conduction disturbances
	QT prolongation
	Hypotension
	Cardiogenic shock
	Distributive shock
Hematologic ADRs	Thrombocytopenia
	Methemoglobinemia
Pulmonary ADRs	Drug-induced respiratory disease
	Airway dysfunction
	Parenchymal and interstitial lung disease
	Pulmonary edema and vasculopathy
	Pulmonary arterial hypertension
	Neuromuscular respiratory disease
Gastrointestinal ADRs	Constipation/ileus
	Delayed absorption
	Diarrhea
	Hepatotoxicity
	Pancreatitis
Renal ADRs	Acute renal failure: prerenal, intrarenal, and postrenal nephrotoxicity and nephrotic syndrome
Neurologic ADRs	Delirium
	Seizures

Abbreviations: drug reaction with eosinophilia and systemic symptoms (*DRESS*), Steven–Johnson syndrome, toxic epidermal necrolysis (*TEN*)

describing various types. ADRs will be summarized by organ system, incorporating post-marketing surveillance to identify higher-risk ICU drugs. Drugs commonly used in the ICU for the management of poisoned patients are the primary focus of this chapter.

Table 2 Naranjo Adverse Drug Reaction Probability Scale. A ten-question probability scale assigns points to each response. If the response is unknown, a score of 0 is assigned. From the total score, drug–ADR causality can be stratified as definite (≥9), probable (5–8), possible (1–4), and doubtful (≤0)

	Question	Yes	No
1	Previous reports on this reaction?	+1	0
2	Timing-ADR appear after drug administration?	+2	−1
3	Did the ADR improve after the drug was discontinued or after an antagonist was administered?	+1	0
4	Did the ADR reappear when the drug was readministered?	+2	−1
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2
6	Did the reaction reappear when a placebo was given?	−1	+1
7	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0
10	Was the ADR confirmed by any objective evidence?	+1	0
	Total:		

Modified from Naranjo et al. [8]

Background

When an ADR is suspected, a Naranjo probability score can be used to standardize the assessment, with presumed causality assigned based on total score (see Table 2) [8].

The higher the score, the more likely an ADR occurred. Mechanisms by which these medications cause ADRs include pharmacogenetic, pharmacokinetic, and metabolite accumulation and/or combinations and are described in Table 3. Table 4 summarizes one commonly used scoring system for grading adverse drug reactions.

The incidence of specific drug–ADR combinations is low, requiring large databases and statistical analysis to identify emerging trends. Advances in information technology have

allowed pharmacovigilance and post-marketing surveillance systems to calculate observed to the expected number of drug-event pairs (proportional reporting ratios (PRRs)) [9–13]. The Empirical Bayesian Geometric Mean (EBGM) is calculated from the PRR and accounts for differences in reporting rates and variables within the dataset [14]. False positives, which are inherent to data mining systems, are avoided by increasing the number of reports and increasing PRR or EBGM, thereby strengthening the signal [12, 14]. Both PRR and EBGM ratios shrink toward one, and values ≥ 2 are considered to be the safety signal thresholds that warrant further evaluation. Previous studies have suggested PRRs to be more sensitive and EBGM more specific [12, 15]. Some studies minimize false negatives by using more than one data mining system; however, well-known drugs associated with ADRs continue to be missed, which is possibly secondary to underreporting. These are often older medications such as nitroglycerine infusions [16]. There are limited literature studies on ICU ADRs compared to medication error evaluation.

Table 3 Types of ADRs

1	Exaggeration of drug's normal/desired pharmacological mode of action
2	Continuing action/reaction, persisting for longer than expected time period
3	Delayed onset of action
4	Withdrawal
5	Unexpected failure of therapy
6	Idiosyncratic response not expected from normal pharmacological mode of action
7	Drug–drug interaction
8	Other pharmacokinetic interaction
9	Other pharmacodynamic interaction

Modified from American College of Medical Toxicology ToxIC Database available at http://www.acmt.net/cgi/page.cgi/ToxIC1.html

Organ System ADRs

Allergic/Hypersensitivity ADRs

Infusion Reactions

Infusion reactions (drug-mediated hypersensitivity, infusion-related toxicity, cytokine storm, cytokine-release syndrome, anaphylactoid reaction, and serum sickness-like illness) are associated with a spectrum of variability and heterogeneity for both individual and drug; symptoms may include anxiety, diaphoresis, rigors/chills, fever, pruritus, urticaria, angioedema, headache, nausea, emesis, diarrhea, chest pain, dyspnea, wheezing/bronchospasm, hypoxia, respiratory failure, hypotension, and death [17–21]. Symptoms can occur shortly after the infusion begins but can have delayed onset; symptoms may decrease when the infusion rate is discontinued or slowed but symptoms may persist.

Drug classes associated with infusion reactions include antimetabolites (drugs interfering with nucleic acid synthesis), antimicrobials, electrolytes and nutrients, enzymes, and immunomodulators [17]. The implicated final common pathway for each medication may include mast cell

Table 4 CTCAE grading of adverse drug reactions. ADRs can be mild or moderate or result in death; signs/symptoms, interventions, and limitations to ADLs are used to grade the severity with a score of 1–5

Grade	Description	Signs/symptoms	Intervention	ADLs
1	Mild	Asymptomatic or mild	None	
2	Moderate	Minimal	Noninvasive intervention	Limited
3	Severe	Significant but not immediately life threatening	Hospitalization and/or prolongation	Disabling
4	Life threatening	Life-threatening consequences	Urgent intervention indicated	Disabling
5	Death			

Modified from the US Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed Aug 18, 2015)
Abbreviations: *ADL* activities of daily living, *CTCAE* common terminology criteria for adverse events

activation and nitric oxide (NO) signaling via nitric oxide synthase (e.g., *N*-acetylcysteine [22, 23] and calcium [24]), NO donors and NO-like compounds (e.g., nitroprusside [25]), reactive oxygen and nitrogen species (e.g., amphotericin [26]), S-nitrosylation and transnitrosylation (e.g., adenosine [27–29], iron, *N*-acetylcysteine, and nitroprusside), histamine release (e.g., amphotericin [26], *N*-acetylcysteine [20], and vancomycin [30]), and cytokine release (e.g., amphotericin [26], *N*-acetylcysteine [20], and immunoglobulins) [31–34]. Sometimes, clinical effects are caused by an excipient such as polyethoxylated castor oil which has been used as the solubilizing vehicle for phytonadione [35]. Some drugs such as *N*-acetylcysteine have been prospectively studied. When administered rapidly, *N*-acetylcysteine has caused mild, moderate, and severe infusion reactions for up to 60%, 30%, and 10% of patients, respectively [20]. This association may be underreported, as this drug does not appear in the table of drugs associated with infusion reactions. The medical toxicologist may see infusion reactions related to IV *N*-acetylcysteine, although slower infusion rates have made this less common [20, 21, 23, 36, 37].

For ICU patients, electrolytes had the highest association with infusion reactions followed by immunomodulatory drugs, antiarrhythmics, antifungals, and antibiotics (Table 5). Treatment involves discontinuing or slowing the rate of infusion for the suspected drug or pretreating with antihistamine and prostaglandin inhibitors.

Drug-Induced Angioedema

Angioedema, or rapid localized edema of the deep dermis, subcutaneous, or submucosal tissues, can be idiopathic, or it can be mediated by bradykinin or mast cells [38]. Angioedema associated with the use of drugs can manifest after the first dose of a drug, but for some drugs, such as those targeting the renin–angiotensin–aldosterone system, it can occur at any time [39]. The presence of angioedema with wheals or urticaria suggests the etiology involves mast cells. Culprit medications include nonsteroidal anti-inflammatory drugs (NSAIDs) or antibiotics, often acting through the inhibition of cyclooxygenase resulting in alteration in the metabolism of arachidonic acid with increased leukotrienes [40–42]. Angioedema without wheals or urticaria could be bradykinin mediated, which implicates angiotensin-converting enzyme inhibitors [38]. Bradykinin

Table 5 ICU drugs highly associated with infusion reactions from two post-marketing surveillance systems: Molecular Analysis of Side Effects (*MASE*) and the FDA's Adverse Event Reporting System (*FAERS*). Statistical criteria for MASE was set as PRR $\geq$ 2.0 and $N \geq 30$ reports and for FAERS as EBGM $\geq$ 2.0 and $N \geq 30$ reports. Drugs are grouped by drug class and then displayed with comparison data. Using two systems improved the sensitivity of drug detection

		FAERS		MASE	
Classification	Generic name	*N*	EBGM	*N*	PRR
Analgesic	Meperidine	–	–	32	3.9
Antiarrhythmic	Adenosine	29	19.4	33	18
Antibiotic	Meropenem	–	–	34	3.1
	Ceftriaxone	20	1.3	33	3.1
	Vancomycin	109	6.8	162	4.7
Antifungal	Amphotericin B	58	7.0	66	4.9
Electrolytes	CaCl and KCl	34	26.6	8	1.7
	Ferric Na Gluc	55	37.6	–	–
	Iron dextran	68	48.1	66	48.9
	Iron sucrose	57	27.0	–	–
Immunomodulator	Ig	314	17.4	68	9
	Rho-Ig	32	13.3	–	–
Mucolytic	Acetylcysteine	16	5.0	25	2.8

Abbreviations: calcium (*Ca*), chloride (*Cl*), immunoglobulin (*Ig*), and potassium (*K*)

accumulation results in an increased vascular permeability resulting in angioedema [42].

Drugs acting on the renin–angiotensin–aldosterone system are commonly implicated, but several other classes have also been implicated including antibiotics, aspirin, NSAIDs, antifungals, calcium channel blockers, diuretics, and lidocaine [43–45]. ACE inhibitors [ACEI] have been associated with angioedema, and incidence rates for specific drugs have been reported for captopril (7.17 events per1000 persons) [46], enalapril (6.85 events per 1000 persons) [45], lisinopril (4.09 events per 1000 persons), and ramipril (2.92 events per 1000 persons) [47]. Other studies have reported cumulative incidence of angioedema per 1000 persons for the class of ACEIs as 1.79, 1.80, and 2.95 [39, 48, 49]. Comparing drugs targeting the renin–angiotensin–aldosterone system, one cohort study found risk for angioedema three times higher for ACEIs and renin inhibitors than for the control group (Table 6) [39].

Treatment involves stopping the implicated medication(s) and monitoring the patient for at least 6 h [42, 50]. If angioedema is secondary to mast cell activation, antihistamines, epinephrine, and corticosteroids may be effective. These will be less effective if bradykinin is implicated [50]. Cases of ACEI-induced angioedema can continue to occur for weeks despite discontinuing therapy [42]. If an ACEI is implicated, changing to angiotensin receptor blockers is associated with a 10% risk of angioedema recurrence [51]. When bradykinin-mediated angioedema is suspected and life threatening, bradykinin antagonists (e.g., icatibant) and C1 inhibitor concentrates (e.g., ecallantide, an inhibitor of kallikrein) may be effective, but their cost is prohibitive for routine use [42, 50,

Table 6 Comparative risk of angioedema (*AE*) associated with drugs that target the renin–angiotensin–aldosterone system (Modified from Toh et al. [39]). Incidence rates were calculated for angiotensin receptor blockers (*ARBs*) and compared to the entire class of angiotensin-converting enzyme inhibitors (*ACEIs*) using beta-blockers as a control group as they are generally not thought to be associated with AE. Incidence reported per 1000 persons with 95% confidence interval. Hazard ratio reported with 95% confidence interval. Severe reactions were those that required ICU admission

Class/generic name	*N*	Incidence	HR	*N* (severe)	Incidence (severe)	HR (severe)
ACEIs	3301	1.79 (1.73–1.85)	3.04 (2.81–3.27)	326	0.18 (0.16–0.20)	4.91 (3.62–6.65)
ARBs	288	0.62 (0.55–0.69)	1.16 (1.00–1.34)	10	0.02 (0.01–0.04)	0.56 (0.28–1.14)
Candesartan	4	0.33 (0.09–0.83)	0.95 (0.35–2.55)			
Eprosartan	0					
Irbesartan	24	0.54 (0.35–0.81)	1.11 (0.73–1.67)			
Losartan	94	0.88 (0.71–1.08)	1.53 (1.23–1.90)	3	0.03 (0.01–0.08)	1.01 (0.31–3.34)
Olmesartan	39	0.42 (0.30–0.57)	0.88 (0.63–1.22)	1	0.01 (0.00–0.06)	0.83 (0.11–6.57)
Telmisartan	11	0.42 (0.21–0.74)	0.86 (0.47–1.56)			
Valsartan	110	0.6 (0.49–0.72)	1.08 (0.88–1.34)	6	0.03 (0.01–0.07)	1.14 (0.46–2.82)
Renin inhibitor						
Aliskiren	7	1.44 (0.58–2.96)	2.85 (1.34–6.04)	1	0.21 (0.01–1.14)	8.84 (1.13–69.41)
Beta-blockers	915	0.58 (0.54–0.61)	1	51	0.03 (0.02–0.04)	1

52, 53]. Fresh frozen plasma contains angiotensin-converting enzyme and C1 esterase inhibitor and can reverse bradykinin-mediated angioedema [52, 53].

Drug-Induced Bronchospasm

A Swiss post-marketing surveillance system found that bronchospasm was present in 2% of reported ADRs; 55% of these cases are classified as serious [54]. Implicated drug classes include analgesics and NSAIDs in 24% (64.5% serious), antimicrobial agents in 18% (52% serious), cardiovascular drugs in 11% (50% serious), and excipients in 5.5% (41% serious) [54]. The nonsterile nebulized bronchodilator solutions contain preservatives that can induce concentration-dependent bronchospasm: sulfites, benzalkonium chloride, or ethylenediaminetetraacetic acid [55]. The critical care toxicologist should keep drug-induced bronchospasm in the differential in the ventilated patient who has a change in oxygenation.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS) is associated with high mortality (47%) and is characterized by an exanthema with facial edema, enlarged lymph nodes, eosinophilia, and high-grade fever [56]. The severity depends on the organs involved (hepatitis, acute renal failure, pneumonitis, myocarditis, hemophagocytic syndrome, encephalitis, and/or multi-organ failure) [57]. DRESS can be easily missed as sometimes the eosinophilia is delayed and skin manifestations vary in severity from mild to severe [58]. Drugs associated with DRESS will usually have been prescribed for at least 2 weeks and include anticonvulsants (e.g., carbamazepine and lamotrigine), sulfonamides, and antibiotics (e.g., amoxicillin, ciprofloxacin, and minocycline) [59–61]. Discontinue all suspected drugs and treat supportively for organ failure and shock. Severe cases may require corticosteroids, intravenous immunoglobulins, and/or antiviral drugs (e.g., ganciclovir) because DRESS can closely resemble herpes virus reactivation with eosinophilia and systemic symptoms ("VRESS") [57, 58].

Dermatologic ADRs

Steven–Johnson Syndrome and Toxic Epidermal Necrolysis

Steven–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe and potentially life-threatening systemic disorders characterized by skin and mucous membrane lesions, sometimes with necrosis. The extent of the surface area involved as well as the presence of necrosis helps to differentiate them. The lesions typically appear on extensor surfaces as well as the palms or the hands and soles of the feet. If there is epidermal and mucous membrane detachment and more than 30% of the body surface area is involved, TEN is implicated. Drugs implicated in SJS and/or TEN are pharmacologically diverse. Data mining implicates multiple pathways and suggests metabolizing enzymes, and transporters increase the intracellular tissue concentrations of reactive metabolites resulting in oxidative stress and the immunologic response. A disproportionate number of drugs associated with SJS were metabolized by cytochrome P450 3A4 and 2C9 and implicated transporters, multidrug resistance protein 1 (MRP-1), organic anion transporter 1 (OAT1), and PEPT2 [62]. Drug targets highly associated with SJS included cyclooxygenases 1 and 2, carbonic anhydrase 2, and sodium channel 2 alpha which overlaps with results of other studies implicating antiepileptic drugs [63]. See Table 7 for drugs identified by the US Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) as being highly associated with SJS. The FDA has issued post-marketing safety alerts for acetaminophen (warning), phenytoin (modified warning), and carbamazepine (boxed warning). Critical care patients often require treatment with drugs highly associated with SJS; treatment involves discontinuing the suspected

Table 7 MASE and FAERS ICU drugs highly associated with Steven–Johnson syndrome when PRR ≥ 2 or EBGM ≥ 2 and $N > 30$

Analgesics: acetaminophen
Antiepileptics: carbamazepine, lamotrigine, phenytoin, zonisamide
Antimicrobials: amoxicillin, ampicillin/sulbactam, amphotericin B, azithromycin, cefdinir, cefepime, ceftriaxone, cefotaxime, cefuroxime, cephalexin, ciprofloxacin, clarithromycin, clindamycin, erythromycin, fluconazole, meropenem, piperacillin/tazobactam, rifampin, sulfamethoxazole, trimethoprim, vancomycin
Barbiturates: phenobarbital
Diuretics: furosemide, torsemide
Mucolytics: acetylcysteine
Proton pump inhibitors: pantoprazole
Vitamins: phytonadione

drug(s) and continuing care in facilities experienced in burn care.

Cardiovascular ADRs

Drug-Induced Arrhythmias and Conduction Disturbances

Arrhythmias and conduction disturbances range from bradycardia to tachycardia, can originate anywhere from the atria to the ventricles, can be regular or irregular, and can be mild or life threatening. Many of the toxin-induced arrhythmias are discussed throughout the medication chapters including cardiovascular digitalis glycosides, beta-receptor antagonists, cardiovascular calcium channel blocking agents, cyclic antidepressants, and lithium.

Drug-Induced QT Prolongation

This section discusses ADRs associated with QT prolongation; for additional details, refer to ▶ Chap. 22, "Toxicant-Induced Torsade de Pointes." QT prolongation is highly prevalent in the ICU, and one prospective study found 24% of patients in a mixed ICU had QTc > 500 ms [64]. QT prolongation can result from hypokalemia, hypomagnesemia, hypocalcemia, genetic predisposition (ion channel polymorphisms), tissue hypoxia, and/or the presence of one or more drugs with potassium-blocking properties. A nomogram exists and should be used to correct for heart rate [65]. For a reference list of QTc prolonging medications, the Arizona Center for Education and Research on Therapeutics (AZCERT) continually updates their list (www.crediblemeds.org). The concurrent use of drugs inhibiting cytochrome 3A4 or 2D6 should also be recognized in the setting of QT prolongation [66–69].

Torsades de pointes (TdP), a potentially fatal ventricular arrhythmia, is associated with QT prolongation but usually requires at least one other risk factor before emerging. One review of QTc prolongation and TdP found 92.2% of TdP cases had at least one additional risk factor for QTc prolongation [70]. In reviews of thorough QT studies, while drug-associated QTc prolongation is associated with and considered a surrogate for predicting TdP, other intrinsic and extrinsic factors modify this risk. Bradycardia may be a major risk factor for TdP; TdP rarely occurs when HR is above 105 beats per minute [65]. A large case-crossover study of more than 17,000 patients who were prescribed with antipsychotic drugs found a drug's arrhythmogenic propensity was related to dose, blockade of potassium channel, and short-term usage [71]. For antipsychotic drugs, the strength of potassium blockade from lowest to highest was quetiapine, chlorpromazine and trifluoperazine, clozapine, aripiprazole, prochlorperazine, olanzapine, zotepine, risperidone, thioridazine, ziprasidone, and haloperidol [71]. Beside potassium channel blockade, tachycardia associated with muscarinic blockade may be a risk factor for cardiotoxicity [72]; however, another large retrospective review of antipsychotic ingestions admitted to a medical toxicology service demonstrated tachycardia may be protective [65]. ICU drugs associated with QTc as listed by AZCERT are highlighted in Table 8.

The treatment for QT prolongation includes discontinuing associated drugs and replacing associated electrolyte deficiencies. Resolution of prolongation will depend on the pharmacokinetics of implicated drugs. Sodium bicarbonate and

Table 8 ICU drugs associated with QTc prolongation as listed by Arizona Center for Education and Research (*AZCERT*)

	AZCERT risk of TdP		
Drug	Possible	Known	Conditional
Antiarrhythmics			
Amiodarone		X	
Disopyramide		X	
Dofetilide		X	
Dronedarone		X	
Flecainide		X	
Ibutilide		X	
Procainamide		X	
Quinidine		X	
Sotalol		X	
Anticonvulsant			
Felbamate	X		
Antidepressant: SARI, SSRI, tricyclic			
Amitriptyline			X
Citalopram		X	
Clomipramine	X		
Desipramine	X		
Doxepin			X
Escitalopram		X	
Fluoxetine			X
Imipramine	X		
Nortriptyline	X		
Paroxetine			X
Sertraline			X
Trimipramine	X		
Trazodone			X
Antiemetics			
Diphenhydramine			X
Dolasetron	X		
Granisetron	X		
Hydroxyzine			X
Metoclopramide			X
Ondansetron		X	
Promethazine	X		
Antihypertensive and/or diuretic			
Furosemide			X
Hydrochlorothiazide			X
Indapamide			X
Isradipine	X		
Nicardipine	X		
Torsemide			X
Antimicrobials			
Azithromycin		X	
Bedaquiline	X		
Chloroquine		X	
Ciprofloxacin		X	
Clarithromycin		X	

(*continued*)

Table 8 (continued)

	AZCERT risk of TdP		
Drug	Possible	Known	Conditional
Erythromycin		X	
Fluconazole		X	
Gemifloxacin	X		
Iloperidone	X		
Itraconazole			X
Ketoconazole			X
Levofloxacin		X	
Metronidazole			X
Moxifloxacin		X	
Norfloxacin	X		
Pentamidine		X	
Posaconazole			X
Telavancin	X		
Telithromycin	X		
Voriconazole			X
Antipsychotics			
Aripiprazole	X		
Clozapine	X		
Chlorpromazine		X	
Droperidol		X	
Haloperidol		X	
Iloperidone	X		
Mirtazapine	X		
Olanzapine	X		
Paliperidone	X		
Pimozide		X	
Quetiapine	X		
Risperidone	X		
Sulpiride		X	
Thioridazine		X	
Ziprasidone	X		
Drugs of abuse			
Cocaine		X	
GI prophylaxis			
Famotidine	X		
Pantoprazole			X
Ranitidine			
Immunosuppressant			
Hydroxychloroquine			X
Tacrolimus	X		
Muscle relaxant			
Solifenacin			X
Tizanidine	X		
Tolterodine	X		
Phosphodiesterase inhibitor			
Anagrelide		X	
Cilostazol		X	

(*continued*)

Table 8 (continued)

Drug	AZCERT risk of TdP		
	Possible	Known	Conditional
Vardenafil	X		
Sedative–analgesia–anesthetic			
Dexmedetomidine	X		
Chloral hydrate			X
Methadone		X	
Propofol		X	
Sevoflurane		X	
Others			
Perflutren lipid microspheres	X		
Ranolazine	X		
Apomorphine	X		
Oxytocin	X		
Amantadine			X

Table 9 Algorithm for the initial assessment of shock. When there are signs of tissue hypoperfusion (altered mental status, mottled/clammy skin, decreased urine output, tachycardia, and/or elevated lactate), an assessment of the type of circulatory shock begins with estimating CO or SvO_2. Echocardiography can be used to differentiate circulatory shock

Type	CO or SvO_2	CVP	Echocardiograph	
			Cardiac chambers	Cardiac contractility
Distributive	Normal or high		Normal	Normal
Hypovolemic	Low	Low	Small	Normal or high
Cardiogenic	Low	High	Large ventricles	Poor
Obstructive	Low	High	Small ventricle(s) depending on location of obstruction	

Modified from Vincent and Backer [76]*Abbreviations*: *CO* cardiac output, *CVP* central venous pressure, *SvO_2* mixed venous oxygen saturation

hyperventilation should be used in the setting of concurrent QRS prolongation; sodium bicarbonate is not known to change QTc [73, 74]; refer to ▶ Chaps. 21, "Cardiac Conduction and Rate Disturbances" and ▶ 22, "Toxicant-Induced Torsade de Pointes" for further information on the management of these patients.

Drug-Induced Hypotension

This section discusses ADRs associated with hypotension; for additional details, refer to ▶ Chap. 14, "The Assessment and Management of Hypotension and Shock in the Poisoned Patient" Drug-induced hypotension can occur in up to 35% of ICU patients, and the most prevalent medications include cardiovascular medications, sedatives, and analgesics [75]. Hypotension may be hypovolemic (intravascular volume loss), distributive (vasodilation or smooth muscle relaxation), cardiogenic (decreased cardiac output via decreased conduction velocity, contractility, and/or heart rate), and/or obstructive (e.g., pulmonary embolism, cardiac tamponade, or tension pneumothorax) [76]. Drug-induced hypotension often involves a combination of hypovolemic, distributive, and/or cardiogenic mechanisms. Table 9 is an overview of the initial assessment of shock, and Table 10 lists ICU drugs associated with hypotension with their known mechanism. For details of the treatment of hypotension, refer to ▶ Chap. 14, "The Assessment and Management of Hypotension and Shock in the Poisoned Patient."

Table 10 ICU drugs associated with hypotension. Common ICU drug classes are listed with examples of generic drugs implicated. Mechanism of hypotension included hypovolemia, distributive (vasodilation), and/or cardiogenic (decreased CO)

Classification		Generic name	Mechanism		
			Hypovolemia	Vasodilation	Decreased CO
Beta-blockers	Selective	Atenolol, bisoprolol, esmolol, and metoprolol			B1B
	Nonselective	Carvedilol		A1B, B2B	B1B
		Labetalol		A1B, B2B	B1B
		Propranolol		B2B	B1B
		Nadolol		B2B	B1B
		Sotalol		B2B	B1B
CCB	Dihydropyridine	Amlodipine, nicardipine, and nifedipine		L-type CCB	
	Non-dihydropyridine	Diltiazem and verapamil		L-type CCB	L-type CCB
Diuretics	Thiazide	Hydrochlorothiazide	inh. Na/Cl symporter		
	Thiazide-like	Metolazone	inh. Na/Cl symporter		
	Potassium sparing	Spironolactone	inh. Na/K exchanger and competitive aldosterone ant.		
	Loop	Bumetanide and furosemide	inh. Na-K-2Cl symporter		
Imidazolines		Clonidine and dexmedetomidine		A2A	
Nitrates		Isosorbide dinitrate and nitroglycerine		NO	
Opioids		Morphine, codeine, hydromorphone, meperidine, fentanyl		Decrease sympathetic outflow, H2	Decreased sympathetic outflow
Renin–angiotensin antagonists	ACEI	Benazepril, fosinopril, lisinopril, and ramipril	Bradykinin natriuresis	Bradykinin	
	ARBs	Candesartan, irbesartan, losartan, and valsartan		ARB	
Sedative/hypnotics		Propofol		Decreased sympathetic outflow	Decreased sympathetic outflow
	Barbiturates	Phenobarbital and pentobarbital		Decreased sympathetic outflow	Decreased sympathetic outflow
	Benzodiazepines	Lorazepam and midazolam		Decreased sympathetic outflow	Decreased sympathetic outflow
Vasodilators		Hydralazine			

Abbreviations: *ACEI* angiotensin-converting enzyme inhibitor, *ant* antagonist, *ARB* angiotensin II receptor blocker, *A1B* alpha-1-adrenergic receptor blocker, *A2A* alpha-2-adrenergic receptor agonist, *B1B* beta-1-adrenergic receptor blocker, *B2B* beta-2-adrenergic receptor blocker, *CCB* calcium channel blocker, *Cl* chloride, *CO* cardiac output, *inh* inhibitor, *K* potassium, *Na* sodium, *NO* nitric oxide

Drug-Induced Cardiogenic Shock

Drugs associated with cardiogenic shock include β1-adrenergic antagonists, muscarinic agonists, and L-type calcium channel antagonists. β1-adrenergic antagonists decrease heart rate, conduction velocity, and contractility. Muscarinic receptor subtype M2 agonists decrease heart rate and cardiac conduction velocities [77, 78]. Calcium channel blockers acting at L-type channels decrease cardiac contractility, conduction velocity, and/or heart rate; dihydropyridine calcium channel blockers are associated with vasodilation, while nondihydropyridines are also associated with decreased cardiac output [79]. Sedatives and analgesics decrease sympathetic outflow that decreases norepinephrine and epinephrine release resulting in both vasodilation and decreased cardiac output.

Drug-Induced Distributive Shock

Vasodilation can result from L-type calcium channel antagonists, angiotensin receptor blockers (ARBs), α1-adrenergic antagonists, α2-adrenergic agonists, β2-adrenergic antagonists, bradykinin receptor agonists, histamine H2 receptor agonists, muscarinic M3 antagonists, and/or prostaglandin E2, D2, and I2 agonists [77, 78, 80–83]. Drugs impacting NO signaling will cause vasodilation when concentrations of either NO or cyclic-guanosine monophosphate are increased. Histamine release can occur proportionately to drug dose and has been associated with drugs such as opioid analgesia and antibiotics such as vancomycin (see section on "Infusion Reactions" for additional drugs associated with histamine release). A double-blind study found meperidine was most frequently associated with histamine release, but morphine and codeine have also been implicated [84]. Opioids can also cause hypotension through vasodilation and vagal activation [85].

Opioids

Opioid receptors are located peripherally and centrally; they are involved in vascular regulation and decrease sympathetic neural regulation [86–88]. Mu-, delta-, and kappa-opioid receptors participate in the complex vasoregulatory process and when blocked centrally decrease hypotension [89–93] and narrow the ability to autoregulate blood flow [94].

Propofol

Propofol is an anticonvulsant and amnestic with rapid onset and short duration of action [95]. Due to its faster recovery time and return of spontaneous respiration time, propofol has been favored by some over benzodiazepines for procedural sedation and for patients in the ICU [95–97]. Propofol is structurally unrelated to other sedative-hypnotics and produces its effects in a dose-dependent manner. Propofol causes hypotension and bradycardia with an average maximum mean arterial pressure (MAP) reduction of 29% after initiation, and severe hypotension develops in 26% of patients [97, 98]. Hypotension occurs through centrally mediated venodilation, sympatholysis and vagolysis [99, 100]. Pretreatment with ketamine, ephedrine, dopamine, or naloxone may decrease risk [101–105], as does the use of the lowest effective dose [106]. Intravenous fluid administration does not appear to be an effective prevention [107, 108].

Propofol is a mitochondrial toxin and can inhibit intracellular energy production resulting in propofol-related infusion syndrome (PRIS) [109]. Signs of PRIS include metabolic acidosis, lipemic serum, rhabdomyolysis, cardiac arrhythmias, acute renal failure, hepatomegaly, and cardiac arrest [109]. PRIS has been associated with longer duration of infusion (>48 h) and faster infusion rates; other risk factors include increased catecholamine and glucocorticoid serum levels, head injury, and respiratory failure [109, 110]. An increase in triglyceride concentration is the most widely accepted marker of PRIS and may be explained by the fat content of the propofol emulsion [109, 110]. PRIS occurs in less than 5% of critically ill patients receiving propofol [109, 111]. One large retrospective study found a mortality of up to 40% in persons with PRIS; a review of FDA MedWatch data found mortality increased to 30% [109, 112]. A predictive tool was created and assigns points based on the presence of six factors: age ≤18, cardiac manifestations, metabolic acidosis, renal failure, hypotension, and rhabdomyolysis. Mortality increases with each point from 24% to 83% [112]. If PRIS is

suspected, propofol should be immediately discontinued. If the patient continues to decline, extracorporeal membrane oxygenation has successful treated cardiac arrest [113, 114].

Treatment

The treatment for hypotension is based on the identified cause. The "VIP" approach guides first steps in therapy: ventilate (oxygenate), infuse (fluid administration), and pump (administration of vasoactive agents) [115]. Initially, resuscitation should be done with crystalloid fluids (Level of Evidence [LoE] I) followed by placement of a central venous catheter if refractory hypotension requires vasoactive agents. The end point for fluid resuscitation is when cardiac output is preload independent [76]. Measuring SvO_2 (LoEI) and serum lactate concentrations (LoE_I) can help guide therapy although additional technologies are evolving. Vasoactive agents include vasopressors and inotropes and should be initiated on a case by case basis, considering each drug's potential adverse reaction profile. Vasopressors cause vasoconstriction from agonism at the β2- and α1-adrenergic receptors. Inotropes increase cardiac output through agonism at the β1-adrenergic receptor (increases heart rate, conduction velocity, and contractility). Adverse effects are related to dose, mechanism, potency, drug–drug, and/or drug–disease interactions.

Inotropic Agents

β-adrenergic agonists increase the heart rate and contractility which may increase the risk of myocardial ischemia in some circumstances [116]; however, a double-blind study found no difference in troponin elevation for treated patients with septic shock [117]. Dobutamine has predominantly beta-adrenergic properties and increases cardiac output and is a consideration when hypotension is mediated by cardiac pump dysfunction. Dobutamine has not demonstrated improved perfusion parameters in patients with septic shock without cardiac failure [118].

Vasopressors

By definition, vasopressors cause vasoconstriction, which can impair tissue perfusion. Epinephrine's range of effects is strongly dose dependent. At low doses (usual dosing range 0.01–0.1 microgram/(kg*min)), epinephrine predominantly targets β-adrenergic receptors; however, as the dose increases, more significant α-adrenergic effects appear [116]. Epinephrine has been associated with arrhythmias, decreased splanchnic blood flow, and increased blood lactate concentrations [119, 120]. Dopamine is an immediate precursor to norepinephrine in the synthetic catecholamine pathway [116]. Dopamine is an agonist at dopamine and β-adrenergic receptors at lower doses (<10 μg/(kg*min)), but with higher doses (10–20 μg/(kg*min)), α-adrenergic effects predominate [76]. The predominant dopaminergic effects observed with low doses of dopamine (<3 μg/kg/min) may preferentially dilate the hepatosplanchnic and renal circulations, but controlled trials have not shown clinically significant protection from renal dysfunction [121]. "Renally dosed" dopamine theoretically could worsen vasodilation resulting in hypotension, and many toxicology patients have minimal tolerance for worsened blood pressure. Dopamine may increase the incidence of arrhythmia when compared to norepinephrine [122]. Beta doses of dopamine (<10 μg/(kg*min)) may cause further vasodilatation and worsen hypotension. Therefore, for critically ill patients, dopamine therapy should be initiated at alpha receptor active doses (≥10 μg/kg/min).

Norepinephrine should be considered as the first-line vasopressor. Several studies demonstrate no advantage of dopamine over norepinephrine, and dopamine is associated with increased rates of arrhythmias and 28-day mortality for patients with cardiogenic and/or septic shock [122, 123]. For tricyclic antidepressant poisoned patients with hypotension refractory to intravenous fluid and serum alkalinization, norepinephrine appeared superior to dopamine as a first-line vasopressor agent [124] (LoE II-3). Norepinephrine may be associated with greater risk for peripheral ischemia and necrosis; however, these effects can occur with other vasopressors including vasopressin, dopamine, and epinephrine; preexisting vascular disease, sepsis, and DIC may be risk factors [116, 125–131].

Hematologic ADRs

Drug-Induced Thrombocytopenia

Thrombocytopenia is a commonly encountered abnormality in the critically ill, occurring in up to 44% of patients. Between 10% and 25% of these cases are thought to be drug induced. Potential mechanisms for this are platelet consumption or destruction, impaired platelet production, and hemodilution [132]. Multifactorial etiology is usually suspected when drug-induced thrombocytopenia (DITP) has occurred; however, single agents are not excluded. Platelets become targeted for destruction when a drug causes an antibody response. Depending on the molecular weight of the drug, this could be hapten dependent (e.g., penicillin) via covalent bonds to platelet glycoproteins or drug dependent (e.g., sulfonamide antibiotics), forming a complex or conformational change [133]. Sometimes autoantibodies are produced that can persist long after drug exposure and result in chronic autoimmune destruction [133].

DITP typically occurs 1–2 weeks after beginning a new drug or suddenly after a single dose of a drug which has previously been taken [134, 135]. Exceptions include first doses of antithrombotic agents such as tirofiban [136–139]. Table 11 contains a list of ICU drugs associated with thrombocytopenia. Antibiotics are associated with thrombocytopenia and, because of their prevalent use in ICU patients, are commonly implicated. Case–control studies have associated quinolones and trimethoprim/sulfamethoxazole with thrombocytopenia [140, 141]. Sample size, exposure rates, and the potential effect of drug combinations likely limited their findings to only these drugs as there are over a thousand case reports of DITP. A database can be found online at http://www.ouhsc.edu/platelets/ditp.html. Other drugs to consider for ICU patients include antifungals, antivirals, anticonvulsants, and glycoprotein IIb/IIIA inhibitors and anticoagulants [141].

Heparin or low-molecular-weight heparin is frequently used in immobile ICU patients. These drugs require careful consideration when evaluating a patient for thrombocytopenia. Heparin-induced thrombocytopenia (HIT) type 2 occurs in 0.5–5% of patients receiving heparin products [142]. Typically this syndrome is characterized by a 50% or greater thrombocytopenia from baseline, occurring 5–15 days after initial heparin therapy. It can occur sooner if there was a prior exposure to heparin. Physiologically, IgG antibodies bind heparin and platelet factor 4 (PF4), forming complexes. These complexes bind platelets and result in thrombocytopenia. If thrombin is activated, thrombosis can occur. If HIT is considered, an HIT score should be calculated to guide therapy. If the HIT score is low (0–3 points), heparin therapy should be continued. For moderate or high scores, further testing is recommended, and the patient started on alternative anticoagulation until the diagnosis can be conclusively excluded. The absence of PF4 IgG antibodies has a high negative predictive value and rules out HIT; specificity is poor so positive tests require additional analysis [142–145]. Serotonin release assay has high specificity (95–100%) and positive predictive value for HIT; however, the availability is limited. Several days are often required for results. Once HIT has been confirmed, duration of therapy should be for 4 weeks or until baseline platelet counts are restored. In the presence of thrombosis, treatment should be continued for 4 months.

When other drugs are suspected, they should be discontinued and platelets monitored for recovery. Recovery time will depend on the pharmacokinetics of the offending drug and the implicated mechanism. Usually, recovery begins 1–2 days after the offending drug has been discontinued and is complete within 1 week [134]. Drug-dependent antibodies can persist for years; patients should be counseled to avoid the implicated drug. See ▶ Chap. 30, "Toxicant-Induced Hematologic Syndromes" for more detail.

Drug-Induced Methemoglobinemia

Methemoglobinemia is discussed in ▶ Chap. 30, "Toxicant-Induced Hematologic Syndromes." Methemoglobinemia can be caused by dapsone

Table 11 ICU drug-induced thrombocytopenia (*DITP*). Drugs are grouped by drug class and mechanism with number of reports and probability score and if an antibody has been detected. University of Oklahoma Health Sciences Center's DITP database was referenced on May 6, 2015, for number of cases from individual and group patient reports. Drugs were added from recently published literature. Additional drugs, in parentheses, were added from recently published literature

Classification	Generic name	*N*[a]	Probability score[b]	Ab
Antibiotics				
Beta-lactamases	Amoxicillin	1	5	+
	Ampicillin	5	2	+
	Penicillin	6	1	
	Piperacillin/tazobactam	14	1	+
Carbapenems	Imipenem	4	2	
	Meropenem	11	2	
Cephalosporins	Cefazolin	1	5	+
	(Cefepime)	(1)	(2)	+
	Ceftriaxone	6	2	+
	Cefuroxime	1	3	
Dihydrofolate reductase inhibitor/sulfonamide	Trimethoprim/ sulfamethoxazole	65	1	+/+
Fluoroquinolones	Ciprofloxacin	6	1	+
	Levofloxacin	2	2	+
	Moxifloxacin	2	2	
Glycopeptide	Vancomycin	27	1	+
Lincosamide	(Clindamycin)	(1)	(3)	+
Macrolide	Clarithromycin	3	2	
Oxazolidinone	Linezolid	221	5	
Antifungals	Amphotericin	3	1	
	Fluconazole	5	2	
	Itraconazole	1	2	
Antivirals	Acyclovir	2	2	
	Ganciclovir	23	4	
Anticonvulsants	Levetiracetam	35	2	
	Valproic acid	231	5	+
Glycoprotein IIb/IIIa inhibitor	Tirofiban	125	1	+
Anticoagulant	(Heparin)		(1)	+

[a]Number of total patients with DITP based on individual and group reports when specified[b]Highest probability score from case reports: 1-thrombocytopenia definitely caused by drug, 2-probably, 3-possibly, 4-unlikely, 5-excluded (reasons included insufficient data and/or agents that cause thrombocytopenia due to marrow suppression)

or local anesthetics placed into the pharynx before nasogastric or orogastric tube placement or other procedures [146–157]. Local anesthetics associated with methemoglobinemia include benzocaine, cocaine, lidocaine, and prilocaine [146, 148, 149, 152, 154–157]. Benzocaine treatment may produce more methemoglobin than lidocaine [158]. Methylene blue is the antidote, but should be dosed carefully as logarithmic dosing errors or very high doses could worsen methemoglobinemia [159, 160].

Pulmonary ADRs

Drug-Induced Respiratory Disease

This section discusses ADRs associated with respiratory disease. For additional reference, see ▶ Chaps. 100, "Irritant and Toxic Pulmonary Injuries" and ▶ 16, "Treatment of Acute Respiratory Distress Syndrome in the Poisoned Patient." Respiration requires the integration of multiple systems. Respiratory failure occurs when any part of this process becomes dysfunctional and is

unable to maintain normal pH and/or adequate tissue oxygenation. Types of drug-induced respiratory disease can be subdivided based on location: airway (small and/or large), parenchymal/interstitial/pleural lung disease, pulmonary vasculopathy (e.g., noncardiogenic pulmonary edema or pulmonary arterial hypertension), neuromuscular respiratory disease (e.g., decreased respiratory drive), and/or circulation (e.g., methemoglobinemia) [161–164]. Neurologic drug-induced respiratory disease is common in the ICU due to the number of sedatives and analgesics administered. When evaluating for drug-induced respiratory disease, initial attention to oxygenation, respiratory rate, and end tidal CO_2 is helpful to determine if respiratory depression is present. Hypercarbia is more sensitive than hypoxia for early respiratory depression, and occasionally respiratory depression occurs in the absence of moderate to severe neurologic abnormality; naloxone and/or other antidote(s) administered can confirm and treat. If cyanosis and low pulse oximetry (90%) are present, arterial co-oximetry should be performed to evaluate for methemoglobinemia.

After excluding hemoglobinopathies and drug-induced respiratory suppression, further evaluation may include white blood cell differential, bronchial-alveolar lavage, chest radiograph, and/or high-resolution computed tomography (HRCT). Eosinophilia on peripheral blood smear or bronchial-alveolar lavage may suggest a drug-induced eosinophilic pneumonia. HRCT can further characterize the pathology [162–164]. Some diagnoses require an echocardiography, right-heart catheterization, and/or biopsy for diagnosis or to exclude other diagnoses. Echocardiography can exclude left-sided congestive heart and evaluate for cardiac comorbidities. A list of drugs associated with respiratory disease is maintained online by the Department of Pulmonary and Intensive Care at a University Hospital in Dijon, France (www.pneumotox.com). Table 12 contains a list of ICU drugs associated with more than 50 reports of respiratory disease.

Drug-Induced Airway Dysfunction

Refer to allergic/hypersensitivity ADRs section within this chapter where drug-induced bronchospasm and angioedema are discussed in detail.

Drug-Induced Parenchymal and Interstitial Lung Disease (ILD)

Parenchymal lung disease includes many subtypes, but commonly associated ICU drugs include amiodarone, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and drugs of abuse (before ICU admission). Frequently encountered conditions include acute ILD, subacute ILD, eosinophilic pneumonia, diffuse alveolar damage, and ILD with a granulomatous component. Patients who previously received chemotherapy can have ADRs based on their previous outpatient treatment regimens. Many chemotherapeutic drugs are associated with ILD. For example, ILD is emerging as a class effect of tyrosine kinase inhibitors (TKIs), inhibiting oncologic drugs that inhibit the vascular endothelial growth factor (VEGF) receptor. Diffuse alveolar damage (DAD) may be the most common manifestation, although other etiologies occur [165].

Amiodarone-induced respiratory disease has a wide spectrum of manifestations that can develop acutely or after many years [166–168]. The elderly may have higher risk. Peak onset occurs after 6–12 months of therapy [169]. Higher doses may be associated with increased risk although toxicity can develop with any dose [167, 170]. Typical presentation includes malaise, cough, fever, and pleuritic chest pain, with imaging demonstrating patchy opacities and/or acute respiratory distress syndrome (ARDS). Sometimes only pulmonary fibrosis is present, but pathological manifestations can include eosinophilic pneumonia, bronchiolitis obliterans organizing pneumonia, or diffuse alveolar damage (DAD) [166]. DAD is a severe respiratory failure involving alveolar fibrin, hyaline membranes, reactive epithelial cells, and diffuse ground-glass opacities [166, 171]. If amiodarone-associated respiratory disease is suspected, the drug should be discontinued and alternative medications titrated to control heart rate.

Table 12 ICU drug-induced respiratory disease. Drugs from www.pneumotox.com were included if ≥50 cases reported for a drug–disease pattern. Pneumotox was referenced on May 17, 2015

Generic drug	Airway disease	Interstitial/parenchymal disease	Pleural disease	Pulmonary vasculopathy
Drugs of abuse (IV/inhaled)		Granulomatous ILD, mass(s), pneumoconiosis	PTX	PAH
Amiodarone		Acute/subacute ILD, PF, lung nodule(s), DAD	Fibrothorax, pleuritic chest pain	ARDS
Beta-2 agonists (parenteral)				NCPE
Beta-blockers	Bronchospasm			NCPE
Crack cocaine	Bronchospasm			
Dopamine agonists			Fibrothorax	
Ethanol				ARDS
Excipients (vehicle)				PAH
Hemotherapy (blood or platelet transfusion)				NCPE, ARDS, TRALI, TACO
Heroin (inhaled, insufflated, snorted)	Bronchospasm			
Heroin (injected)	Bronchospasm		PTX	NCPE, flash pulmonary edema
Hydrochlorothiazide				NCPE
Latex	Bronchospasm			
Minocycline		EP		
Nitrofurantoin		Acute pneumonitis/ILD, subacute pneumonitis/ILD, PF	Acute pleuritis	
NSAIDS	Bronchospasm	EP		
Salicylate	Bronchospasm			NCPE

Key: acute respiratory distress syndrome (*ARDS*), diffuse alveolar damage (*DAD*), dopamine (*DA*), eosinophilic pneumonia (*EP*), inhaled (*INH*), interstitial lung disease or pneumonitis (*ILD*), intravenous (*IV*), noncardiogenic pulmonary edema (*NCPE*), parenchymal lung disease (*PLD*), pneumothorax (*PTX*), pulmonary arterial hypertension (*PAH*), pulmonary fibrosis (*PF*), transfusion-associated circulatory overload (*TACO*), transfusion-related lung injury (*TRALI*)

Nitrofurantoin is associated with acute or subacute pneumonitis (ILD) characterized generally with bilateral and symmetric pulmonary opacities. Pulmonary fibrosis, eosinophilic pneumonia, or pleuropathy (discussed later) may be present with restrictive lung dysfunction and hypoxemia, which usually resolve after the drug is discontinued [172–174].

Eosinophilic pneumonias (EP) have been associated with a significant number of drugs; antibiotics and NSAIDS are the most commonly reported [175–184]. Historically, there have been epidemics of EP associated with exposure to a toxic–oil spill in 1981 and L-tryptophan ingestion in 1989. Minocycline was the antibiotic most commonly reported by www.pneumotox.com (between 50 and 100 cases reported); daptomycin, nitrofurantoin, and sulfasalazine followed with 10–50 reported cases. The FDA has issued a warning regarding daptomycin and risk for eosinophilic pneumonia. Signs and symptoms of EP include fever, fatigue, dyspnea, wheezes with pulmonary infiltrates, and eosinophilia in blood, bronchial–alveolar lavage, and/or tissue [182]. Symptoms usually resolve after the implicated drug is discontinued; however, sometimes steroids are required.

ILD with a granulomatous component has been associated with drugs of abuse and mimics pulmonary and/or systemic sarcoidosis [185, 186].

The culprit could be a cutting agent such as levamisole or talc since the primary drug of abuse is more likely to cause other drug-induced respiratory disease (see Table 11). Heroin has been associated with bronchospasm, noncardiogenic pulmonary edema (NCPE), flash (fulminate) pulmonary edema, and/or pneumothorax [187, 188]. Crack cocaine has been associated with bronchospasm [189]. Other cutting agents such as clenbuterol, a beta-agonist, have been associated with NCPE [190], and topical anesthetics have been associated with methemoglobinemia [191]. Characteristically, ILD with a granulomatous component appears radiographically as sterile non-necrotizing granulomas and/or with a miliary appearance; lymphadenopathy may also be present [185, 186]. Patients may have granulomatous skin lesions.

Drug-Induced Pulmonary Edema and Vasculopathy

The lungs have an extensive vascular surface used for oxygenation and gas exchange, but this increases the risk for significant morbidity and mortality when endothelial and/or vascular injury occurs [192]. ARDS and noncardiogenic pulmonary edema (NCPE) are common clinical manifestations of drug-induced respiratory disease. Their clinical and radiographic features are difficult to distinguish from other causes of pulmonary edema; therefore, timing is an important consideration to determine etiology [193]. Patients may present with dyspnea, chest pain, tachypnea, and hypoxemia [193]. Chest imaging will demonstrate bilateral opacities not fully explained by effusions, atelectasis or nodules, and the absence of cardiomegaly and pulmonary vascular redistribution. Echocardiography or wedge pressure may be used to exclude cardiogenic causes, a requirement for the diagnosis of NCPE.

ARDS is defined and graded based on gas exchange abnormalities. The diagnosis is used interchangeably for mixed pathology but morphologically best characterized by DAD. ARDS is an acute, diffuse, inflammatory lung injury that increases pulmonary vascular permeability, hypoxemia, shunting, and pulmonary dead space. Using the Berlin definition, ARDS is defined based on the degree of hypoxemia as mild ($PaO_2/FIO_2 \leq 300$ mmHg or $P/F \leq 300$), moderate ($100 < P/F \leq 200$), and severe ($P/F \leq 100$) [194]. Mortality increased for each stage, 27%, 32%, and 45%, respectively [194]. Duration of mechanical ventilation in survivors increased for each stage: 5, 7, and 9 days, respectively [194]. When an ADR is suspected, the drug should be immediately discontinued.

NCPE, or permeability edema, is associated with opioids [187, 188, 195–197]; the mechanism may involve histamine release with capillary leak [198]. These effects usually occur within hours of opioid use and may persist. Decreasing the doses of opioids and/or changing to less histaminergic opioids may be helpful. When pulmonary edema develops within minutes of drug administration, it is called flash (fulminate) pulmonary edema.

Transfusion-related acute lung injury (TRALI) is a type of drug-induced pulmonary edema associated with hemotherapy and should be differentiated from transfusion-associated circulatory overload (TACO). TRALI can occur with transfusion of blood, platelets, plasma, IVIG, or any blood product. TRALI has an incidence rate of 22.5 per 100,000 hospital stays; risk factors include continued platelet and plasma transfusions, amount transfused, female gender, white ethnicity, and 6-month histories of pulmonary fibrosis and/or tobacco use [199, 200]. Decreasing female donation of blood products significantly reduced the incidence but suggests there is both an immune and nonimmune mechanism [199, 201]. Symptoms of TRALI develop within 8 h of infusion and can be difficult to differentiate from TACO, a type of overload pulmonary edema. TACO can occur when the rate or amount of fluid infused is more than the circulatory system can accommodate. Assessing fluid balance and measurement of brain natriuretic peptide may suggest an etiology as TRALI and/or TACO [202].

Pulmonary Arterial Hypertension

Drugs increasing serotonin and/or norepinephrine levels may cause pulmonary arterial hypertension (PAH) because of the vasoconstrictive and growth-modulating effects on smooth muscle

cells, resulting in an increased pulmonary vascular resistance, right cardiac failure, and death. Another proposed mechanism includes endothelial dysfunction [203]. PAH associated with ICU drugs could occur through excipients (vehicle), as reported by Pneumotox. Other considerations include drugs of abuse such as amphetamines and cocaine, anorexic or appetite suppressants, and other over-the-counter drugs such as nasal decongestants [203–205]. Fenfluramine, an appetite suppressant, was withdrawn from the market and had been associated with PAH. Phenylpropanolamine, a nasal decongestant, was withdrawn because of an increased risk of hemorrhagic stroke and may have been a risk factor for PAH.

Drug-Induced Neuromuscular Respiratory Disease

Respiratory pump function is dependent on central respiratory drive, peripheral nerves, neuromuscular junctions, and respiratory muscles. Drug-induced neuromuscular respiratory disease is discussed in the neurologic ADR section.

Gastrointestinal ADRs

Drug-Induced Constipation/Ileus

Constipation is the irregular and/or infrequent evacuation of the bowels. Multiple causes have been identified including poor nutritional intake (low dietary fiber); emotional disturbances; systemic, structural, and infectious conditions; and drugs. Drug-induced constipation has been associated with drugs affecting muscarinic, opioid, and gamma-aminobutyric-acid (GABA) receptors. Opioids are the drug class most frequently associated with constipation, which occurs in up to 71% of patients with chronic non-cancer pain whom are prescribed with opioids [206].

Opioid-induced constipation has significant economic ramifications as it is associated with longer inpatient stays (3–5 days vs. 1–2 days) and higher costs (US$16923–US$23631 vs. US$11117–US$12652) [206]. For ICU patients, the costs could be even higher, and patients should be prescribed with bowel regimens to promote daily motility. When conservative measures have failed, opioid antagonists may be considered (LoE_I). Cost is preclusive to widespread implementation. Naloxone, naltrexone, and nalmefene are opioid antagonists with low systemic bioavailability because of first-pass metabolism [61]. If given in sufficient doses, naloxone crosses the blood–brain barrier to reverse opioid analgesia; naloxone has a narrow therapeutic window when administered to treat opioid-induced constipation. Quaternary analogues of the opioid antagonists such as methylnaltrexone and alvimopan have greater polarity and lower lipid solubility; these analogues poorly cross the blood barrier. Methylnaltrexone is administered parenterally (0.15–0.3 mg/kg every other day) and alvimopan orally (0.5 or 1 mg once daily).

Delayed Absorption

Critically ill patients may already be at increased risk for delayed absorption of enteral medications. Some ICU drugs delay gastric emptying or slow motility and can interfere with the absorption of other drugs. Common drugs include anticholinergic, opioid agonists, anesthetics, and other sedatives. In the setting of overdose, absorption can continue longer than predicted by pharmacokinetics, especially for enteric coated or extended release medications, anticholinergics, and/or opioids [207–219].

Diarrhea

Many of the withdrawal states can be associated with diarrhea as can many antibiotics. Twenty-nine percent of 743 prospectively treated patients prescribed with inpatient antibiotics developed diarrhea during hospitalization, and four cases were confirmed of *Clostridium difficile* infection (CDI) [220]. Diarrhea started between 1 and 16 days after initiation with median onset on day 4. Potentially any antibiotic is associated with diarrhea, but cephalosporins, clindamycin, penicillins, and quinolones may carry a higher risk, especially for CDI [221]. Antibiotic-associated diarrhea was associated with increased age, proton pump inhibitor use, and being critically ill. The prevalence of CDI for ICU patients prescribed with antibiotics may be higher than other

Table 13 Clinical phenotypes for DILI associated with ICU drugs. Clinical phenotypes associated with ICU drugs with latency, initial bilirubin, and R value. R is calculated: (ALT/ULN)/(ALP/ULN) (Source: http://livertox.nlm.nih.gov (Accessed 5/18/2015))

Clinical phenotype	Latency	Bilirubin (mg/dL)	R	Drugs
Acute hepatic necrosis	<2 weeks	<10	>5	Acetaminophen, amiodarone, aspirin, cocaine, methylenedioxymethamphetamine (MDMA, ecstasy), niacin
Acute hepatitis	2–24 weeks	>2.5	>5	Disulfiram, isoniazid (INH), nitrofurantoin, sulfonamides
Cholestatic hepatitis	2–12 weeks	>2.5	<2	Ceftriaxone, clavulanate, fluoroquinolones (ciprofloxacin, levofloxacin), macrolides, penicillins, rifampin, sulfonamides, sulfonylureas
Mixed hepatitis	4–24 weeks	>2.5	2–5	Aromatic antipsychotics (e.g., carbamazepine, phenytoin), lamotrigine, NSAIDS, sulfonamides

Abbreviations: alanine aminotransferase (*ALT*), alkaline phosphatase (*ALP*), bilirubin (*BILI*), upper limit of normal (*ULN*)

hospitalized patients and has been reported as 25% in patients with antibiotic-associated diarrhea [222]. CDI-associated mortality rate may be as high as 9% [223], and for ICU patients, the unadjusted rate may be as high as 23–37% [222, 224, 225]; however, other literature suggests early recognition and treatment of ICU-acquired CDI decreases the risk for mortality [226].

The development of antibiotic-induced diarrhea results in an additional hour of nursing care per day which decreases nurse time spent with other critically ill patients [220]. Patients who develop CDI have a longer length of stay of 2.2 ICU days, 4.5 hospital days [224]. Probiotics have been studied for the prevention of antibiotic-associated diarrhea and/or *Clostridium difficile* diarrhea; in older hospitalized patients, they may not be as helpful when compared to other age groups [227–229]. Decreasing hospital use of quinolones may decrease the overall incidence of *Clostridium difficile* [230–233]. Antimotility agents should be avoided until CDI is ruled out with a rapid screening ELISA test.

Drug-Induced Hepatotoxicity

This section briefly discusses ADRs associated with hepatotoxicity; for additional information refer to ▶ Chap. 17, "Toxicant-Induced Hepatic Injury." Drug-induced liver injury (DILI) is the major reason for drug removal or restriction by regulatory agencies and is estimated to occur in 1 in 1,000,000 patient-years or 35 cases in 100,000 using EMR data [5, 234]. Fewer than 10% of DILI cases progress to drug-induced acute liver failure and up to 80% of these will die or require transplantation [235, 236].

DILI mimics many forms of liver disease and is usually a diagnosis of exclusion. Complicating the diagnosis is the latency period or the time from first dose of a new drug to the onset of hepatotoxicity. For hepatotoxic ADRs, the latency period is usually days to weeks after starting a new medication, but there are exceptions. The clinical signs and symptoms are usually nonspecific but temporally can be used to guide the differential. A good reference to published case reports is Livertox (http://livertox.nlm.nih.gov), which is continuously updated (Table 13) [234, 237]. Patterns of hepatic enzyme elevation can suggest hepatocellular, cholestatic, or mixed injury patterns (Table 14). These patterns of elevation also guide workup for alternative explanations (e.g., hepatocellular or mixed DILI should be tested for acute viral hepatitis, while a cholestatic pattern should be evaluated for biliary tract pathology).

The most common phenotype is serum enzyme elevation without jaundice or other symptoms. The most characteristic phenotype suggesting DILI is cholestatic and/or mixed hepatitis. Between 30% and 50% of DILI cases are described as acute hepatitis and resemble acute viral hepatitis. The most concerning phenotype is acute hepatic necrosis, characterized by many-fold elevations of ALT within days of drug exposure; however, the most likely phenotype to result in DIALF is acute hepatitis.

Table 14 Laboratory criteria for diagnosing and classifying drug-induced liver injury (*DILI*). DILI can be diagnosed when either ALT or ALP is elevated or when both BILI and ALT are elevated. R is calculated (ALT/ULN)/(ALP/ULN) and patterned based on earliest identified liver chemistry available that qualifies as DILI

DILI diagnosis	ALT ≥5× ULN	ALP ≥2× ULN	Bilirubin ≥2× ULN and ALT ≥3×ULN
DILI classification	**R**		
Hepatocellular	≥5		
Mixed	2 < R < 5		
Cholestatic	≤2		

Abbreviations: alanine aminotransferase (*ALT*), alkaline phosphatase (*ALP*), upper limit of normal (*ULN*)

Drug properties and certain host factors increase risk for DILI. High lipophilicity (LogP ≥3) and high daily dose (≥100 mg) predict DILI [238]. Patients with fatal outcomes are more likely to have chronic liver disease and satisfy Hy's Law (ALT or AST >3× ULN and bilirubin >2×ULN with no initial findings of elevated serum ALP or other reason for abnormal liver biochemistries) [239]. Mechanisms for DILI include the formation of toxic metabolites (e.g., *N*-acetyl-p-benzoquinone imine from metabolism of acetaminophen), mitochondrial dysfunction [240], modification of allergic mediators [242] and altered bile acid homeostasis [241]. Minocycline can induce an allergic or autoimmune injury with antinuclear antibodies (ANA) and perinuclear antineutrophil cytoplasmic antibodies, pANCA. Nitrofurantoin autoimmune hepatitis is associated with antinuclear and smooth muscle antibodies [243, 244]. DILI associated with amoxicillin–clavulanate has been associated with the HLA alleles A*02:01, DRB1*15:01-DQB1*06:02 [245]. Some drugs may cause DILI through hypotension and/or increased metabolic demand. Drugs that can cause hypoxia or hypotension, or increase metabolic demands, may worsen acute liver failure because each of these conditions by itself can cause ALF.

Causality can be difficult to determine, but the suspected drug(s) should be immediately discontinued and the liver biochemistries monitored; the liver has an amazing capacity to recover from injury [246]. Rechallenge is dangerous and should be avoided. Currently available biomarkers [247–252] (Table 15) are not specific enough and/or not widely available; a liver biopsy should be considered if signs of liver function continue to decline or if peak ALT level has not fallen by >50% at 30–60 or 180 days, respectively, for hepatocellular and cholestatic DILI [253]. Exceptions, or drugs to consider restarting, may include an immunomodulatory drug if no alternatives are available.

Drug-Induced Pancreatitis

Acute pancreatitis is a sudden inflammation of the pancreas and can be fatal; however, drug-induced acute pancreatitis is usually mild or moderate in intensity. The most commonly identified cause of acute pancreatitis is gallstone followed by ethanol, drugs, and cannabis [254]. Drug-induced acute pancreatitis (DIAP) occurs for less than 5% of patients with acute pancreatitis, and drugs with stronger causality are listed in Table 16 [255, 256]. Mechanisms for DIAP include pancreatic duct constriction, cytotoxic and metabolic effects, accumulation of a toxic metabolite, or intermediary and/or hypersensitivity reactions [257, 258].

There are many drugs possibly associated with pancreatitis but causality is not definitively established. There have been numerous reports of adverse effects with drugs such as the antipsychotics clozapine, olanzapine, and risperidone, but when a cause–effect relationship is scrutinized, the data is questionable [10, 259]. For glucagon-like peptide-1 drugs such as exenatide, pancreatitis was seen in the clinical trials but other studies have demonstrated mixed results [260]. Class labeling warnings have been added to the FDA labels. ICU drugs associated with acute pancreatitis with stronger causality (positive rechallenge and other causes excluded) include ace inhibitors (ACEI; enalapril), antiepileptics (divalproate), antimicrobials (dapsone,

Table 15 Liver biochemical and function tests. Most of these biomarkers are located intracellularly and released after hepatocyte injury

Biomarker	Clinical significance
Hepatocellular injury	
ALT	Remains elevated longer than AST (longer half-life)
AST	Less specific than ALT
APAP-CYS	Early and specific marker for APAP hepatotoxicity; remains elevated for days
GSTA	Centrilobular injury; more rapid assessment because of shorter half-life than ALT/AST
HMGB1	Associated with immune activation followed by apoptotic and necrotic hepatocytes; earlier marker of hepatotoxicity than ALT; prognostic marker
K18	Necrotic hepatocytes; prognostic marker
K18, cleaved	Apoptotic hepatocytes; prognostic marker
miR-122	Earlier marker of hepatotoxicity than ALT; can be used to predict injury
SDH	Earlier marker of hepatotoxicity than ALT
Biliary injury	
ALP	Nonspecific and can be elevated with bile duct obstruction, cholestasis, and hepatocellular injury as well as released from bone and placental tissue
GGT	More sensitive and specific marker of biliary injury than ALP
Mitochondrial injury	
GLDH	Earlier marker of hepatotoxicity than ALT, released from mitochondria
Hepatic biosynthetic capacity	
Albumin	Produced by the liver and decreased in chronic liver disease; decreased in nephrotic syndrome
Ammonia	Released by intestines and metabolized by liver
PT	Decreased production of hepatic coagulation factors increases PT
Hepatic regeneration	
AFP	May have value as prognostic marker
LECT2	May have value as prognostic marker; inversely proportional to ALT

Abbreviations: acetaminophen (*APAP*), acetaminophen–cysteine adducts (*APAP-CYS*), alanine aminotransferase (*ALT*), alkaline phosphatase (*ALP*), alpha-fetoprotein (*AFP*), alpha-glutathione-S-transferase (*GSTA*), aspartate aminotransferase (*AST*), gamma glutamyl-transpeptidase (*GGT*), glutamate dehydrogenase (*GLDH*), high-mobility group box-1 (*HMGB1*), keratin 18 full length (*K18*), leukocyte cell-derived chemotaxin-2 (*LECT2*), microRNA-122 (*MiR-122*), prothrombin time (protime, *PT*), sorbitol dehydrogenase (*SDH*)

metronidazole, tetracycline), cannabis, diuretics (furosemide), and statins (pravastatin, simvastatin) [256]. Drugs with positive rechallenge but without other causes excluded include amiodarone, antimicrobials (sulfamethoxazole/tazobactam), ARBs (losartan), and proton pump inhibitors (omeprazole) [256]. ICU drugs with more than four case reports of acute pancreatitis include acetaminophen, erythromycin, and propofol [256].

The proposed mechanism for pancreatitis caused by statins is via accumulation of a toxic metabolite or drug interactions through cytochrome P450 3A4 [261]. Valproic acid may cause pancreatitis by a direct toxic effect of free radicals and depletion of superoxide dismutase, catalase, and glutathione peroxidase [261]. When drug-induced pancreatitis is suspected, the implicated agent should be discontinued [255].

Renal ADRs

Drug-Induced Acute Renal Failure

This section discusses ADRs associated with acute renal failure. For additional details, refer to ▶ Chap. 18, "Toxicant-Induced Renal Injury." Drugs are a common cause of renal insufficiency because a major route for drug excretion occurs

Table 16 Drug-induced pancreatitis. Drugs are grouped by drug class and listed when stronger causality has been documented

Class	Drug(s)
ACEI/ARBs	Enalapril and losartan
Antiarrhythmics	Amiodarone
Antiepileptics	Divalproate
Antimicrobials	Dapsone, metronidazole, sulfamethoxazole/tazobactam, and tetracycline
Cannabis	
Diuretics	Furosemide
Ethanol	
Glucagon-like peptide-1 (GLP1) receptor agonists	Exenatide, liraglutide, albiglutide, dulaglutide
Proton pump inhibitors	Omeprazole
Statins	Pravastatin and simvastatin

Table 17 Nephrotoxicity associated with ICU drugs

Clinical syndrome	Drug
Acute renal failure	
Prerenal/hemodynamic	Contrast, amphotericin B, ACEI, NSAIDs
Intrarenal	
ATN	Acetaminophen, aminoglycosides, amphotericin B, cephalosporins, cocaine
AIN	Penicillins, cephalosporins, cocaine, sulfonamides, NSAIDs
Postrenal/obstructive	Acyclovir, analgesic abuse
Nephrotic syndrome	NSAIDs
Chronic renal failure	Lithium, analgesic abuse

Abbreviations: acute tubular necrosis (*ATN*), acute interstitial nephritis (*AIN*)

renally. During this process, drugs concentrate in nephric tissues which increase the potential for local tissue toxicity [262]. The high renal rate of blood flow increases nephric tissue exposure to drugs when compared to tissue in organs with lower rates of blood flow.

Drug-induced nephrotoxicity should be considered when the serum concentration of creatinine rises temporally in relation to drug administration. Good ICU care noting a diminishing urine output should avoid this complication. Drug toxicity in the kidney can manifest through the same clinical syndromes associated with other kidney diseases (refer to Table 17 for common clinical syndromes matched with associated drugs). Antibiotics are the most common cause of drug-induced renal failure; aminoglycosides are the most common cause of acute tubular necrosis (ATN), with an incidence of at least 10% of all cases of acute renal failure [263]. Penicillins and sulfonamides are more commonly associated with acute interstitial nephritis (AIN). Some drugs such as cephalosporins, cocaine, and NSAIDs can be associated with multiple renal syndromes [264–267]. When considering drug-induced nephrotoxicity, consider the dose, timing, duration of exposure, concurrent use of nephrotoxic drugs, and individual patient risk factors (age, chronic kidney disease, sepsis, etc.) [262, 263, 268–271].

Prerenal Nephrotoxicity

Prerenal azotemia is a hemodynamically mediated renal insufficiency associated with low urine sodium excretion and is usually reversible when the offending agent is discontinued early. Some drugs, such as radiocontrast agents, cause vasoconstriction through increased production of endothelin and/or thromboxane A2 which reduces renal blood flow and glomerular perfusion [272]. Radiocontrast agents can impair renal blood flow by both vasodilation and vasoconstriction; contrast nephropathy usually develops within 24 h after administration [272]. Risk factors include preexisting renal impairment, severe congestive heart failure, volume depletion, age, dose, and concurrent use of other nephrotoxins; there was no statistical difference in the complication rate when changing the type of contrast prescribed (high/low osmolarity or ionic/nonionic) [272, 273].

NSAIDs inhibit cyclooxygenase and decrease the synthesis of vasodilating prostaglandins, which in patients with chronic renal disease can impair glomerular perfusion [270, 274]. ACEIs

inhibit the conversion of angiotensin I to II; angiotensin II is a potent vasoconstrictor which helps to maintain glomerular perfusion at the efferent arteriole when renal blood flow is compromised [274]. Azotemia initially occurred for 25% of patients receiving vancomycin, but when the impurities were addressed, the incidence of nephrotoxicity decreased to less than 7% and was associated with a significantly elevated vancomycin trough [275].

Intrarenal Nephrotoxicity

Drug-induced nephrotoxicity from intrarenal mechanisms occurs through ATN or AIN [262, 265, 276]. ATN is often a result of direct drug toxicity on the renal tubular cells; the urinalysis can demonstrate proteinuria, tubular epithelial cells, and noncellular casts. ATN outcomes may be predicted based on the number of cells and casts visualized on the urinalysis [277]. Aminoglycosides accumulate within the renal cortex tubular cells with nephrotoxicity occurring 5–7 days into the antibiotic course; rank order for nephrotoxicity from greatest to least includes gentamicin, amikacin, and tobramycin [278]. Acetaminophen has been associated with ATN with therapeutic doses or following overdose [279–281]. Cephalosporins can cause ATN and/or AIN; a rank order for potential tubular toxicity from animal studies suggests cephazolin has increased risk compared to cephalexin and ceftazidime [276, 282, 283]. AIN is a result of intrarenal inflammation and often has systemic signs of hypersensitivity such as fever or rash; urinalysis can contain proteinuria, red and/or white cells, and/or cellular casts [265].

Postrenal Nephrotoxicity and Nephrotic Syndrome

Postrenal or obstructive nephrotoxicity associated with ICU drugs can occur when insoluble drugs such as acyclovir precipitate into the renal tubular lumen [284]. Acyclovir has been associated with nephrotoxicity when administered intravenously and at high doses [284]. Urine sediment can contain red and/or white cells with needle-shaped birefringent crystals. Drug-induced nephrotic syndrome has occurred with NSAIDS and is diagnosed when proteinuria, hypoalbuminemia, and edema are present [266, 285–287].

Treatment

Modalities such as therapeutic drug monitoring programs may decrease risk for nephrotoxicity [288]. Drugs such as vancomycin and gentamicin can be monitored with trough and/or peak blood concentrations; risk for nephrotoxicity is avoided with shorter courses of treatment and the use of the lowest effective drug concentration [275, 278]. Once nephrotoxicity has occurred, treatment is based on identifying potential nephrotoxins and avoidance of concurrent use of other nephrotoxic drugs [274, 289]. Intravenous hydration is beneficial in some circumstances, as are diuretics [271]. After the nephrotoxicity has resolved, the drug can be resumed with renal dosing in some circumstances, but in the setting of nephrotic syndrome or AIN, the drug should not be restarted.

Neurologic ADRs

Drug-Induced Delirium

This section discusses ADRs associated with delirium. For additional reference, see ► Chap. 19, "Toxicant-Induced Alterations in Consciousness." ICU delirium has been referred to as ICU psychosis, acute brain dysfunction or failure, and acute encephalopathy, among other terms. ICU delirium can prolong mechanical ventilation and is associated with a threefold higher rate of re-intubation, an increased rate of ventilator-associated infections, prolonged hospital stays, and increased 1-year mortality [290, 291]. Delirium is defined as a fluctuating change in attention, cognition, consciousness, and/or perception and can be further categorized as hyperactive, hypoactive, and mixed [290, 292]. Vanderbilt University Medical Center maintains the website www.icudelirium.org as a resource for delirium and includes screening and management tools for emergency department, ICU and non-ICU patients. When assessing delirium, workup for toxicologic or pharmacologic causes should occur simultaneously with

Table 18 ICU drugs associated with delirium by class. ICU delirium can prolong mechanical ventilation and is associated with increased risk of infection, prolonged hospital stay, and 1-year mortality. Workup for toxicologic or pharmacologic causes should occur simultaneously with evaluation for other causes as delirium is often multifactorial. Some conditions not normally associated with delirium when occurring concurrently with other pathologies may be considered. Consider drug or withdrawal states resulting in disturbances in the production, release, and/or effects of acetylcholine, endorphins, GABA, glutamate, 5HT, and dopamine neurotransmitters. Substance-induced psychosis is associated with the longer duration use of alcohol, amphetamines, cannabimimetic agonists, cocaine, and hallucinogens. Drug withdrawal delirium occurs classically with alcohol, benzodiazepine, and barbiturates

Class	Generic name	Mechanism
Analgesic – opioid	Fentanyl	5HT, kappa-opioid agonist
	Meperidine	5HT, MAOI
	Hydromorphine	kappa-opioid agonist
Analgesic – dissociative hypnotic	Cyclohexanone–ketamine	NMDA antagonist
Antibiotic – aminoglycoside	Gentamicin	NMDA agonist, decrease ACh release and effect. Iron complexes inhibit mitochondria resulting in lipid peroxidation
Antibiotic – penicillins	Penicillin	GABA-A antagonism
Antibiotic – cephalosporin	Cefepime	GABA-A antagonism
Antibiotic – carbapenem	Imipenem	GABA-A antagonism
Antibiotic – fluoroquinolones	Moxifloxacin or levofloxacin	GABA-A antagonism and NMDA agonist
Antibiotic – oxazolidinones	Linezolid	MAOI
Anticholinergics	Some antiemetics, antihistamines, antipsychotics, and muscle relaxants	Muscarinic acetylcholine antagonist
Antiemetics	Diphenhydramine	Muscarinic acetylcholine antagonist
Antipsychotics	Haloperidol	Dopamine antagonism
	Olanzapine or quetiapine	Muscarinic acetylcholine antagonist
Benzodiazepines	Midazolam or lorazepam	GABA-A agonist
Corticosteroids	Solumedrol	Disturbances in the hypothalamo–pituitary–adrenal axis

Abbreviations: gamma-aminobutyric acid (*GABA*), monoamine oxidase inhibitor (*MAOI*), serotonin (5HT)

evaluation for other causes as delirium is often multifactorial [293]. Table 18 discusses drugs associated with delirium by class.

Consider the timing and progression of neurological symptoms in relation to all prescribed hospital drugs. Consider previous medications (prescribed or non-prescribed) that have been abruptly discontinued and their propensity to cause withdrawal (for additional information, refer to ▶ Chap. 27, "Withdrawal Syndromes"). Certain withdrawal states not normally associated with delirium, when occurring concurrently with certain pathologies, may be considered. Examples include nicotine, opioid, and cannabis withdrawal. Nicotine withdrawal in the setting of brain injury has been associated with delirium [294]; however, larger review studies have not clearly implicated nicotine withdrawal with delirium in hospitalized patients [295]. Opioid withdrawal is not normally associated with delirium but in the ICU should be considered as a contributor, as opioid withdrawal can occur after only 5 days of continuous opioid analgesia and by day 9 occurred in 100% of patients [296]. Cannabis withdrawal is associated with anger, aggression, and

irritability; performing urine drug screens at admission could help to identify patients at risk since this is the most common illicit drug used in the USA and withdrawal symptoms can persist for 3 or more weeks [297–301]. Synthetic cannabinoid withdrawal has been reported, but the propensity for delirium is not yet clear [302].

Consider previous medications (prescribed or non-prescribed) that may interact with currently prescribed ICU drugs; commonly implicated drugs include serotonergic, anticholinergic, and *N*-methyl-D-aspartate (NMDA) receptor antagonists [303–305]. Previous substance misuse should be considered, especially for dopaminergic drugs, as these drugs are associated with substance-induced psychosis and may be a function of the severity of use and dependence and persist for months after last use. Drugs implicated include alcohol, amphetamines, cannabimimetic agonists, cocaine, hallucinogens (e.g., methylenedioxymethamphetamine MDMA), and NMDA antagonists (e.g., phencyclidine and ketamine) [306]. Independent precipitating factors for delirium such as bladder catheters, fecal management systems, immobilizing therapies, and restraints should be avoided [290, 307, 308]. Major groups of ICU drugs associated with delirium that may be evaluated by a medical toxicologist include analgesics, antibiotics, antipsychotics, and sedative-hypnotics.

Analgesics

Analgesic-induced delirium could occur by interaction with other medications, opioids with serotonergic properties, and/or kappa-opioid agonism [309]. Fentanyl and/or methadone may interact with linezolid or other monoamine oxidase inhibitors (MAOI) or serotonergic medication resulting in serotonin syndrome [310–316]. A retrospective review of 4538 patients treated with fentanyl and concurrent serotonergic agents suggests the incidence of serotonin syndrome was low [311], but prospective studies are needed before ignoring this ADR as there are many case reports suggesting a higher incidence [310–312, 317–322].

Furthermore, the hospital stay and mortality among patients prescribed with serotonin reuptake inhibitors prior to ICU admission are higher and may be related to an analgesic reaction [323]. Serotonin reuptake inhibitors may also increase risks secondary to platelet serotonin inhibition and increased bleeding risk or other mechanisms [324–328]. Propensity for kappa-opioid agonism may be another factor to consider when evaluating delirium after opioid administration; fentanyl and hydromorphone may have higher risk in animal studies [309].

When delirium is suspected to be drug mediated, the implicated drug(s) should be discontinued. If opioid-induced delirium is suspected, opioid avoidance or lower doses are recommended by one large prospective study [329]. If a patient has a history of prescription or illicit serotonergic substance use, consider avoiding serotonergic drugs such as fentanyl until more prospective data is available. For opioid withdrawal, initiating a long-acting full or partial opioid agonist may be best until the patient has been extubated and then further tapered and/or provided with symptomatic treatment.

Antibiotics

Major groups of antibiotics associated with delirium include aminoglycosides, beta-lactams (penicillins, cephalosporins, and carbapenems), fluoroquinolones, oxazolidinones (linezolid), and trimethoprim/sulfamethoxazole. Aminoglycosides activate NMDA receptors, inhibit presynaptic release of acetylcholine, and bind postsynaptic receptors. Chronic toxicity (increased trough levels) occurs when iron complexes inhibit mitochondria and cause lipid peroxidation. Aminoglycosides are associated with peripheral neuropathy and neuromuscular blockade; case reports have linked gentamicin to encephalopathy [330] (Table 19).

The beta-lactam ring itself is known to be neurotoxic and drugs containing this structure cause neurotoxicity by GABA-A antagonism. For beta-lactams, symptoms of neurotoxicity usually present 12–72 h after initial administration, but can occur later after increased dosing or when metabolic and/or elimination pathways are inhibited. Previous case reports have identified the following risk factors: being critically ill,

Table 19 Major antibiotic classes associated with neurotoxicity. The beta-lactam ring is epileptogenic with variability depending on side chains and other substitutions

Drug or class	Mechanism	Onset	Signs/symptoms
Penicillins and cephalosporins	Inhibit GABA binding to GABA-A receptor, blocks GABA-A chloride channel	12–72 h	Confusion, dysarthria/aphasia, agitation, lethargy/coma, myoclonus, seizures, and/or NCSE
Carbapenems	Affinity for GABA-A receptor complex	3–7 days	Focal and generalized seizures
Fluoroquinolones	Inhibit GABA binding to GABA-A receptor, NMDA agonist	1–4 days	brief tonic–clonic, sustained generalized myoclonus
Isoniazid	Inhibit pyridoxine kinase	30 min–2 h	Recurrent, generalized tonic–clonic seizures
Metronidazole	Increased hydroxy and 1-acetic acid metabolites	5–7 days	Seizures, peripheral neuropathy

Abbreviations: gamma-aminobutyric acid (*GABA*), nonconvulsive status epilepticus (*NCSE*)

reduced creatinine clearance, preexisting CNS conditions and/or damage to the blood–brain barrier, concurrent use of other neurotoxic drugs, and dosing errors [330–335]. Symptoms of beta-lactam neurotoxicity are secondary to impaired GABA-A transmission [335]. Cephalosporins with higher affinity for GABA-A receptors and those with higher CNS penetrance are more neurotoxic. Resulting clinical effects range from coma to agitation and can fluctuate with delirium, aphasia, myoclonus, seizures, and nonconvulsive status epilepticus. Cefazolin, cefepime, and ceftazidime may have higher risk for neurotoxicity, while cephalexin and ceftriaxone may be lower. A retrospective review of 100 patients prescribed with cefepime found the incidence of encephalopathy was 15% [336].

Fluoroquinolone's mechanism of toxicity includes inhibition of GABA-A receptors and activation of NMDA receptors. CNS reactions occurred for 3% of patients prescribed with gemifloxacin, but other quinolone derivatives implicated include gatifloxacin, moxifloxacin, ofloxacin, and, its levo-stereoisomer, levofloxacin. Neurotoxicity can be manifested as delirium associated with psychotic features including delusions and hallucinations as well as restlessness and seizures.

Antipsychotics

Literature suggests that quetiapine decreases the incidence of ICU delirium although other antipsychotics can be used to effectively treat ICU delirium after it has occurred [337–340] (LoE 1). As with the initiation of any medication, the antipsychotic side-effect profile should be considered when prescribing an antipsychotic for delirium; haloperidol may be associated with extrapyramidal symptoms, while olanzapine was found to be the most sedating [341]. Combining the critical care and toxicology literature, antipsychotics with anticholinergic properties should be used at low doses when treating delirium not suspected to be anticholinergic; some antipsychotics such as olanzapine and quetiapine cause agitation because of anticholinergic mechanism. Anticholinergic toxicity from olanzapine and/or quetiapine (or any other anticholinergic medication) can be diagnosed and treated with appropriately dosed physostigmine [342–344].

Benzodiazepines

Benzodiazepine use increases the risk of delirium [308, 345–347]. This could be through a paradoxical reaction, after prolonged ICU use, or benzodiazepine withdrawal [348]. If benzodiazepine delirium is suspected, appropriately dosed flumazenil can diagnose and treat patients following intubation or after benzodiazepine overuse and following alcohol withdrawal with little if any risk for seizures or precipitating withdrawal [346, 349–355]. Historically, patients with benzodiazepine dependence has been used as a contraindication to flumazenil, and a meta-analysis warns against the use of flumazenil, but when patients who received an initial flumazenil dose

of 1 mg or more were excluded, there were no significant adverse events in either the placebo or flumazenil groups [356]. Benzodiazepine dependence is not an absolute contraindication to flumazenil (LoE II-1). Flumazenil, therefore, should be dosed at 0.2–0.3 mg if there are concerns about rapid awakening or, otherwise, 0.5 mg; if improvement is observed, discontinue benzodiazepines and repeat flumazenil as needed when symptoms recur (LoE II-1) [346]. If benzodiazepine withdrawal is suspected, replace with a longer-acting benzodiazepine such as diazepam or with phenobarbital (LoE III) [357]. Another option for patients at risk for benzodiazepine withdrawal is a phenobarbital taper [358]; this may be beneficial for patients who received benzodiazepines with extended duration while mechanically ventilated.

Steroids

Neuropsychiatric effects including agitation occur in about 6% of patients who receive steroids; dose is the most significant risk factor [359]. ICU patients may experience agitation, delirium, and/or failure to wean [360–364]. Treatment includes reducing or avoiding steroids; however, some studies have suggested steroid switching (LoE III) and treatment with antipsychotics such as risperidone [360, 362, 365–369] (LoE_III).

Disturbances in Circadian Rhythm

ICU delirium is often multifactorial, and disturbances in circadian rhythm and sleep deprivation can contribute to hypoxia, infectious, metabolic, and ADRs. Risk factors may include age and existing dementia or cognitive impairment. Circadian rhythm disturbance is a diagnosis of exclusion. Melatonin can be used to facilitate circadian rhythm and can decrease need for sedation improving neurologic indicators although further study is needed [370, 371] (LoE1).

Treatment

Pharmacologic sedation should be titrated to the least effective dose with at least daily sedation holidays to minimize the incidence of delirium. Avoiding infusions is one method for titrating sedation to the least effective dose. Once delirium has occurred, treatment is based on identifying and discontinuing potential causative medications. Consider previous medications (prescribed or non-prescribed) that have been abruptly discontinued and their propensity to cause withdrawal. Also, consider previous medications (prescribed or non-prescribed) that may interact with currently prescribed ICU drugs.

If benzodiazepine or anticholinergic delirium is high on the differential, flumazenil and/or physostigmine can be administered safely; positive results may avoid costly and unnecessary radiographic testing that place the patient at increased risk for morbidity and mortality (e.g., during transport and while outside of the ICU setting [372]). If opioid withdrawal is a suspected contributor, the administration of a long-acting opioid will ameliorate the delirium. The patient can later be treated symptomatically for opioid withdrawal if not a candidate for outpatient opioid maintenance therapy.

Dexmedetomidine is an imidazole alpha-2 agonist that increases days alive without delirium or coma while in the ICU when compared to lorazepam [373]. The incidence of delirium was 54% in dexmedetomidine vs 77% in midazolam-treated patients ($P < 0.001$). There was no significant difference in time at targeted sedation level for 375 patients located in 68 centers in five countries who were treated in a double-blind, randomized trial [374]. Dexmedetomidine has caused hypotension during the initial bolus in between 25% and 56% of patients and, compared to benzodiazepines, may be more likely to cause bradycardia, which is the most significant ADR [373, 374]. Since dexmedetomidine is not usually associated with respiratory depression, it can be used to treat withdrawal syndromes in non-ventilated patients [374–376]. Cost is a consideration when considering dexmedetomidine; compared to midazolam, dexmedetomidine lowered total ICU costs and decreased ventilator time and ICU length of stay [377]. However, for moderate to severe anticholinergic delirium, physostigmine would be expected to be a more cost-effective primary therapy; dexmedetomidine could be used as an adjunct to avoid higher doses of benzodiazepines, but additional studies are needed.

An alternative to dexmedetomidine for pharmacies who restrict its use may be clonidine, and one study proposed the use of a short course of dexmedetomidine before transitioning to sublingual or orally administered clonidine [378]. The mechanism of these drugs differs such that the ratio of alpha-1 to alpha-2 may predispose clonidine to more hypotension and bradycardia and less sedation compared to dexmedetomidine, but the cost savings are difficult to ignore.

Drug-Induced Seizures

This section discusses ADRs associated with seizures. For additional details refer to ▶ Chap. 20, "Toxicant-Induced Seizures." Six percent of new-onset seizures and 9% of status epilepsy may be drug related [379]. Major classes of drugs associated with seizures include antidepressants, anticholinergics/antihistamines, and stimulants, but the clinician should also consider NSAIDS, beta-lactams, quinolones, and drug withdrawal [336, 380–385]. Consider drugs previously prescribed that have not been continued in the ICU such as baclofen, gabapentin, pregabalin, zolpidem, and zopiclone; any drug acting at the GABA complex should be considered [386–391]. ICU drugs cause seizures by inadequate inhibitory neurotransmitters (e.g., GABA), excessive excitatory neurotransmitters (e.g., glutamate), and/or interfering with sodium channels [385, 392]. Antimicrobials impair GABA-A transmission [335, 393]. Magnesium homeostasis may be associated with seizures as diuretics, proton pump inhibitor, and antimicrobials may decrease the seizure threshold [335, 393].

Seizures are treated with either benzodiazepines or barbiturates; generally barbiturates are considered to be a second-line therapy [385]. Antiepileptics are ineffective when the mechanism of toxicity is caused by metabolic abnormalities or drugs impairing GABA-A transmission. Antiepileptics could be considered if seizures persist despite first- and second-line treatment.

Strategies to Decrease ICU ADRs

Patients admitted to the ICU have a higher mortality compared to hospitalized patients; 30-day mortality ranges from 12% to 44% depending on the ICU patient subtype [394]. Thirty-four to forty-five percent of ADRs are preventable and represent an opportunity for risk reduction and improved patient safety [5, 7, 395]. Prior studies have demonstrated that technology, multispecialty care teams, specialized treatment centers, and standardized treatment algorithms can assist with these goals.

Technology has facilitated the development of medication databases and systems to identify potential drug–drug interactions, and one study identified that 11% of ICU admissions have potential drug–drug interactions [396]. As with any technology with an alarm, there is potential for alarm fatigue and technology should be curtailed to the ICU population to minimize this [397]. Conversely, when an ICU ADR has been identified, technology can be used to identify medications potentially causing the condition, medications to avoid, and the appropriate medications to use.

Multispecialty care teams consist of admitting physicians, consulting physicians, pharmacists, nurses, specialty therapists, care coordinators, and social workers. In the ICU, the value of the pharmacist is especially important. Pharmacists obtain medication histories; develop and manage policies and protocols for optimal patient care, drug expenditures, and cost avoidance (i.e., analgesia, anticoagulation, delirium, pharmacokinetic, sedation, and transfusion guidelines); optimize antimicrobial stewardship; respond to resuscitation events; verify accuracy of computerized order entry; educate other ICU personal; assist in discussing treatment modalities with patients and/or families; prospectively evaluate drug therapy; and monitor and identify ADRs [398–410]. The impact of the clinical pharmacist in the ICU has significantly decreased ADRs, antimicrobial resistance, medication costs, transfusions, hemorrhage, ventilator days, and length of stay. Unfortunately, pharmacist services are not directly reimbursable; pharmacy departments receive funds from a hospital's general operating budget. Pharmacy departments are penalized when they increase the ratio of clinical pharmacists to occupied beds from 1/100 to 1/20, an increased expenditure which was shown to

decrease ADRs by 48% [410]. The optimal pharmacist to patient ratio is unclear, but considering the services of a medical toxicologist are reimbursable, could a medical toxicologist enable a group of clinical pharmacists, thereby increasing the reimbursement of the pharmacy? Medical toxicologists, when available, are experts in pharmacokinetics and toxicokinetics and should develop relationships with multidisciplinary teams to aid in the reduction of the incidence of ADRs, length of stay, and mortality.

In addition to pharmacist to patient ratio and their impact on ADRs and mortality, patient to physician and/or nurse ratios should be considered. When nurse to patient ratio was greater than 2.5, the risk of death increased by 3.5. When the physician to ICU patient ratio exceeded 14, the risk of death increased by two [411]. High patient turnover and a high volume of life-sustaining procedures were also predictive of increased mortality. Admissions during weekday rounds did not increase mortality [412]. High-intensity daytime staffing reduced mortality [413].

Specialized treatment centers have been shown to improve care, especially for ICUs. Medical toxicology admitting services are not widely available, but there is great need as demonstrated by one large study of 3581 patients cared for primarily by toxicologists and non-toxicologists within the same hospital system as well as a third group of patients cared for by non-toxicologists outside of the hospital system. During the 2-year study period, there was a median savings of 1483 hospital days and $4.3 million dollars, as well as a significant decrease in mortality for patients cared for by toxicologists [414]. Extrapolating from other specialty data, when only specialists are allowed to admit and care for critically ill patients, length of stay and mortality in the ICU were shortened [413, 415]. All things considered, patients cared for by non-specialists have increased risk for extended length of stay and mortality, which suggests that medical toxicologists and critical care intensivists should remain involved in patient care potentially until hospital discharge. On admission, general recommendations may include holding any nonessential medication potentially resulting in drug–drug or disease–drug interactions; for example, many ICU patients may be started on antimicrobials, calcium channel blockers, and/or amiodarone, and these drugs increase concentration of simvastatin by inhibiting CYP3A4, thereby increasing drug levels resulting in an increased risk for rhabdomyolysis, renal failure, and hepatotoxicity [416–424]. Medical toxicologists may also provide daily recommendations for restarting or modifying home medications, as well as querying potential medication interactions, substance use disorders, and drug withdrawal. Until there are more admitting toxicology physicians, consultants should provide daily recommendations directly to the care team until the day of patient discharge. Interactive audio–video telemedicine consultation may be an alternative when traditional bedside care is not possible as this service has been useful for other specialties [425].

References

1. Davies EC, Green CF, Mottram DR, Pirmohamed M. Adverse drug reactions in hospitals: a narrative review. Curr Drug Saf. 2007;2(1):79–87.
2. Miguel A, Azevedo LF, Araujo M, Pereira AC. Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis. Pharmacoepidemiol Drug Saf. 2012;21(11):1139–54. doi:10.1002/pds.3309.
3. Steel K, Gertman PM, Crescenzi C, Anderson J. Iatrogenic illness on a general medical service at a university hospital. N Engl J Med. 1981;304(11):638–42. doi:10.1056/NEJM198103123041104.
4. Kane-Gill SL, Jacobi J, Rothschild JM. Adverse drug events in intensive care units: risk factors, impact, and the role of team care. Crit Care Med. 2010;38(6 Suppl):S83–9. doi:10.1097/CCM.0b013e3181dd8364.
5. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279(15):1200–5.
6. Vallano Ferraz A, Agusti Escasany A, Pedros Xolvi C, Arnau de Bolos JM. Systematic review of

studies assessing the cost of adverse drug reactions. Gac Sanit/SESPAS. 2012;26(3):277–83. doi:10.1016/j.gaceta.2011.09.014.
7. Rothschild JM, Landrigan CP, Cronin JW, Kaushal R, Lockley SW, Burdick E, et al. The Critical Care Safety Study: the incidence and nature of adverse events and serious medical errors in intensive care. Crit Care Med. 2005;33(8):1694–700.
8. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239–45.
9. Kadoyama K, Kuwahara A, Yamamori M, Brown JB, Sakaeda T, Okuno Y. Hypersensitivity reactions to anticancer agents: data mining of the public version of the FDA adverse event reporting system, AERS. J Exp Clin Cancer Res. 2011;30:93. doi:10.1186/1756-9966-30-93.
10. Hauben M. Application of an empiric Bayesian data mining algorithm to reports of pancreatitis associated with atypical antipsychotics. Pharmacotherapy. 2004;24(9):1122–9.
11. Hauben M. Early postmarketing drug safety surveillance: data mining points to consider. Ann Pharmacother. 2004;38(10):1625–30. doi:10.1345/aph.1E023.
12. Hauben M, Horn S, Reich L. Potential use of data-mining algorithms for the detection of 'surprise' adverse drug reactions. Drug Saf. 2007;30(2):143–55.
13. Hauben M, Reich L. Data mining, drug safety, and molecular pharmacology: potential for collaboration. Ann Pharmacother. 2004;38(12):2174–5. doi:10.1345/aph.1E373.
14. Szarfman A, Tonning JM, Doraiswamy PM. Pharmacovigilance in the 21st century: new systematic tools for an old problem. Pharmacotherapy. 2004;24(9):1099–104.
15. Hauben M, Reich L. Safety related drug-labelling changes: findings from two data mining algorithms. Drug Saf. 2004;27(10):735–44.
16. Torfgard KE, Ahlner J. Mechanisms of action of nitrates. Cardiovasc Drugs Ther. 1994;8(5):701–17; sponsored by the Int Soc Cardiovasc Pharmacother.
17. Moore PW, Burkhart KK, Jackson D. Drugs highly associated with infusion reactions reported using two different data-mining methodologies. Blood Disord Transfus. 2014;5(2):1–6. doi:10.4172/2155-9864.1000195.
18. Dillman RO. Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. Cancer Metastasis Rev. 1999;18(4):465–71.
19. Miebach E. Management of infusion-related reactions to enzyme replacement therapy in a cohort of patients with mucopolysaccharidosis disorders. Int J Clin Pharmacol Ther. 2009;47 Suppl 1:S100–6.
20. Pakravan N, Waring WS, Sharma S, Ludlam C, Megson I, Bateman DN. Risk factors and mechanisms of anaphylactoid reactions to acetylcysteine in acetaminophen overdose. Clin Toxicol (Phila). 2008;46(8):697–702. doi:10.1080/15563650802245497 [pii] 902580688.
21. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. Clin Toxicol (Phila). 2009;47(2):81–8. doi:10.1080/15563650802665587.
22. Horowitz BZ, Hendrickson RG, Pizarro-Osilla C. Not so fast! Ann Emerg Med. 2006;47(1):122–3. doi:10.1016/j.annemergmed.2005.05.039; author reply 4–5.
23. Kerr F, Dawson A, Whyte IM, Buckley N, Murray L, Graudins A, et al. The Australasian clinical toxicology investigators collaboration randomized trial of different loading infusion rates of *N*-acetylcysteine. Ann Emerg Med. 2005;45(4):402–8. doi:10.1016/j.annemergmed.2004.08.040.
24. Lantoine F, Iouzalen L, Devynck MA, Millanvoye-Van Brussel E, David-Dufilho M. Nitric oxide production in human endothelial cells stimulated by histamine requires Ca^{2+} influx. Biochem J. 1998;330(Pt 2):695–9.
25. Kilic M, Ozturk F, Genc G, Guner SN, Yildiz L, Sancak R. Sodium nitroprusside and toxic epidermal necrolysis. Asian Pac J Allergy Immunol. 2012;30(3):243–5; launched by the Allergy Immunol Soc Thai.
26. Lowery MM, Greenberger PA. Amphotericin-induced stridor: a review of stridor, amphotericin preparations, and their immunoregulatory effects. Ann Allergy Asthma Immunol. 2003;91(5):460–6. doi:10.1016/S1081-1206(10)61514-1.
27. Skinner MR, Marshall JM. Studies on the roles of ATP, adenosine and nitric oxide in mediating muscle vasodilatation induced in the rat by acute systemic hypoxia. J Physiol. 1996;495(Pt 2):553–60.
28. Ray CJ, Abbas MR, Coney AM, Marshall JM. Interactions of adenosine, prostaglandins and nitric oxide in hypoxia-induced vasodilatation: in vivo and in vitro studies. J Physiol. 2002;544(Pt 1):195–209.
29. Ray CJ, Marshall JM. Measurement of nitric oxide release evoked by systemic hypoxia and adenosine from rat skeletal muscle in vivo. J Physiol. 2005;568(Pt 3):967–78. doi:10.1113/jphysiol.2005.094854.
30. Renz CL, Laroche D, Thurn JD, Finn HA, Lynch JP, Thisted R, et al. Tryptase levels are not increased during vancomycin-induced anaphylactoid reactions. Anesthesiology. 1998;89(3):620–5.
31. Toledo JC, Augusto O. Connecting the chemical and biological properties of nitric oxide. Chem Res

Toxicol. 2012;25(5):975–89. doi:10.1021/tx300042g.
32. Nakamura T, Lipton SA. Emerging role of protein-protein transnitrosylation in cell signaling pathways. Antioxid Redox Signal. 2013;18(3):239–49. doi:10.1089/ars.2012.4703.
33. Pawloski JR, Hess DT, Stamler JS. Export by red blood cells of nitric oxide bioactivity. Nature. 2001;409(6820):622–6. doi:10.1038/35054560.
34. Nossaman B, Pankey E, Kadowitz P. Stimulators and activators of soluble guanylate cyclase: review and potential therapeutic indications. Crit Care Res Pract. 2012;2012:290805. doi:10.1155/2012/290805.
35. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K1): a 5-year retrospective review. Ann Allergy Asthma Immunol. 2002;89(4):400–6. doi:10.1016/S1081-1206(10)62042-X.
36. Bebarta VS, Kao L, Froberg B, Clark RF, Lavonas E, Qi M, et al. A multicenter comparison of the safety of oral versus intravenous acetylcysteine for treatment of acetaminophen overdose. Clin Toxicol (Phila). 2010;48(5):424–30. doi:10.3109/15563650.2010.486381.
37. Zyoud SH, Awang R, Sulaiman SA, Al-Jabi SW. Effects of delay in infusion of *N*-acetylcysteine on appearance of adverse drug reactions after acetaminophen overdose: a retrospective study. Pharmacoepidemiol Drug Saf. 2010;19(10):1064–70. doi:10.1002/pds.1955.
38. Schulkes KJ, Van den Elzen MT, Hack EC, Otten HG, Bruijnzeel-Koomen CA, Knulst AC. Clinical similarities among bradykinin-mediated and mast cell-mediated subtypes of non-hereditary angioedema: a retrospective study. Clin Transl Allergy. 2015;5(1):5. doi:10.1186/s13601-015-0049-8.
39. Toh S, Reichman ME, Houstoun M, Ross Southworth M, Ding X, Hernandez AF, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med. 2012;172(20):1582–9. doi:10.1001/2013.jamainternmed.34.
40. Kaplan AP, Greaves MW. Angioedema. J Am Acad Dermatol. 2005;53(3):373–88. doi:10.1016/j.jaad.2004.09.032; quiz 89–92.
41. Tan EK, Grattan CE. Drug-induced urticaria. Expert Opin Drug Saf. 2004;3(5):471–84.
42. Lipski SM, Casimir G, Vanlommel M, Jeanmaire M, Dolhen P. Angiotensin-converting enzyme inhibitors-induced angioedema treated by C1 esterase inhibitor concentrate (Berinert(R)): about one case and review of the therapeutic arsenal. Clin Case Rep. 2015;3(2):126–30. doi:10.1002/ccr3.171.
43. Byrd JB, Touzin K, Sile S, Gainer JV, Yu C, Nadeau J, et al. Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor associated angioedema. Hypertension. 2008;51(1):141–7. doi:10.1161/HYPERTENSIONAHA.107.096552.
44. Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P. Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. Clin Exp Allergy. 2010;40(1):50–61. doi:10.1111/j.1365-2222.2009.03323.x.
45. Kostis JB, Kim HJ, Rusnak J, Casale T, Kaplan A, Corren J, et al. Incidence and characteristics of angioedema associated with enalapril. Arch Intern Med. 2005;165(14):1637–42. doi:10.1001/archinte.165.14.1637.
46. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349(20):1893–906. doi:10.1056/NEJMoa032292.
47. Investigators O, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547–59. doi:10.1056/NEJMoa0801317.
48. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension. 2008;51(6):1624–30. doi:10.1161/HYPERTENSIONAHA.108.110270.
49. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther. 1996;60(1):8–13. doi:10.1016/S0009-9236(96)90161-7.
50. Nosbaum A, Bouillet L, Floccard B, Javaud N, Launay D, Boccon-Gibod I, et al. Management of angiotensin-converting enzyme inhibitor-related angioedema: recommendations from the French National Center for Angioedema. Rev Med Interne. 2013;34(4):209–13. doi:10.1016/j.revmed.2012.12.017.
51. Beavers CJ, Dunn SP, Macaulay TE. The role of angiotensin receptor blockers in patients with angiotensin-converting enzyme inhibitor-induced angioedema. Ann Pharmacother. 2011;45(4):520–4. doi:10.1345/aph.1P630.
52. Nielsen EW, Gramstad S. Angioedema from angiotensin-converting enzyme (ACE) inhibitor treated with complement 1 (C1) inhibitor concentrate. Acta Anaesthesiol Scand. 2006;50(1):120–2. doi:10.1111/j.1399-6576.2005.00819.x.
53. Gelee B, Michel P, Haas R, Boishardy F. Angiotensin-converting enzyme inhibitor-related angioedema: emergency treatment with complement C1 inhibitor concentrate. Rev Med Interne. 2008;29(6):516–9. doi:10.1016/j.revmed.2007.09.038.
54. Leuppi JD, Schnyder P, Hartmann K, Reinhart WH, Kuhn M. Drug-induced bronchospasm: analysis of 187 spontaneously reported cases. Respiration. 2001;68(4):345–51. doi:50525.
55. Asmus MJ, Sherman J, Hendeles L. Bronchoconstrictor additives in bronchodilator solutions. J Allergy Clin Immunol. 1999;104(2 Pt 2):S53–60.

56. Kimmoun A, Dubois E, Perez P, Barbaud A, Levy B. Shock state: an unrecognized and underestimated presentation of drug reaction with eosinophilia and systemic symptoms. Shock. 2013;40(5):387–91. doi:10.1097/SHK.0000000000000041.
57. Descamps V. Diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms) in the intensive care unit: essential but challenging. Shock. 2013;40(5):437–8. doi:10.1097/SHK.0000000000000054.
58. Descamps V, Ranger-Rogez S. DRESS syndrome. Joint Bone Spine. 2014;81(1):15–21. doi:10.1016/j.jbspin.2013.05.002.
59. Eshki M, Allanore L, Musette P, Milpied B, Grange A, Guillaume JC, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. Arch Dermatol. 2009;145(1):67–72. doi:10.1001/archderm.145.1.67.
60. Mardivirin L, Valeyrie-Allanore L, Branlant-Redon E, Beneton N, Jidar K, Barbaud A, et al. Amoxicillin-induced flare in patients with DRESS (drug reaction with eosinophilia and systemic symptoms): report of seven cases and demonstration of a direct effect of amoxicillin on human herpesvirus 6 replication in vitro. Eur J Dermatol. 2010;20(1):68–73. doi:10.1684/ejd.2010.0821.
61. Alkhateeb H, Said S, Cooper CJ, Gaur S, Porres-Aguilar M. DRESS syndrome following ciprofloxacin exposure: an unusual association. Am J Case Rep. 2013;14:526–8. doi:10.12659/AJCR.889703.
62. Burkhart KK, Abernethy D, Jackson D. Data mining FAERS to analyze molecular targets of drugs highly associated with Stevens-Johnson syndrome. J Med Toxicol. 2015;11(2):265–73. doi:10.1007/s13181-015-0472-1.
63. Hur J, Zhao C, Bai JP. Systems pharmacological analysis of drugs inducing Stevens-Johnson syndrome and toxic epidermal necrolysis. Chem Res Toxicol. 2015. doi:10.1021/tx5005248.
64. Pickham D, Helfenbein E, Shinn JA, Chan G, Funk M, Weinacker A, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in Practice (QTIP) Study. Crit Care Med. 2012;40(2):394–9. doi:10.1097/CCM.0b013e318232db4a.
65. Berling I, Isbister GK. Prolonged QT risk assessment in antipsychotic overdose using the QT nomogram. Ann Emerg Med. 2015;66(2):154–64. doi:10.1016/j.annemergmed.2014.12.005.
66. Thomas AR, Chan LN, Bauman JL, Olopade CO. Prolongation of the QT interval related to cisapride-diltiazem interaction. Pharmacotherapy. 1998;18(2):381–5.
67. Potkin SG, Preskorn S, Hochfeld M, Meng X. A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. J Clin Psychopharmacol. 2013;33(1):3–10. doi:10.1097/JCP.0b013e31827c0314.
68. Ehret GB, Desmeules JA, Broers B. Methadone-associated long QT syndrome: improving pharmacotherapy for dependence on illegal opioids and lessons learned for pharmacology. Expert Opin Drug Saf. 2007;6(3):289–303. doi:10.1517/14740338.6.3.289.
69. Desta Z, Kerbusch T, Flockhart DA. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). Clin Pharmacol Ther. 1999;65(1):10–20. doi:10.1016/S0009-9236(99)70117-7.
70. Hasnain M, Vieweg WV. QTc interval prolongation and torsade de pointes associated with second-generation antipsychotics and antidepressants: a comprehensive review. CNS Drugs. 2014;28(10):887–920. doi:10.1007/s40263-014-0196-9.
71. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-crossover study. J Am Heart Assoc. 2015;4(2). doi:10.1161/JAHA.114.001568.
72. Ikeno T, Okumara Y, Kugiyama K, Ito H. Analysis of the cardiac side effects of antipsychotics: Japanese Adverse Drug Event Report Database (JADER). Nihon Shinkei Seishin Yakurigaku Zasshi. 2013;33(4):179–82.
73. Bou-Abboud E, Nattel S. Relative role of alkalosis and sodium ions in reversal of class I antiarrhythmic drug-induced sodium channel blockade by sodium bicarbonate. Circulation. 1996;94(8):1954–61.
74. Brucculeri M, Kaplan J, Lande L. Reversal of citalopram-induced junctional bradycardia with intravenous sodium bicarbonate. Pharmacotherapy. 2005;25(1):119–22. doi:10.1592/phco.25.1.119.55630.
75. Benkirane RR, Abouqal R, Haimeur CC, SS SECEK, Azzouzi AA, Mdaghri Alaoui AA, et al. Incidence of adverse drug events and medication errors in intensive care units: a prospective multicenter study. J Patient Saf. 2009;5(1):16–22. doi:10.1097/PTS.0b013e3181990d51.
76. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726–34. doi:10.1056/NEJMra1208943.
77. Eglen RM, Reddy H, Watson N, Challiss RA. Muscarinic acetylcholine receptor subtypes in smooth muscle. Trends Pharmacol Sci. 1994;15(4):114–9. doi:10.1016/0165-6147(94)90047-7.
78. Goyal RK. Muscarinic receptor subtypes. Physiology and clinical implications. N Engl J Med. 1989;321(15):1022–9. doi:10.1056/NEJM198910123211506.
79. Louis S, Kutt H, McDowell F. The cardiocirculatory changes caused by intravenous Dilantin and its solvent. Am Heart J. 1967;74(4):523–9.
80. Schindler C, Dobrev D, Grossmann M, Francke K, Pittrow D, Kirch W. Mechanisms of beta-adrenergic receptor-mediated venodilation in humans. Clin Pharmacol Ther. 2004;75(1):49–59. doi:10.1016/j.clpt.2003.09.009.

81. Barbato E. Role of adrenergic receptors in human coronary vasomotion. Heart. 2009;95(7):603–8. doi:10.1136/hrt.2008.150888.
82. Armstrong EP, Malone DC. The impact of nonsteroidal anti-inflammatory drugs on blood pressure, with an emphasis on newer agents. Clin Ther. 2003;25(1): 1–18.
83. Connell JM, Whitworth JA, Davies DL, Lever AF, Richards AM, Fraser R. Effects of ACTH and cortisol administration on blood pressure, electrolyte metabolism, atrial natriuretic peptide and renal function in normal man. J Hypertens. 1987;5(4):425–33.
84. Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine release by four narcotics: a double-blind study in humans. Anesth Analg. 1987;66(8):723–30.
85. Fahmy NR, Sunder N, Soter NA. Role of histamine in the hemodynamic and plasma catecholamine responses to morphine. Clin Pharmacol Ther. 1983;33(5):615–20.
86. Ang KK, McRitchie RJ, Minson JB, Llewellyn-Smith IJ, Pilowsky PM, Chalmers JP, et al. Activation of spinal opioid receptors contributes to hypotension after hemorrhage in conscious rats. Am J Physiol. 1999;276(5 Pt 2):H1552–8.
87. Henderson LA, Keay KA, Bandler R. Delta- and kappa-opioid receptors in the caudal midline medulla mediate haemorrhage-evoked hypotension. Neuroreport. 2002;13(5):729–33.
88. Kienbaum P, Heuter T, Scherbaum N, Gastpar M, Peters J. Chronic mu-opioid receptor stimulation alters cardiovascular regulation in humans: differential effects on muscle sympathetic and heart rate responses to arterial hypotension. J Cardiovasc Pharmacol. 2002;40(3):363–9.
89. Xu T, Wang T, Han J. Involvement of opioid receptors in nucleus tractus solitarii in modulating endotoxic hypotension in rats. Neurosci Lett. 1992;146(1):72–4.
90. Cavun S, Goktalay G, Millington WR. The hypotension evoked by visceral nociception is mediated by delta opioid receptors in the periaqueductal gray. Brain Res. 2004;1019(1–2):237–45. doi:10.1016/j.brainres.2004.06.003.
91. Frithiof R, Rundgren M. Activation of central opioid receptors determines the timing of hypotension during acute hemorrhage-induced hypovolemia in conscious sheep. Am J Physiol Regul Integr Comp Physiol. 2006;291(4):R987–96. doi:10.1152/ajpregu.00070.2006.
92. Frithiof R, Eriksson S, Rundgren M. Central inhibition of opioid receptor subtypes and its effect on haemorrhagic hypotension in conscious sheep. Acta Physiol (Oxf). 2007;191(1):25–34. doi:10.1111/j.1748-1716.2007.01720.x.
93. Millington WR. Sheep have the last word: kappa and delta opioid receptors initiate haemorrhagic hypotension. Acta Physiol (Oxf). 2007;191(1):1. doi:10.1111/j.1748-1716.2007.01735_1.x.
94. Komjati K, Velkei-Harvich M, Toth J, Dallos G, Nyary I, Sandor P. Endogenous opioid mechanisms in hypothalamic blood flow autoregulation during haemorrhagic hypotension and angiotensin-induced acute hypertension in cats. Acta Physiol Scand. 1996;157(1):53–61. doi:10.1046/j.1365-201X.1996.d01-723.x.
95. Fulton B, Sorkin EM. Propofol. An overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. Drugs. 1995;50(4):636–57.
96. Bryson HM, Fulton BR, Faulds D. Propofol. An update of its use in anaesthesia and conscious sedation. Drugs. 1995;50(3):513–59.
97. McKeage K, Perry CM. Propofol: a review of its use in intensive care sedation of adults. CNS Drugs. 2003;17(4):235–72.
98. Jones GM, Doepker BA, Erdman MJ, Kimmons LA, Elijovich L. Predictors of severe hypotension in neurocritical care patients sedated with propofol. Neurocrit Care. 2014;20(2):270–6. doi:10.1007/s12028-013-9902-6.
99. Muzi M, Berens RA, Kampine JP, Ebert TJ. Venodilation contributes to propofol-mediated hypotension in humans. Anesth Analg. 1992;74(6): 877–83.
100. Maruyama K, Nishikawa Y, Nakagawa H, Ariyama J, Kitamura A, Hayashida M. Can intravenous atropine prevent bradycardia and hypotension during induction of total intravenous anesthesia with propofol and remifentanil? J Anesth. 2010;24(2):293–6. doi:10.1007/s00540-009-0860-2.
101. el-Beheiry H, Kim J, Milne B, Seegobin R. Prophylaxis against the systemic hypotension induced by propofol during rapid-sequence intubation. Can J Anaesth. 1995;42(10):875–8. doi:10.1007/BF03011034.
102. Gin T. Prevention of hypotension after propofol for rapid sequence intubation. Can J Anaesth. 1996; 43(8):877–8. doi:10.1007/BF03013044.
103. Kasaba T, Yamaga M, Iwasaki T, Yoshimura Y, Takasaki M. Ephedrine, dopamine, or dobutamine to treat hypotension with propofol during epidural anesthesia. Can J Anaesth. 2000;47(3):237–41.
104. Ozkocak I, Altunkaya H, Ozer Y, Ayoglu H, Demirel CB, Cicek E. Comparison of ephedrine and ketamine in prevention of injection pain and hypotension due to propofol induction. Eur J Anaesthesiol. 2005;22(1): 44–8.
105. Maracaja-Neto LF, Mello Silva GA, de Moura RS, Tibirica E, Lessa MA. Opioid receptor blockade prevents propofol-induced hypotension in rats. J Neurosurg Anesthesiol. 2012;24(3):191–6. doi:10.1097/ANA.0b013e318248ad01.
106. Hsu WH, Wang SS, Shih HY, Wu MC, Chen YY, Kuo FC, et al. Low effect-site concentration of propofol target-controlled infusion reduces the risk of hypotension during endoscopy in a Taiwanese population. J Dig Dis. 2013;14(3):147–52. doi:10.1111/1751-2980.12020.

107. Morley AP, Nalla BP, Vamadevan S, Strandvik G, Natarajan A, Prevost AT, et al. The influence of duration of fluid abstinence on hypotension during propofol induction. Anesth Analg. 2010;111 (6):1373–7. doi:10.1213/ANE.0b013e3181f62a2b.
108. Jager MD, Aldag JC, Deshpande GG. A presedation fluid bolus does not decrease the incidence of propofol-induced hypotension in pediatric patients. Hosp Pediatr. 2015;5(2):85–91. doi:10.1542/hpeds.2014-0075.
109. Diaz JH, Prabhakar A, Urman RD, Kaye AD. Propofol infusion syndrome: a retrospective analysis at a level 1 trauma center. Crit Care Res Pract. 2014;2014:346968. doi:10.1155/2014/346968.
110. Ozturk I, Serin S, Gurses E. Biochemical markers in total intravenous anesthesia and propofol infusion syndrome: a preliminary study. Eur Rev Med Pharmacol Sci. 2013;17(24):3385–90.
111. Roberts RJ, Barletta JF, Fong JJ, Schumaker G, Kuper PJ, Papadopoulos S, et al. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. Crit Care. 2009; 13(5):R169. doi:10.1186/cc8145.
112. Fong JJ, Sylvia L, Ruthazer R, Schumaker G, Kcomt M, Devlin JW. Predictors of mortality in patients with suspected propofol infusion syndrome. Crit Care Med. 2008;36(8):2281–7. doi:10.1097/CCM.0b013e318180c1eb.
113. Mayette M, Gonda J, Hsu JL, Mihm FG. Propofol infusion syndrome resuscitation with extracorporeal life support: a case report and review of the literature. Ann Intensive Care. 2013;3(1):32. doi:10.1186/2110-5820-3-32.
114. Diedrich DA, Brown DR. Analytic reviews: propofol infusion syndrome in the ICU. J Intensive Care Med. 2011;26(2):59–72. doi:10.1177/0885066610384195.
115. Weil MH, Shubin H. The "VIP" approach to the bedside management of shock. JAMA. 1969;207(2): 337–40.
116. Overgaard CB, Dzavik V. Inotropes and vasopressors: review of physiology and clinical use in cardiovascular disease. Circulation. 2008;118(10):1047–56. doi:10.1161/CIRCULATIONAHA.107.728840.
117. Mehta S, Granton J, Gordon AC, Cook DJ, Lapinsky S, Newton G, et al. Cardiac ischemia in patients with septic shock randomized to vasopressin or norepinephrine. Crit Care. 2013;17(3):R117. doi:10.1186/cc12789.
118. Jardin F, Sportiche M, Bazin M, Bourokba A, Margairaz A. Dobutamine: a hemodynamic evaluation in human septic shock. Crit Care Med. 1981;9(4): 329–32.
119. Levy B, Perez P, Perny J, Thivilier C, Gerard A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med. 2011;39(3): 450–5. doi:10.1097/CCM.0b013e3181ffe0eb.
120. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J, et al. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med. 2008;34(12):2226–34. doi:10.1007/s00134-008-1219-0.
121. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet. 2000;356(9248):2139–43.
122. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362(9):779–89. doi:10.1056/NEJMoa0907118.
123. De Backer D, Aldecoa C, Njimi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis*. Crit Care Med. 2012;40(3):725–30. doi:10.1097/CCM.0b013e31823778ee.
124. Tran TP, Panacek EA, Rhee KJ, Foulke GE. Response to dopamine vs norepinephrine in tricyclic antidepressant-induced hypotension. Acad Emerg Med. 1997;4(9):864–8.
125. Bonamigo RR, Razera F, Cartell A. Extensive skin necrosis following use of noradrenaline and dopamine. J Eur Acad Dermatol Venereol. 2007;21(4): 565–6. doi:10.1111/j.1468-3083.2006.01963.x.
126. Dunser MW, Mayr AJ, Tur A, Pajk W, Barbara F, Knotzer H, et al. Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. Crit Care Med. 2003;31(5):1394–8. doi:10.1097/01.CCM.0000059722.94182.79.
127. Gul M, Kaynar M, Sekmenli T, Ciftci I, Goktas S. Epinephrine injection associated scrotal skin necrosis. Case Rep Urol. 2015;2015:187831. doi:10.1155/2015/187831.
128. Hayes MA, Yau EH, Hinds CJ, Watson JD. Symmetrical peripheral gangrene: association with noradrenaline administration. Intensive Care Med. 1992;18 (7):433–6.
129. Kahn JM, Kress JP, Hall JB. Skin necrosis after extravasation of low-dose vasopressin administered for septic shock. Crit Care Med. 2002;30(8): 1899–901.
130. Kim EH, Lee SH, Byun SW, Kang HS, Koo DH, Park HG, et al. Skin necrosis after a low-dose vasopressin infusion through a central venous catheter for treating septic shock. Korean J Intern Med. 2006;21(4): 287–90.
131. Pillgram-Larsen J, Nicolaisen B. Skin necrosis due to dopamine infusion. Tidsskr Nor Laegeforen. 1982;102(30):1583–4.
132. Wang HL, Aguilera C, Knopf KB, Chen TM, Maslove DM, Kuschner WG. Thrombocytopenia in the intensive care unit. J Intensive Care Med. 2013; 28(5):268–80. doi:10.1177/0885066611431551.

133. Visentin GP, Liu CY. Drug-induced thrombocytopenia. Hematol Oncol Clin North Am. 2007;21(4):685–96, vi. doi:10.1016/j.hoc.2007.06.005.
134. George JN, Aster RH. Drug-induced thrombocytopenia: pathogenesis, evaluation, and management. Hematology Am Soc Hematol Educ Program. 2009:153–8. doi:10.1182/asheducation-2009.1.153.
135. Dhakal P, Giri S, Pathak R, Bhatt VR. Heparin reexposure in patients with a history of heparin-induced thrombocytopenia. Clin Appl Thromb Hemost. 2015. doi:10.1177/1076029615578167.
136. Yurtdas M, Yaylali YT, Aladag N, Ozdemir M, Atay MH. Acute serious thrombocytopenia associated with intracoronary tirofiban use for primary angioplasty. Case Rep Med. 2014;2014:190149. doi:10.1155/2014/190149.
137. Velibey Y, Golcuk Y, Ekmekci A, Altay S, Gunay E, Eren M. Tirofiban-induced acute profound thrombocytopenia: what is the optimal approach to treatment? Platelets. 2015;26(2):197–8. doi:10.3109/09537104.2013.787406.
138. Dursunoglu D, Taskoylu O, Gur S, Sari I. Tirofiban-induced acute profound thrombocytopenia after primary angioplasty. Asian Cardiovasc Thorac Ann. 2013;21(1):74–6. doi:10.1177/0218492312445142.
139. Panduranga P, Sulaiman K. Severe thrombocytopenia following tirofiban infusion. Indian J Pharmacol. 2011;43(6):726–8. doi:10.4103/0253-7613.89837.
140. Williamson DR, Lesur O, Tetrault JP, Pilon D. Drug-induced thrombocytopenia in the critically ill: a case–control study. Ann Pharmacother. 2014;48(6):697–704. doi:10.1177/1060028013519065.
141. Garbe E, Andersohn F, Bronder E, Salama A, Klimpel A, Thomae M, et al. Drug-induced immune thrombocytopaenia: results from the Berlin Case–control Surveillance Study. Eur J Clin Pharmacol. 2012;68(5):821–32. doi:10.1007/s00228-011-1184-3.
142. Krzych LJ, Nowacka E, Knapik P. Heparin-induced thrombocytopenia. Anaesthesiol Intensive Ther. 2015;47(1):63–76. doi:10.5603/AIT.2015.0006.
143. Linkins LA, Bates SM, Lee AY, Heddle NM, Wang G, Warkentin TE. Combination of 4Ts score and PF4/H-PaGIA for diagnosis and management of heparin-induced thrombocytopenia: prospective cohort study. Blood. 2015. doi:10.1182/blood-2014-12-618165.
144. Nazi I, Arnold DM, Moore JC, Smith JW, Ivetic N, Horsewood P, et al. Pitfalls in the diagnosis of heparin-induced thrombocytopenia: a 6-year experience from a reference laboratory. Am J Hematol. 2015. doi:10.1002/ajh.24025.
145. Warkentin TE, Arnold DM, Nazi I, Kelton JG. The platelet serotonin-release assay. Am J Hematol. 2015. doi:10.1002/ajh.24006.
146. Taleb M, Ashraf Z, Valavoor S, Tinkel J. Evaluation and management of acquired methemoglobinemia associated with topical benzocaine use. Am J Cardiovasc Drugs. 2013;13(5):325–30. doi:10.1007/s40256-013-0027-2.
147. Hall A, Stessel B, Bergmans D, Schnabel R. Two cases of acquired methemoglobinemia. Acta Anaesthesiol Belg. 2012;63(2):97–100.
148. Akbayram S, Akgun C, Dogan M, Gundogdu M, Caksen H, Oner AF. Acquired methemoglobinemia due to application of prilocaine during circumcision. J Emerg Med. 2012;43(1):120–1. doi:10.1016/j.jemermed.2010.05.090.
149. Vallurupalli S, Manchanda S. Risk of acquired methemoglobinemia with different topical anesthetics during endoscopic procedures. Local Reg Anesth. 2011;4:25–8. doi:10.2147/LRA.S22711.
150. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. Medicine (Baltimore). 2004;83(5):265–73.
151. Patel PB, Logan GW, Karnad AB, Byrd Jr RP, Roy TM. Acquired methemoglobinemia: a rare but serious complication. Tenn Med. 2003;96(8):373–6.
152. Haynes JM. Acquired methemoglobinemia following benzocaine anesthesia of the pharynx. Am J Crit Care. 2000;9(3):199–201.
153. Wilburn-Goo D, Lloyd LM. When patients become cyanotic: acquired methemoglobinemia. J Am Dent Assoc. 1999;130(6):826–31.
154. Svecova D, Bohmer D. Congenital and acquired methemoglobinemia and its therapy. Cas Lek Cesk. 1998;137(6):168–70.
155. Conroy JM, Baker 3rd JD, Martin WJ, Bailey MK, Dorman BH. Acquired methemoglobinemia from multiple oxidants. South Med J. 1993;86(10):1156–9.
156. Tada K, Tokaji A, Odaka Y, Kurasako T, Mutoh J, Takatori M, et al. A resuscitation puzzle: acute acquired methemoglobinemia. Crit Care Med. 1987;15(6):614–5.
157. Foxworth JW, Roberts JA, Mahmoud SF. Acquired methemoglobinemia. A case report. Mo Med. 1987;84(4):187–9.
158. Hartman NR, Mao JJ, Zhou H, Boyne 2nd MT, Wasserman AM, Taylor K, et al. More methemoglobin is produced by benzocaine treatment than lidocaine treatment in human in vitro systems. Regul Toxicol Pharmacol. 2014;70(1):182–8. doi:10.1016/j.yrtph.2014.07.002.
159. Juffermans NP, Vervloet MG, Daemen-Gubbels CR, Binnekade JM, de Jong M, Groeneveld AB. A dose-finding study of methylene blue to inhibit nitric oxide actions in the hemodynamics of human septic shock. Nitric Oxide. 2010;22(4):275–80. doi:10.1016/j.niox.2010.01.006.
160. Majithia A, Stearns MP. Methylene blue toxicity following infusion to localize parathyroid adenoma. J Laryngol Otol. 2006;120(2):138–40. doi:10.1017/S0022215105005098.
161. Similowski T, Straus C. Iatrogenic-induced dysfunction of the neuromuscular respiratory system. Clin

Chest Med. 2004;25(1):155–66. doi:10.1016/S0272-5231(03)00142-4.
162. Rossi SE, Erasmus JJ, McAdams HP, Sporn TA, Goodman PC. Pulmonary drug toxicity: radiologic and pathologic manifestations. Radiographics. 2000;20(5):1245–59. doi:10.1148/radiographics.20.5.g00se081245.
163. Hodnett PA, Naidich DP. Fibrosing interstitial lung disease. A practical high-resolution computed tomography-based approach to diagnosis and management and a review of the literature. Am J Respir Crit Care Med. 2013;188(2):141–9. doi:10.1164/rccm.201208-1544CI.
164. Cleverley JR, Screaton NJ, Hiorns MP, Flint JD, Muller NL. Drug-induced lung disease: high-resolution CT and histological findings. Clin Radiol. 2002;57(4):292–9. doi:10.1053/crad.2001.0792.
165. Min JH, Lee HY, Lim H, Ahn MJ, Park K, Chung MP, et al. Drug-induced interstitial lung disease in tyrosine kinase inhibitor therapy for non-small cell lung cancer: a review on current insight. Cancer Chemother Pharmacol. 2011;68(5):1099–109. doi:10.1007/s00280-011-1737-2.
166. Wolkove N, Baltzan M. Amiodarone pulmonary toxicity. Can Respir J. 2009;16(2):43–8.
167. Viswam D, Nair SG, Patel V, Nagaraj. Ultra-short course of low-dose amiodarone-induced post-operative fatal pulmonary toxicity. J Assoc Physicians India. 2011;59:443–7.
168. Van Cott TE, Yehle KS, DeCrane SK, Thorlton JR. Amiodarone-induced pulmonary toxicity: case study with syndrome analysis. Heart Lung. 2013;42(4):262–6. doi:10.1016/j.hrtlng.2013.05.004.
169. Ernawati DK, Stafford L, Hughes JD. Amiodarone-induced pulmonary toxicity. Br J Clin Pharmacol. 2008;66(1):82–7. doi:10.1111/j.1365-2125.2008.03177.x.
170. Vorperian VR, Havighurst TC, Miller S, January CT. Adverse effects of low dose amiodarone: a meta-analysis. J Am Coll Cardiol. 1997;30(3):791–8.
171. Beasley MB. The pathologist's approach to acute lung injury. Arch Pathol Lab Med. 2010;134(5):719–27. doi:10.1043/1543-2165-134.5.719.
172. Singh A, Singh P, Sidhu US. Reversible interstitial lung disease with prolonged use of nitrofurantoin: do the benefits outweigh the risks? Lung India. 2013;30(3):212–4. doi:10.4103/0970-2113.116271.
173. Viejo MA, Fernandez Montes A, Montes JV, Gomez-Roman JJ, Ibarbia CG, Hernandez JL. Rapid resolution of nitrofurantoin-induced interstitial lung disease. Arch Bronconeumol. 2009;45(7):352–5. doi:10.1016/j.arbres.2008.05.009.
174. Schelhorn J, Hofer L, Syrbe G, Polzer U. Drug-induced eosinophilic pneumonia. Nervenarzt. 2008;79(6):696–8. doi:10.1007/s00115-008-2437-y.
175. Yamasawa H, Ohno S, Nakaya T, Ishii Y, Hosono T, Tsujita A, et al. Case of minocycline-induced acute eosinophilic pneumonia accompanied by marked neutrophilia in the peripheral blood. Nihon Kokyuki Gakkai Zasshi. 2008;46(10):820–4.
176. Shimizu T, Shimizu N, Kinebuchi S, Toyama J. Case of acute eosinophilic pneumonia probably induced by minocycline. Nihon Kokyuki Gakkai Zasshi. 2008;46(2):136–40.
177. Rosen E. Eosinophilic pneumonia induced by minocycline. Harefuah. 2000;139(11–12):438–40, 94.
178. Rikken NE, Klinkhamer PJ, Haak HR. Interstitial pneumonia and hepatitis caused by minocycline. Neth J Med. 2004;62(2):62–4.
179. Osanai S, Fukuzawa J, Akiba Y, Ishida S, Nakano H, Matsumoto H, et al. Minocycline-induced pneumonia and pleurisy – a case report. Nihon Kyobu Shikkan Gakkai Zasshi. 1992;30(2):322–7.
180. Kondo H, Fujita J, Inoue T, Horiuchi N, Nakao K, Iwata M, et al. Minocycline-induced pneumonitis presenting as multiple ring-shaped opacities on chest CT, pathologically diagnosed bronchiolitis obliterans organizing pneumonia (BOOP). Nihon Kokyuki Gakkai Zasshi. 2001;39(3):215–9.
181. Klerkx S, Pat K, Wuyts W. Minocycline induced eosinophilic pneumonia: case report and review of literature. Acta Clin Belg. 2009;64(4):349–54. doi:10.1179/acb.2009.056.
182. Horikx PE, Gooszen HC. Minocycline as a cause of acute eosinophilic pneumonia. Ned Tijdschr Geneeskd. 1992;136(11):530–2.
183. Bentur L, Bar-Kana Y, Livni E, Finkelstein R, Ben-Izhak O, Keidar S, et al. Severe minocycline-induced eosinophilic pneumonia: extrapulmonary manifestations and the use of in vitro immunoassays. Ann Pharmacother. 1997;31(6):733–5.
184. Solomon J, Schwarz M. Drug-, toxin-, and radiation therapy-induced eosinophilic pneumonia. Semin Respir Crit Care Med. 2006;27(2):192–7. doi:10.1055/s-2006-939522.
185. Vital Durand D, Durieu I, Rousset H. Toxic or drug-induced granulomatous reactions. Rev Med Interne. 2008;29(1):33–8. doi:10.1016/j.revmed.2007.09.039.
186. El-Zammar OA, Katzenstein AL. Pathological diagnosis of granulomatous lung disease: a review. Histopathology. 2007;50(3):289–310. doi:10.1111/j.1365-2559.2006.02546.x.
187. Sterrett C, Brownfield J, Korn CS, Hollinger M, Henderson SO. Patterns of presentation in heroin overdose resulting in pulmonary edema. Am J Emerg Med. 2003;21(1):32–4. doi:10.1053/ajem.2003.50006.
188. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema: a case series. Chest. 2001;120(5):1628–32.
189. Osborn HH, Tang M, Bradley K, Duncan BR. New-onset bronchospasm or recrudescence of asthma associated with cocaine abuse. Acad Emerg Med. 1997;4(7):689–92.
190. Schechter E, Hoffman RS, Stajic M, McGee MP, Cuevas S, Tarabar A. Pulmonary edema and

respiratory failure associated with clenbuterol exposure. Am J Emerg Med. 2007;25(6):735 e1–3. doi:10.1016/j.ajem.2006.12.022.
191. do Nascimento TS, Pereira RO, de Mello HL, Costa J. Methemoglobinemia: from diagnosis to treatment. Rev Bras Anestesiol. 2008;58(6):651–64.
192. Kumar K, Holden WE. Drug-induced pulmonary vascular disease – mechanisms and clinical patterns. West J Med. 1986;145(3):343–9.
193. Lee-Chiong Jr T, Matthay RA. Drug-induced pulmonary edema and acute respiratory distress syndrome. Clin Chest Med. 2004;25(1):95–104. doi:10.1016/S0272-5231(03)00128-X.
194. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33. doi:10.1001/jama.2012.5669.
195. Turturro MA, O'Toole KS. Oxycodone-induced pulmonary edema. Am J Emerg Med. 1991;9(2):201–3.
196. Gould DB. Buprenorphine causes pulmonary edema just like all other mu-opioid narcotics. Upper airway obstruction, negative alveolar pressure. Chest. 1995;107(5):1478–9.
197. Sklar J, Timms RM. Codeine-induced pulmonary edema. Chest. 1977;72(2):230–1.
198. Hakim TS, Grunstein MM, Michel RP. Opiate action in the pulmonary circulation. Pulm Pharmacol. 1992;5(3):159–65.
199. Menis M, Anderson SA, Forshee RA, McKean S, Johnson C, Warnock R, et al. Transfusion-related acute lung injury and potential risk factors among the inpatient US elderly as recorded in Medicare claims data, during 2007 through 2011. Transfusion. 2014;54(9):2182–93. doi:10.1111/trf.12626.
200. Clifford L, Jia Q, Subramanian A, Yadav H, Wilson GA, Murphy SP, et al. Characterizing the epidemiology of postoperative transfusion-related acute lung injury. Anesthesiology. 2015;122(1):12–20. doi:10.1097/ALN.0000000000000514.
201. Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet. 2013;382(9896):984–94. doi:10.1016/S0140-6736(12)62197-7.
202. Skeate RC, Eastlund T. Distinguishing between transfusion related acute lung injury and transfusion associated circulatory overload. Curr Opin Hematol. 2007;14(6):682–7. doi:10.1097/MOH.0b013e3282ef195a.
203. Montani D, Seferian A, Savale L, Simonneau G, Humbert M. Drug-induced pulmonary arterial hypertension: a recent outbreak. Eur Respir Rev. 2013;22(129):244–50. doi:10.1183/09059180.00003313.
204. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996;335(9):609–16. doi:10.1056/NEJM199608293350901.
205. Seferian A, Chaumais MC, Savale L, Gunther S, Tubert-Bitter P, Humbert M, et al. Drugs induced pulmonary arterial hypertension. Presse Med. 2013;42(9 Pt 2):e303–10. doi:10.1016/j.lpm.2013.07.005.
206. Wan Y, Corman S, Gao X, Liu S, Patel H, Mody R. Economic burden of opioid-induced constipation among long-term opioid users with noncancer pain. Am Health Drug Benefits. 2015;8(2):93–102.
207. Burda T, Sigg T. Double peak and prolonged absorption after large acetaminophen extended release and diphenhydramine ingestion. Am J Ther. 2012;19(2):e101–4. doi:10.1097/MJT.0b013e3181e7a536.
208. Graudins A, Chiew A, Chan B. Overdose with modified-release paracetamol results in delayed and prolonged absorption of paracetamol. Intern Med J. 2010;40(1):72–6. doi:10.1111/j.1445-5994.2009.02096.x.
209. Roberts DM, Buckley NA. Prolonged absorption and delayed peak paracetamol concentration following poisoning with extended-release formulation. Med J Aust. 2008;188(5):310–1.
210. Dutta S, Reed RC, O'Dea RF. Comparative absorption profiles of divalproex sodium delayed-release versus extended-release tablets – clinical implications. Ann Pharmacother. 2006;40(4):619–25. doi:10.1345/aph.1G617.
211. LoVecchio F, Thole D, Bagnasco T. Delayed absorption of valproic acid, resulting in coma. Acad Emerg Med. 2002;9(12):1464.
212. Pons S, Gonzva J, Prunet B, Gaillard T, Brisou P, Vest P, et al. Acute overdose of enteric-coated valproic acid and olanzapine: unusual presentation and delayed toxicity. Clin Toxicol (Phila). 2012;50(4):268. doi:10.3109/15563650.2012.657760.
213. Herres J, Ryan D, Salzman M. Delayed salicylate toxicity with undetectable initial levels after large-dose aspirin ingestion. Am J Emerg Med. 2009;27(9):1173 e1–3. doi:10.1016/j.ajem.2009.01.013.
214. Payen C, Frantz P, Martin O, Parant F, Moulsma M, Pulce C, et al. Delayed toxicity following acute ingestion of valpromide. Hum Exp Toxicol. 2004;23(3):145–8.
215. Ingels M, Beauchamp J, Clark RF, Williams SR. Delayed valproic acid toxicity: a retrospective case series. Ann Emerg Med. 2002;39(6):616–21.
216. Graudins A, Peden G, Dowsett RP. Massive overdose with controlled-release carbamazepine resulting in delayed peak serum concentrations and life-threatening toxicity. Emerg Med (Fremantle). 2002;14(1):89–94.
217. Drummond R, Kadri N, St-Cyr J. Delayed salicylate toxicity following enteric-coated acetylsalicylic acid overdose: a case report and review of the literature. CJEM. 2001;3(1):44–6.
218. Brubacher JR, Dahghani P, McKnight D. Delayed toxicity following ingestion of enteric-coated divalproex sodium (Epival). J Emerg Med. 1999;17(3):463–7.

219. Rhyee SH, Pedapati EV, Thompson J. Prolonged delirium after quetiapine overdose. Pediatr Emerg Care. 2010;26(10):754–6. doi:10.1097/PEC.0b013e3181f39d5b.
220. Elseviers MM, Van Camp Y, Nayaert S, Dure K, Annemans L, Tanghe A, et al. Prevalence and management of antibiotic associated diarrhea in general hospitals. BMC Infect Dis. 2015;15(1):129. doi:10.1186/s12879-015-0869-0.
221. Mylonakis E, Ryan ET, Calderwood SB. *Clostridium difficile* – associated diarrhea: a review. Arch Intern Med. 2001;161(4):525–33.
222. Wang X, Cai L, Yu R, Huang W, Zong Z. ICU-onset *Clostridium difficile* infection in a university hospital in China: a prospective cohort study. PLoS One. 2014;9(11):e111735. doi:10.1371/journal.pone.0111735.
223. Armbruster S, Goldkind L. A 5-year retrospective review of experience with *Clostridium difficile*-associated diarrhea. Mil Med. 2012;177(4):456–9.
224. Kenneally C, Rosini JM, Skrupky LP, Doherty JA, Hollands JM, Martinez E, et al. Analysis of 30-day mortality for *Clostridium difficile*-associated disease in the ICU setting. Chest. 2007;132(2):418–24. doi:10.1378/chest.07-0202.
225. Ang CW, Heyes G, Morrison P, Carr B. The acquisition and outcome of ICU-acquired *Clostridium difficile* infection in a single centre in the UK. J Infect. 2008;57(6):435–40. doi:10.1016/j.jinf.2008.10.002.
226. Zahar JR, Schwebel C, Adrie C, Garrouste-Orgeas M, Francais A, Vesin A, et al. Outcome of ICU patients with *Clostridium difficile* infection. Crit Care. 2012;16(6):R215. doi:10.1186/cc11852.
227. Ziakas PD, Mylonakis E. ACP Journal Club. Probiotics did not prevent antibiotic-associated or *C. difficile* diarrhea in hospitalized older patients. Ann Intern Med. 2014;160(12):JC6. doi:10.7326/0003-4819-160-12-201406170-02006.
228. Weed HG. ACP Journal Club. Review: probiotics prevent *C. difficile*-associated diarrhea in patients using antibiotics. Ann Intern Med. 2013;159(8):JC7. doi:10.7326/0003-4819-159-8-201310150-02007.
229. Pattani R, Palda VA, Hwang SW, Shah PS. Probiotics for the prevention of antibiotic-associated diarrhea and *Clostridium difficile* infection among hospitalized patients: systematic review and meta-analysis. Open Med. 2013;7(2):e56–67.
230. Akerlund T, Alefjord I, Dohnhammar U, Struwe J, Noren T, Tegmark-Wisell K, et al. Geographical clustering of cases of infection with moxifloxacin-resistant *Clostridium difficile* PCR-ribotypes 012, 017 and 046 in Sweden, 2008 and 2009. Euro Surveill. 2011;16(10):1–7.
231. Biller P, Shank B, Lind L, Brennan M, Tkatch L, Killgore G, et al. Moxifloxacin therapy as a risk factor for *Clostridium difficile*-associated disease during an outbreak: attempts to control a new epidemic strain. Infect Control Hosp Epidemiol. 2007;28(2):198–201. doi:10.1086/511789.
232. Khurana A, Vinayek N, Recco RA, Go ES, Zaman MM. The incidence of *Clostridium difficile*-associated and non-*C. difficile*-associated diarrhea after use of gatifloxacin and levofloxacin in an acute-care facility. Clin Infect Dis. 2004;39(4):602–3. doi:10.1086/422525.
233. Walkty A, Boyd DA, Gravel D, Hutchinson J, McGeer A, Moore D, et al. Molecular characterization of moxifloxacin resistance from Canadian *Clostridium difficile* clinical isolates. Diagn Microbiol Infect Dis. 2010;66(4):419–24. doi:10.1016/j.diagmicrobio.2009.12.002.
234. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf. 2009;32(1):55–68. doi:10.2165/00002018-200932010-00005.
235. Andrade RJ, Lucena MI, Fernandez MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology. 2005;129(2):512–21. doi:10.1016/j.gastro.2005.05.006.
236. Bjornsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology. 2005;42(2):481–9. doi:10.1002/hep.20800.
237. Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, et al. Features and outcomes of 889 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology. 2015. doi:10.1053/j.gastro.2015.03.006.
238. Chen M, Borlak J, Tong W. High lipophilicity and high daily dose of oral medications are associated with significant risk for drug-induced liver injury. Hepatology. 2013;58(1):388–96. doi:10.1002/hep.26208.
239. Fontana RJ, Hayashi PH, Gu J, Reddy KR, Barnhart H, Watkins PB, et al. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. Gastroenterology. 2014;147(1):96–108 e4. doi:10.1053/j.gastro.2014.03.045.
240. Labbe G, Pessayre D, Fromenty B. Drug-induced liver injury through mitochondrial dysfunction: mechanisms and detection during preclinical safety studies. Fundam Clin Pharmacol. 2008;22(4):335–53. doi:10.1111/j.1472-8206.2008.00608.x.
241. Aleo MD, Luo Y, Swiss R, Bonin PD, Potter DM, Will Y. Human drug-induced liver injury severity is highly associated with dual inhibition of liver mitochondrial function and bile salt export pump. Hepatology. 2014;60(3):1015–22. doi:10.1002/hep.27206.
242. Ju C, Reilly T. Role of immune reactions in drug-induced liver injury (DILI). Drug Metab Rev.

2012;44(1):107–15. doi:10.3109/03602532.2011.645579.
243. Sherigar JM, Fazio R, Zuang M, Arsura E. Autoimmune hepatitis induced by nitrofurantoin. The importance of the autoantibodies for an early diagnosis of immune disease. Clin Pract. 2012;2(4):e83. doi:10.4081/cp.2012.e83.
244. Appleyard S, Saraswati R, Gorard DA. Autoimmune hepatitis triggered by nitrofurantoin: a case series. J Med Case Reports. 2010;4:311. doi:10.1186/1752-1947-4-311.
245. Lucena MI, Molokhia M, Shen Y, Urban TJ, Aithal GP, Andrade RJ, et al. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. Gastroenterology. 2011;141(1):338–47. doi:10.1053/j.gastro.2011.04.001.
246. Bucher NL. Experimental aspects of hepatic regeneration (conclusion). N Engl J Med. 1967;277(14):738–46. doi:10.1056/NEJM196710052771405.
247. Antoine DJ, Jenkins RE, Dear JW, Williams DP, McGill MR, Sharpe MR, et al. Molecular forms of HMGB1 and keratin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetaminophen hepatotoxicity. J Hepatol. 2012;56(5):1070–9. doi:10.1016/j.jhep.2011.12.019.
248. Harrill AH, Roach J, Fier I, Eaddy JS, Kurtz CL, Antoine DJ, et al. The effects of heparins on the liver: application of mechanistic serum biomarkers in a randomized study in healthy volunteers. Clin Pharmacol Ther. 2012;92(2):214–20. doi:10.1038/clpt.2012.40.
249. Aubrecht J, Schomaker SJ, Amacher DE. Emerging hepatotoxicity biomarkers and their potential to improve understanding and management of drug-induced liver injury. Genome Med. 2013;5(9):85. doi:10.1186/gm489.
250. Amacher DE, Schomaker SJ, Aubrecht J. Development of blood biomarkers for drug-induced liver injury: an evaluation of their potential for risk assessment and diagnostics. Mol Diagn Ther. 2013;17(6):343–54. doi:10.1007/s40291-013-0049-0.
251. Schomaker S, Warner R, Bock J, Johnson K, Potter D, Van Winkle J, et al. Assessment of emerging biomarkers of liver injury in human subjects. Toxicol Sci. 2013;132(2):276–83. doi:10.1093/toxsci/kft009.
252. Vliegenthart AD, Antoine DJ, Dear JW. Target biomarker profile for the clinical management of paracetamol overdose. Br J Clin Pharmacol. 2015. doi:10.1111/bcp.12699.
253. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ, et al. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109(7):950–66. doi:10.1038/ajg.2014.131; quiz 67.
254. Culetto A, Bournet B, Haennig A, Alric L, Peron JM, Buscail L. Prospective evaluation of the aetiological profile of acute pancreatitis in young adult patients. Dig Liver Dis. 2015;47(7):584–9. doi:10.1016/j.dld.2015.03.009.
255. Koenigsknecht RA. Learning from our consumers. ASHA. 1990;32(6–7):33–4.
256. Tenner S. Drug induced acute pancreatitis: does it exist? World J Gastroenterol. 2014;20(44):16529–34. doi:10.3748/wjg.v20.i44.16529.
257. Underwood TW, Frye CB. Drug-induced pancreatitis. Clin Pharm. 1993;12(6):440–8.
258. Maier KP, Volk B, Hoppe-Seyler G, Gerok W. Urea-cycle enzymes in normal liver and in patients with alcoholic hepatitis. Eur J Clin Invest. 1974;4(3):193–5.
259. Hauben M, Reich L. Drug-induced pancreatitis: lessons in data mining. Br J Clin Pharmacol. 2004;58(5):560–2. doi:10.1111/j.1365-2125.2004.02203.x.
260. Thomsen RW, Pedersen L, Moller N, Kahlert J, Beck-Nielsen H, Sorensen HT. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case–control study. Diabetes Care. 2015;38(6):1089–98. doi:10.2337/dc13-2983.
261. Kaurich T. Drug-induced acute pancreatitis. Proceedings. 2008;21(1):77–81.
262. Kaloyanides GJ. Antibiotic-related nephrotoxicity. Nephrol Dial Transplant. 1994;9 Suppl 4:130–4.
263. Humes HD, Weinberg JM, Knauss TC. Clinical and pathophysiologic aspects of aminoglycoside nephrotoxicity. Am J Kidney Dis. 1982;2(1):5–29.
264. Elsayed MG, Elkomy AA, Gaballah MS, Elbadawy M. Nephrotoxicity of cefepime: a new cephalosporin antibiotic in rats. J Pharmacol Pharmacother. 2014;5(1):33–8. doi:10.4103/0976-500X.124419.
265. Alfaro R, Vasavada N, Paueksakon P, Hernandez GT, Aronoff GR. Cocaine-induced acute interstitial nephritis: a case report and review of the literature. J Nephropathol. 2013;2(3):204–9. doi:10.12860/JNP.2013.33.
266. Nortier J, Depierreux M, Bourgeois V, Ducobu J, Dupont P. Progression of a naproxen and amoxicillin induced acute interstitial nephritis with nephrotic syndrome: case report. Clin Nephrol. 1991;35(5):187–9.
267. Nortier J, Depierreux M, Bourgeois V, Dupont P. Acute interstitial nephritis with nephrotic syndrome after intake of naproxen and amoxycillin. Nephrol Dial Transplant. 1990;5(12):1055.
268. Brown AE, Quesada O, Armstrong D. Minimal nephrotoxicity with cephalosporin-aminoglycoside combinations in patients with neoplastic disease. Antimicrob Agents Chemother. 1982;21(4):592–4.
269. Hinrichs JH. Cephalosporin nephrotoxicity. Lancet. 1979;1(8131):1408.

270. Perazella MA, Buller GK. NSAID nephrotoxicity revisited: acute renal failure due to parenteral ketorolac. South Med J. 1993;86(12):1421–4.
271. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med. 1994;331(21):1416–20. doi:10.1056/NEJM199411243312104.
272. Parfrey PS, Griffiths SM, Barrett BJ, Paul MD, Genge M, Withers J, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med. 1989;320(3):143–9. doi:10.1056/NEJM198901193200303.
273. Schwab SJ, Hlatky MA, Pieper KS, Davidson CJ, Morris KG, Skelton TN, et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. N Engl J Med. 1989;320(3):149–53. doi:10.1056/NEJM198901193200304.
274. Seelig CB, Maloley PA, Campbell JR. Nephrotoxicity associated with concomitant ACE inhibitor and NSAID therapy. South Med J. 1990;83(10):1144–8.
275. Appel GB, Given DB, Levine LR, Cooper GL. Vancomycin and the kidney. Am J Kidney Dis. 1986;8(2):75–80.
276. Tune BM, Fravert D. Cephalosporin nephrotoxicity. Transport, cytotoxicity and mitochondrial toxicity of cephaloglycin. J Pharmacol Exp Ther. 1980;215(1):186–90.
277. Kanbay M, Kasapoglu B, Perazella MA. Acute tubular necrosis and pre-renal acute kidney injury: utility of urine microscopy in their evaluation- a systematic review. Int Urol Nephrol. 2010;42(2):425–33. doi:10.1007/s11255-009-9673-3.
278. Whelton A. Therapeutic initiatives for the avoidance of aminoglycoside toxicity. J Clin Pharmacol. 1985;25(2):67–81.
279. Alkhuja S, Aboudan M, Menkel R. Acetaminophen toxicity induced non-oliguric acute tubular necrosis. Nephrol Dial Transplant. 2001;16(1):190.
280. Kato H, Fujigaki Y, Inoue R, Asakawa S, Shin S, Shima T, et al. Therapeutic dose of acetaminophen as a possible risk factor for acute kidney injury: learning from two healthy young adult cases. Intern Med. 2014;53(14):1531–4.
281. Ito T, Watanabe S, Tsuruga K, Aizawa T, Hirono K, Ito E, et al. Severe intrinsic acute kidney injury associated with therapeutic doses of acetaminophen. Pediatr Int. 2015;57(2):e53–5. doi:10.1111/ped.12607.
282. Tune BM, Browning MC, Hsu CY, Fravert D. Prevention of cephalosporin nephrotoxicity by other cephalosporins and by penicillins without significant inhibition of renal cortical uptake. J Infect Dis. 1982;145(2):174–80.
283. Tune BM, Hsu CY, Fravert D. Cephalosporin and carbacephem nephrotoxicity. Roles of tubular cell uptake and acylating potential. Biochem Pharmacol. 1996;51(4):557–61.
284. Sawyer MH, Webb DE, Balow JE, Straus SE. Acyclovir-induced renal failure. Clinical course and histology. Am J Med. 1988;84(6):1067–71.
285. El Bakkali L, Rodrigues Pereira R, Kuik DJ, Ket JC, van Wijk JA. Nephrotic syndrome in The Netherlands: a population-based cohort study and a review of the literature. Pediatr Nephrol. 2011;26(8):1241–6. doi:10.1007/s00467-011-1851-8.
286. Schwartzman M, D'Agati V. Spontaneous relapse of naproxen-related nephrotic syndrome. Am J Med. 1987;82(2):329–32.
287. Tolins JP, Seel P. Ibuprofen-induced interstitial nephritis and the nephrotic syndrome. Minn Med. 1987;70(9):509–11.
288. Welty TE, Copa AK. Impact of vancomycin therapeutic drug monitoring on patient care. Ann Pharmacother. 1994;28(12):1335–9.
289. Zhang Q, Matsumura Y, Teratani T, Yoshimoto S, Mineno T, Nakagawa K, et al. The application of an institutional clinical data warehouse to the assessment of adverse drug reactions (ADRs). Evaluation of aminoglycoside and cephalosporin associated nephrotoxicity. Methods Inf Med. 2007;46(5):516–22.
290. Schiemann A, Hadzidiakos D, Spies C. Managing ICU delirium. Curr Opin Crit Care. 2011;17(2):131–40. doi:10.1097/MCC.0b013e32834400b5.
291. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell Jr FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004;291(14):1753–62. doi:10.1001/jama.291.14.1753.
292. Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. Palliat Support Care. 2004;2(2):171–9.
293. Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. Crit Care Clin. 2008;24(4):657–722, vii. doi:10.1016/j.ccc.2008.05.008.
294. Mayer SA, Chong JY, Ridgway E, Min KC, Commichau C, Bernardini GL. Delirium from nicotine withdrawal in neuro-ICU patients. Neurology. 2001;57(3):551–3.
295. Hsieh SJ, Shum M, Lee AN, Hasselmark F, Gong MN. Cigarette smoking as a risk factor for delirium in hospitalized and intensive care unit patients. A systematic review. Ann Am Thorac Soc. 2013;10(5):496–503. doi:10.1513/AnnalsATS.201301-001OC.
296. Anand KJ, Willson DF, Berger J, Harrison R, Meert KL, Zimmerman J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. Pediatrics. 2010;125(5):e1208–25. doi:10.1542/peds.2009-0489.

297. Gates P, Albertella L, Copeland J. Cannabis withdrawal and sleep: a systematic review of human studies. Subst Abus. 2015. doi:10.1080/08897077.2015.1023484.
298. Katz G, Lobel T, Tetelbaum A, Raskin S. Cannabis withdrawal – a new diagnostic category in DSM-5. Isr J Psychiatry Relat Sci. 2014;51(4):270–5.
299. Lee D, Schroeder JR, Karschner EL, Goodwin RS, Hirvonen J, Gorelick DA, et al. Cannabis withdrawal in chronic, frequent cannabis smokers during sustained abstinence within a closed residential environment. Am J Addict. 2014;23(3):234–42. doi:10.1111/j.1521-0391.2014.12088.x.
300. Milin R, Manion I, Dare G, Walker S. Prospective assessment of cannabis withdrawal in adolescents with cannabis dependence: a pilot study. J Am Acad Child Adolesc Psychiatry. 2008;47(2):174–8. doi:10.1097/chi.0b013e31815cdd73.
301. Tetrault JM, O'Connor PG. Substance abuse and withdrawal in the critical care setting. Crit Care Clin. 2008;24(4):767–88, viii. doi:10.1016/j.ccc.2008.05.005.
302. Macfarlane V, Christie G. Synthetic cannabinoid withdrawal: a new demand on detoxification services. Drug Alcohol Rev. 2015;34(2):147–53. doi:10.1111/dar.12225.
303. Anton E, Marti J. Delirium in older persons. N Engl J Med. 2006;354(23):2509–11. doi:10.1056/NEJMc061003; author reply –11.
304. Excited Delirium Task Force. Excited delirium task force white paper report to the council and board of directors; 10 Sept 2009; 2009.
305. Flacker JM, Cummings V, Mach Jr JR, Bettin K, Kiely DK, Wei J. The association of serum anticholinergic activity with delirium in elderly medical patients. Am J Geriatr Psychiatry. 1998;6(1):31–41.
306. Fiorentini A, Volonteri LS, Dragogna F, Rovera C, Maffini M, Mauri MC, et al. Substance-induced psychoses: a critical review of the literature. Curr Drug Abuse Rev. 2011;4(4):228–40.
307. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA. 1996;275(11):852–7.
308. McPherson JA, Wagner CE, Boehm LM, Hall JD, Johnson DC, Miller LR, et al. Delirium in the cardiovascular intensive care unit: exploring modifiable risk factors. Crit Care Med. 2014;41(2):405–13. doi:10.1097/CCM.0b013e31826ab49b.
309. Gharagozlou P, Hashemi E, DeLorey TM, Clark JD, Lameh J. Pharmacological profiles of opioid ligands at kappa opioid receptors. BMC Pharmacol. 2006;6:3. doi:10.1186/1471-2210-6-3.
310. Greenier E, Lukyanova V, Reede L. Serotonin syndrome: fentanyl and selective serotonin reuptake inhibitor interactions. AANA J. 2014;82(5):340–5.
311. Koury KM, Tsui B, Gulur P. Incidence of serotonin syndrome in patients treated with fentanyl on serotonergic agents. Pain Physician. 2015;18(1):E27–30.
312. Samartzis L, Savvari P, Kontogiannis S, Dimopoulos S. Linezolid is associated with serotonin syndrome in a patient receiving amitriptyline, and fentanyl: a case report and review of the literature. Case Rep Psychiatry. 2013;2013:617251. doi:10.1155/2013/617251.
313. Bush E, Miller C, Friedman I. A case of serotonin syndrome and mutism associated with methadone. J Palliat Med. 2006;9(6):1257–9. doi:10.1089/jpm.2006.9.1257.
314. Hillman AD, Witenko CJ, Sultan SM, Gala G. Serotonin syndrome caused by fentanyl and methadone in a burn injury. Pharmacotherapy. 2015;35(1):112–7. doi:10.1002/phar.1528.
315. Lee J, Franz L, Goforth HW. Serotonin syndrome in a chronic-pain patient receiving concurrent methadone, ciprofloxacin, and venlafaxine. Psychosomatics. 2009;50(6):638–9. doi:10.1176/appi.psy.50.6.638.
316. Martinez TT, Martinez DN. A case of serotonin syndrome associated with methadone overdose. Proc West Pharmacol Soc. 2008;51:42–4.
317. Ailawadhi S, Sung KW, Carlson LA, Baer MR. Serotonin syndrome caused by interaction between citalopram and fentanyl. J Clin Pharm Ther. 2007;32(2):199–202. doi:10.1111/j.1365-2710.2007.00813.x.
318. Alkhatib AA, Peterson KA, Tuteja AK. Serotonin syndrome as a complication of fentanyl sedation during esophagogastroduodenoscopy. Dig Dis Sci. 2010;55(1):215–6. doi:10.1007/s10620-009-0711-x.
319. Gaffney RR, Schreibman IR. Serotonin syndrome in a patient on trazodone and duloxetine who received fentanyl following a percutaneous liver biopsy. Case Rep Gastroenterol. 2015;9(2):132–6. doi:10.1159/000382069.
320. Giese SY, Neborsky R. Serotonin syndrome: potential consequences of Meridia combined with Demerol or fentanyl. Plast Reconstr Surg. 2001;107(1):293–4.
321. Kirschner R, Donovan JW. Serotonin syndrome precipitated by fentanyl during procedural sedation. J Emerg Med. 2010;38(4):477–80. doi:10.1016/j.jemermed.2008.01.003.
322. Ozkardesler S, Gurpinar T, Akan M, Koca U, Sarikaya H, Olmez T, et al. A possible perianesthetic serotonin syndrome related to intrathecal fentanyl. J Clin Anesth. 2008;20(2):143–5. doi:10.1016/j.jclinane.2007.06.024.
323. Ghassemi M, Marshall J, Singh N, Stone DJ, Celi LA. Leveraging a critical care database: selective serotonin reuptake inhibitor use prior to ICU admission is associated with increased hospital mortality. Chest. 2014;145(4):745–52. doi:10.1378/chest.13-1722.

324. Turner MS, May DB, Arthur RR, Xiong GL. Clinical impact of selective serotonin reuptake inhibitors therapy with bleeding risks. J Intern Med. 2007;261 (3):205–13. doi:10.1111/j.1365-2796.2006.01720.x.
325. Oka Y, Okamoto K, Kawashita N, Shirakuni Y, Takagi T. Meta-analysis of the risk of upper gastrointestinal hemorrhage with combination therapy of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs. Biol Pharm Bull. 2014;37(6):947–53.
326. Tully PJ, Cardinal T, Bennetts JS, Baker RA. Selective serotonin reuptake inhibitors, venlafaxine and duloxetine are associated with in hospital morbidity but not bleeding or late mortality after coronary artery bypass graft surgery. Heart Lung Circ. 2012;21(4):206–14. doi:10.1016/j.hlc.2011.12.002.
327. Hackam DG, Mrkobrada M. Selective serotonin reuptake inhibitors and brain hemorrhage: a meta-analysis. Neurology. 2012;79(18):1862–5. doi:10.1212/WNL.0b013e318271f848.
328. Serebruany VL, Gurbel PA, O'Connor CM. Platelet inhibition by sertraline and *N*-desmethylsertraline: a possible missing link between depression, coronary events, and mortality benefits of selective serotonin reuptake inhibitors. Pharmacol Res. 2001;43(5): 453–62. doi:10.1006/phrs.2001.0817.
329. Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci. 2003;58(1):76–81.
330. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. Br J Clin Pharmacol. 2011;72(3):381–93. doi:10.1111/j.1365-2125.2011.03991.x.
331. Chow KM, Hui AC, Szeto CC. Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside. Eur J Clin Microbiol Infect Dis. 2005;24(10):649–53. doi:10.1007/s10096-005-0021-y.
332. Kolb R, Gogolak G, Huck S, Jaschek I, Stumpf C. Neurotoxicity and CSF level of three penicillins. Arch Int Pharmacodyn Ther. 1976;222(1): 149–56.
333. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. Pharmacotherapy. 2006;26(8):1169–74. doi:10.1592/phco.26.8.1169.
334. Schliamser SE, Cars O, Norrby SR. Neurotoxicity of beta-lactam antibiotics: predisposing factors and pathogenesis. J Antimicrob Chemother. 1991;27 (4):405–25.
335. Sugimoto M, Uchida I, Mashimo T, Yamazaki S, Hatano K, Ikeda F, et al. Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. Neuropharmacology. 2003;45(3):304–14.
336. Fugate JE, Kalimullah EA, Hocker SE, Clark SL, Wijdicks EF, Rabinstein AA. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. Crit Care. 2013;17(6): R264. doi:10.1186/cc13094.
337. Hawkins SB, Bucklin M, Muzyk AJ. Quetiapine for the treatment of delirium. J Hosp Med. 2013;8 (4):215–20. doi:10.1002/jhm.2019.
338. Maneeton B, Maneeton N, Srisurapanont M, Chittawatanarat K. Quetiapine versus haloperidol in the treatment of delirium: a double-blind, randomized, controlled trial. Drug Des Devel Ther. 2013;7:657–67. doi:10.2147/DDDT.S45575.
339. van den Boogaard M, Schoonhoven L, van Achterberg T, van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Crit Care. 2013;17(1): R9. doi:10.1186/cc11933.
340. Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial*. Crit Care Med. 2012;40(3):731–9. doi:10.1097/CCM.0b013e318 2376e4f.
341. Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: a comparison of efficacy, safety, and side effects. Palliat Support Care. 2014;1–7. doi:10.1017/S1478951514001059.
342. Cole JB, Stellpflug SJ, Ellsworth H, Harris CR. Reversal of quetiapine-induced altered mental status with physostigmine: a case series. Am J Emerg Med. 2012;30(6):950–3. doi:10.1016/j.ajem.2011.05.015.
343. Hail SL, Obafemi A, Kleinschmidt KC. Successful management of olanzapine-induced anticholinergic agitation and delirium with a continuous intravenous infusion of physostigmine in a pediatric patient. Clin Toxicol (Phila). 2013;51(3):162–6. doi:10.3109/15563650.2013.773006.
344. Weizberg M, Su M, Mazzola JL, Bird SB, Brush DE, Boyer EW. Altered mental status from olanzapine overdose treated with physostigmine. Clin Toxicol (Phila). 2006;44(3):319–25.
345. Lat I, McMillian W, Taylor S, Janzen JM, Papadopoulos S, Korth L, et al. The impact of delirium on clinical outcomes in mechanically ventilated surgical and trauma patients. Crit Care Med. 2009;37(6):1898–905. doi:10.1097/CCM.0b013e31819ffe38.
346. Moore PW, Donovan JW, Burkhart KK, Waskin JA, Hieger MA, Adkins AR, et al. Safety and efficacy of flumazenil for reversal of iatrogenic benzodiazepine-associated delirium toxicity during treatment of alcohol withdrawal, a retrospective review at one center. J Med Toxicol. 2014;10(2):126–32. doi:10.1007/s13181-014-0391-6.

347. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21–6.
348. Best KM, Boullata JI, Curley MA. Risk factors associated with iatrogenic opioid and benzodiazepine withdrawal in critically ill pediatric patients: a systematic review and conceptual model. Pediatr Crit Care Med. 2015;16(2):175–83. doi:10.1097/PCC.0000000000000306.
349. Treatment of benzodiazepine overdose with flumazenil. The Flumazenil in Benzodiazepine Intoxication Multicenter Study Group. Clin Ther. 1992;14(6):978–95.
350. Bosanko NC, Barrett D, Emm C, Lycett W, O'Toole S, Evans K, et al. The routine use of a flumazenil infusion following percutaneous endoscopic gastrostomy placement to reduce early post-procedure mortality. J R Coll Physicians Edinb. 2010;40(2):111–4. doi:10.4997/JRCPE.2010.204.
351. Kreshak AA, Cantrell FL, Clark RF, Tomaszewski CA. A poison center's ten-year experience with flumazenil administration to acutely poisoned adults. J Emerg Med. 2012. doi:10.1016/j.jemermed.2012.01.059.
352. Lewis D. Summary of: the use of flumazenil after midazolam-induced conscious sedation. Br Dent J. 2010;209(11):568–9. doi:10.1038/sj.bdj.2010.1107.
353. Potokar J, Coupland N, Glue P, Groves S, Malizia A, Bailey J, et al. Flumazenil in alcohol withdrawal: a double-blind placebo-controlled study. Alcohol Alcohol. 1997;32(5):605–11.
354. Veiraiah A, Dyas J, Cooper G, Routledge PA, Thompson JP. Flumazenil use in benzodiazepine overdose in the UK: a retrospective survey of NPIS data. Emerg Med J. 2012;29(7):565–9. doi:10.1136/emj.2010.095075.
355. Weinbroum A, Rudick V, Sorkine P, Nevo Y, Halpern P, Geller E, et al. Use of flumazenil in the treatment of drug overdose: a double-blind and open clinical study in 110 patients. Crit Care Med. 1996;24(2):199–206.
356. Penninga EI, Graudal N, Ladekarl MB, Jurgens G. Adverse events associated with flumazenil treatment for the management of suspected benzodiazepine intoxication – a systematic review with meta-analyses of randomised trials. Basic Clin Pharmacol Toxicol. 2015. doi:10.1111/bcpt.12434.
357. Sellers EM. Alcohol, barbiturate and benzodiazepine withdrawal syndromes: clinical management. CMAJ. 1988;139(2):113–20.
358. Kawasaki SS, Jacapraro JS, Rastegar DA. Safety and effectiveness of a fixed-dose phenobarbital protocol for inpatient benzodiazepine detoxification. J Subst Abuse Treat. 2012;43(3):331–4. doi:10.1016/j.jsat.2011.12.011.
359. Brown ES. An epidemiological approach to "steroid psychosis". Am J Psychiatry. 2012;169(5):447–9. doi:10.1176/appi.ajp.2012.12020181.
360. Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. Psychosomatics. 2012;53(2):103–15. doi:10.1016/j.psym.2011.12.007.
361. Demir T, Karacetin G, Dogangun B, Kocabasoglu N. Report of a case of steroid-induced psychosis and inappropriate sexual behaviour in an adolescent. Pharmacopsychiatry. 2012;45(2):77–9. doi:10.1055/s-0031-1291234.
362. Bag O, Erdogan I, Onder ZS, Altinoz S, Ozturk A. Steroid-induced psychosis in a child: treatment with risperidone. Gen Hosp Psychiatry. 2012;34(1):103 e5–6. doi:10.1016/j.genhosppsych.2011.09.003.
363. Airagnes G, Rouge-Maillart C, Garre JB, Gohier B. Homicide and associated steroid acute psychosis: a case report. Case Rep Med. 2011;2011:564521. doi:10.1155/2011/564521.
364. Khan FY. Failure to wean due to steroid psychosis. Saudi Med J. 2005;26(9):1470–1.
365. Yoshimura R, Saito K, Terada T, Yunoue N, Umene-Nakano W, Hirata S, et al. Steroid psychosis in a polyarteritis nodosa patient successfully treated with risperidone: tracking serum brain-derived neurotrophic factor levels longitudinally. Ann Gen Psychiatry. 2012;11(1):2. doi:10.1186/1744-859X-11-2.
366. Ross DA, Cetas JS. Steroid psychosis: a review for neurosurgeons. J Neurooncol. 2012;109(3):439–47. doi:10.1007/s11060-012-0919-z.
367. Okishiro N, Tanimukai H, Tsuneto S, Ito N. Can "steroid switching" improve steroid-induced psychosis in a patient with advanced cancer? J Palliat Med. 2009;12(5):487–90. doi:10.1089/jpm.2009.9628.
368. Herguner S, Bilge I, Yavuz Yilmaz A, Tuzun DU. Steroid-induced psychosis in an adolescent: treatment and prophylaxis with risperidone. Turk J Pediatr. 2006;48(3):244–7.
369. Kato O, Misawa H. Steroid-induced psychosis treated with valproic acid and risperidone in a patient with systemic lupus erythematosus. Prim Care Companion J Clin Psychiatry. 2005;7(6):312.
370. Huang HW, Zheng BL, Jiang L, Lin ZT, Zhang GB, Shen L, et al. Effect of oral melatonin and wearing earplugs and eye masks on nocturnal sleep in healthy subjects in a simulated intensive care unit environment: which might be a more promising strategy for ICU sleep deprivation? Crit Care. 2015;19:124. doi:10.1186/s13054-015-0842-8.
371. Mistraletti G, Umbrello M, Sabbatini G, Miori S, Taverna M, Cerri B, et al. Melatonin reduces the need for sedation in ICU patients. A randomized controlled trial. Minerva Anestesiol. 2015;81:1298.

372. Hope WW, von der Embse K, Mostafa G, Redvanly RD, Kelley MJ, Sing RF, et al. Cardiopulmonary arrest occurring in the radiology department: patient characteristics, incidence, and outcomes. Am Surg. 2011;77(3):273–6.
373. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007; 298(22):2644–53. doi:10.1001/jama.298.22.2644.
374. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489–99. doi:10.1001/jama.2009.56.
375. Albertson TE, Chenoweth J, Ford J, Owen K, Sutter ME. Is it prime time for alpha2-adrenocepter agonists in the treatment of withdrawal syndromes? J Med Toxicol. 2014;10(4):369–81. doi:10.1007/s13181-014-0430-3.
376. Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. Ann Pharmacother. 2009;43(12):2064–74. doi:10.1345/aph.1M310.
377. Dasta JF, Kane-Gill SL, Pencina M, Shehabi Y, Bokesch PM, Wisemandle W, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. Crit Care Med. 2010;38(2):497–503. doi:10.1097/CCM.0b013e3181bc81c9.
378. Gagnon DJ, Riker RR, Glisic EK, Kelner A, Perrey HM, Fraser GL. Transition from dexmedetomidine to enteral clonidine for ICU sedation: an observational pilot study. Pharmacotherapy. 2015;35(3):251–9. doi:10.1002/phar.1559.
379. Drees JC, Stone JA, Olson KR, Meier KH, Gelb AM, Wu AH. Clinical utility of an LC-MS/MS seizure panel for common drugs involved in drug-induced seizures. Clin Chem. 2009;55(1):126–33. doi:10.1373/clinchem.2008.110858.
380. Auriel E, Regev K, Korczyn AD. Nonsteroidal anti-inflammatory drugs exposure and the central nervous system. Handb Clin Neurol. 2014;119:577–84. doi:10.1016/B978-0-7020-4086-3.00038-2.
381. Finkelstein Y, Hutson JR, Freedman SB, Wax P, Brent J, Toxicology Investigators Consortium Case Registry. Drug-induced seizures in children and adolescents presenting for emergency care: current and emerging trends. Clin Toxicol (Phila). 2013;51(8): 761–6. doi:10.3109/15563650.2013.829233.
382. Thundiyil JG, Rowley F, Papa L, Olson KR, Kearney TE. Risk factors for complications of drug-induced seizures. J Med Toxicol. 2011;7(1):16–23. doi:10.1007/s13181-010-0096-4.
383. Rubinstein E. History of quinolones and their side effects. Chemotherapy. 2001;47 Suppl 3:3–8. doi:57838; discussion 44–8.
384. Ruha AM, Levine M. Central nervous system toxicity. Emerg Med Clin North Am. 2014;32(1):205–21. doi:10.1016/j.emc.2013.09.004.
385. Cock HR. Drug-induced status epilepticus. Epilepsy Behav. 2015. doi:10.1016/j.yebeh.2015.04.034.
386. Rolland B, Jaillette E, Carton L, Bence C, Deheul S, Saulnier F, et al. Assessing alcohol versus baclofen withdrawal syndrome in patients treated with baclofen for alcohol use disorder. J Clin Psychopharmacol. 2014;34(1):153–6. doi:10.1097/JCP.0000000000000054.
387. Aranko K, Henriksson M, Hublin C, Seppalainen AM. Misuse of zopiclone and convulsions during withdrawal. Pharmacopsychiatry. 1991;24(4): 138–40. doi:10.1055/s-2007-1014457.
388. Barrueto Jr F, Green J, Howland MA, Hoffman RS, Nelson LS. Gabapentin withdrawal presenting as status epilepticus. J Toxicol Clin Toxicol. 2002;40 (7):925–8.
389. Kofler M, Arturo Leis A. Prolonged seizure activity after baclofen withdrawal. Neurology. 1992;42(3 Pt 1): 697–8.
390. Sethi PK, Khandelwal DC. Zolpidem at supratherapeutic doses can cause drug abuse, dependence and withdrawal seizure. J Assoc Physicians India. 2005;53:139–40.
391. Wang LJ, Ree SC, Chu CL, Juang YY. Zolpidem dependence and withdrawal seizure – report of two cases. Psychiatr Danub. 2011;23(1):76–8.
392. Barry JD, Wills BK. Neurotoxic emergencies. Neurol Clin. 2011;29(3):539–63. doi:10.1016/j.ncl.2011.05.006.
393. Lameris AL, Monnens LA, Bindels RJ, Hoenderop JG. Drug-induced alterations in Mg^{2+} homoeostasis. Clin Sci (Lond). 2012;123(1):1–14. doi:10.1042/CS20120045.
394. Nielsson MS, Christiansen CF, Johansen MB, Rasmussen BS, Tonnesen E, Norgaard M. Mortality in elderly ICU patients: a cohort study. Acta Anaesthesiol Scand. 2014;58(1):19–26. doi:10.1111/aas.12211.
395. Giraud T, Dhainaut JF, Vaxelaire JF, Joseph T, Journois D, Bleichner G, et al. Iatrogenic complications in adult intensive care units: a prospective two-center study. Crit Care Med. 1993;21(1): 40–51.
396. Askari M, Eslami S, Louws M, Wierenga PC, Dongelmans DA, Kuiper RA, et al. Frequency and nature of drug-drug interactions in the intensive care unit. Pharmacoepidemiol Drug Saf. 2013;22 (4):430–7. doi:10.1002/pds.3415.
397. Seidling HM, Storch CH, Bertsche T, Senger C, Kaltschmidt J, Walter-Sack I, et al. Successful strategy to improve the specificity of electronic statin-drug interaction alerts. Eur J Clin Pharmacol. 2009;65 (11):1149–57. doi:10.1007/s00228-009-0704-x.
398. Bond CA, Raehl CL. Pharmacist-provided anticoagulation management in United States

hospitals: death rates, length of stay, Medicare charges, bleeding complications, and transfusions. Pharmacotherapy. 2004;24(8):953–63.
399. Bond CA, Raehl CL. Clinical and economic outcomes of pharmacist-managed aminoglycoside or vancomycin therapy. Am J Health Syst Pharm. 2005;62(15):1596–605. doi:10.2146/ajhp040555.
400. Bond CA, Raehl CL. Clinical and economic outcomes of pharmacist-managed antimicrobial prophylaxis in surgical patients. Am J Health Syst Pharm. 2007;64(18):1935–42. doi:10.2146/ajhp060631.
401. Hahn L, Beall J, Turner RS, Woolley TW, Hahn M. Pharmacist-developed sedation protocol and impact on ventilator days. J Pharm Pract. 2013; 26(4):406–8. doi:10.1177/0897190012467209.
402. Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA. 1999;282(3): 267–70.
403. MacLaren R, Bond CA. Effects of pharmacist participation in intensive care units on clinical and economic outcomes of critically ill patients with thromboembolic or infarction-related events. Pharmacotherapy. 2009;29 (7):761–8. doi:10.1592/phco.29.7.761.
404. Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. Crit Care Med. 2008;36(2):427–33. doi:10.1097/01.CCM.0000300275.63811.B3.
405. Ng TM, Bell AM, Hong C, Hara JM, Touchette DR, Danskey KN, et al. Pharmacist monitoring of QTc interval-prolonging medications in critically ill medical patients: a pilot study. Ann Pharmacother. 2008;42(4):475–82. doi:10.1345/aph.1K458.
406. Petitta A. Assessing the value of pharmacists' health-systemwide services: clinical pathways and treatment guidelines. Pharmacotherapy. 2000;20 (10 Pt 2):327S–32.
407. Preslaski CR, Lat I, MacLaren R, Poston J. Pharmacist contributions as members of the multidisciplinary ICU team. Chest. 2013;144(5):1687–95. doi:10.1378/chest.12-1615.
408. Schumock GT, Butler MG, Meek PD, Vermeulen LC, Arondekar BV, Bauman JL, et al. Evidence of the economic benefit of clinical pharmacy services: 1996–2000. Pharmacotherapy. 2003;23(1):113–32.
409. Schumock GT, Meek PD, Ploetz PA, Vermeulen LC. Economic evaluations of clinical pharmacy services – 1988–1995. The Publications Committee of the American College of Clinical Pharmacy. Pharmacotherapy. 1996;16(6):1188–208.
410. Bond CA, Raehl CL. Clinical pharmacy services, pharmacy staffing, and hospital mortality rates. Pharmacotherapy. 2007;27(4):481–93. doi:10.1592/phco.27.4.481.
411. Neuraz A, Guerin C, Payet C, Polazzi S, Aubrun F, Dailler F, et al. Patient mortality is associated with staff resources and workload in the ICU: a multicenter observational study. Crit Care Med. 2015;43(8):1587–94. doi:10.1097/CCM.0000000000001015.
412. Latham HE, Pinion A, Chug L, Rigler SK, Brown AR, Mahnken JD, et al. Medical ICU admissions during weekday rounds are not associated with mortality: a single-center analysis. Am J Med Qual. 2014;29(5):423–9. doi:10.1177/1062860613502218.
413. Wilcox ME, Chong CA, Niven DJ, Rubenfeld GD, Rowan KM, Wunsch H, et al. Do intensivist staffing patterns influence hospital mortality following ICU admission? A systematic review and meta-analyses. Crit Care Med. 2013;41(10):2253–74. doi:10.1097/CCM.0b013e318292313a.
414. Curry SC, Brooks DE, Skolnik AB, Gerkin RD, Glenn S. Effect of a medical toxicology admitting service on length of stay, cost, and mortality among inpatients discharged with poisoning-related diagnoses. J Med Toxicol. 2015;11(1):65–72. doi:10.1007/s13181-014-0418-z.
415. Chittawatanarat K, Pamorsinlapathum T. The impact of closed ICU model on mortality in general surgical intensive care unit. J Med Assoc Thai. 2009;92 (12):1627–34.
416. Methaneethorn J, Chamnansua M, Kaewdang N, Lohitnavy M. A pharmacokinetic drug-drug interaction model of simvastatin and verapamil in humans. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:5711–4. doi:10.1109/EMBC.2014.6944924.
417. Methaneethorn J, Chaiwong K, Pongpanich K, Sonsingh P, Lohitnavy M. A pharmacokinetic drug-drug interaction model of simvastatin and clarithromycin in humans. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:5703–6. doi:10.1109/EMBC.2014.6944922.
418. Bastida C, Also MA, Pericas JM, Letang E, Tuset M, Miro JM. Rhabdomyolysis and severe hepatotoxicity due to a drug-drug interaction between ritonavir and simvastatin. Could we use the most cost-effective statin in all human immunodeficiency virus-infected patients? Enferm Infecc Microbiol Clin. 2014;32(9):579–82. doi:10.1016/j.eimc.2014.03.014.
419. Prom R, Umscheid CA, Kasbekar N, Spinler SA. Effect of simvastatin-amiodarone drug interaction alert on appropriate prescribing. Am J Health Syst Pharm. 2013;70(21):1878–9. doi:10.2146/ajhp120553.
420. Tiessen RG, Lagerwey HJ, Jager GJ, Sprenger HG. Drug interaction caused by communication problems. Rhabdomyolysis due to a combination of itraconazole and simvastatin. Ned Tijdschr Geneeskd. 2010;154:A762.

421. Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. Ann Pharmacother. 2001;35(1):26–31.
422. Kanathur N, Mathai MG, Byrd Jr RP, Fields CL, Roy TM. Simvastatin-diltiazem drug interaction resulting in rhabdomyolysis and hepatitis. Tenn Med. 2001;94(9):339–41.
423. Ishigami M, Kawabata K, Takasaki W, Ikeda T, Komai T, Ito K, et al. Drug interaction between simvastatin and itraconazole in male and female rats. Drug Metab Dispos. 2001;29(7):1068–72.
424. Nakai A, Nishikata M, Matsuyama K, Ichikawa M. Drug interaction between simvastatin and cholestyramine in vitro and in vivo. Biol Pharm Bull. 1996;19(9):1231–3.
425. Kohl BA, Fortino-Mullen M, Praestgaard A, Hanson CW, Dimartino J, Ochroch EA. The effect of ICU telemedicine on mortality and length of stay. J Telemed Telecare. 2012;18(5):282–6. doi:10.1258/jtt.2012.120208.