Adverse Drug Reactions in the Intensive Care Unit

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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
describing various types. ADRs will be summarized by organ system, incorporating postmarketing 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 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 | |
| Neuronal 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*)

**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        | +1  | 0  |
| 2        | +2  | -1 |
| 3        | +1  | 0  |
| 4        | +2  | -1 |
| 5        | -1  | +2 |
| 6        | -1  | +1 |
| 7        | +1  | 0  |
| 8        | +1  | 0  |
| 9        | +1  | 0  |
| 10       | +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.

**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

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**Table 3** Types of ADRs

| 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 American College of Medical Toxicology ToxIC Database available at [http://www.acmt.net/cgi/page.cgi/ToxIC1.html](http://www.acmt.net/cgi/page.cgi/ToxIC1.html)

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**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](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-nitrosoylation 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].

### 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 ≥ 2.0 and N ≥ 30

| Classification      | Generic name       | FAERS |       |       |       | MASE |       |       |
|---------------------|--------------------|-------|-------|-------|-------|------|-------|-------|
|                     |                    |       | 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 per 1000 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, 51].

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             |
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...
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.credibledmeds.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

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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, ceftiraxone, cefotaxime, cefpodoxim, cephalaxin, 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 |

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

| Drug                          | AZCERT risk of TdP | Possible | Known | Conditional |
|-------------------------------|--------------------|---------|-------|-------------|
| **Antiarrhythmics**           |                    |         |       |             |
| Amiodarone                    |                    | X       |       |             |
| Disopyramide                  |                    | X       |       |             |
| Dofetilide                    |                    | X       |       |             |
| Dronedarone                   |                    | X       |       |             |
| Flecaïnidé                   |                    | X       |       |             |
| Ibutilide                     |                    | X       |       |             |
| Procainamidé                  |                    | 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       |       |             |
| Paroxetiné                    |                    | 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       |       |             |
| Ciprofloxacine                |                    | X       |       |             |
| Clarithromycin                |                    | X       |       |             |

(continued)
### Table 8 (continued)

| Drug                     | AZCERT risk of TdP |
|--------------------------|---------------------|
|                          | Possible | Known | Conditional |
| Erythromycin             | X        |       |             |
| Fluconazole              | X        |       |             |
| Gemifloxacin             | X        |       |             |
| Iloperidone              | X        |       |             |
| Itraconazole             | X        |       |             |
| Ketoconazole             | X        |       |             |
| Levofoxacin              | 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               | X        |       |             |
| **Immunosuppressant**    |          |       |             |
| Hydroxychloroquine       | X        |       |             |
| Tacrolimus               | X        |       |             |
| **Muscle relaxant**      |          |       |             |
| Solifenacin              | X        |       |             |
| Tizanidine               | X        |       |             |
| Tolterodine              | X        |       |             |
| **Phosphodiesterase inhibitor** | | | | |
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.

### 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 SvO2. Echocardiography can be used to differentiate circulatory shock.

| Type       | CO or SvO2 | CVP | Echocardiograph | Cardiac contractility |
|------------|------------|-----|-----------------|-----------------------|
| Distributive | Normal or high | Normal | Cardiac chambers | 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, SvO2 mixed venous oxygen saturation

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                                         | A1B, B2B                       | B1B         |              |              |
| Beta-blockers        | Nonselective                                      | A1B, B2B                       | B1B         |              |              |
| CCB                  | Dihydropyridine                                   | Amlodipine, nicardipine, and nifedipine | L-type CCB  |              |              |
| Diuretics            | Thiazide                                          | Hydrochlorothiazide             | inh. Na/Cl symporter |              |              |
| Diuretics            | Thiazide-like                                     | Metolazone                     | inh. Na/Cl symporter |              |              |
| Diuretics            | Potassium sparing                                 | Spironolactone                 | inh. Na/K exchanger and competitive aldosterone ant. |              |              |
| Diuretics            | 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 |              |
| Renin–angiotensin antagonists | ARBs   | Candesartan, irbesartan, losartan, and valsartan | ARB          |              |              |
| Sedative/hypnotics   | Propofol                                          | Decreased sympathetic outflow  | Decreased sympathetic outflow |              |              |
| Sedative/hypnotics   | Barbiturates                                      | Phenobarbital and pentobarbital | Decreased sympathetic outflow | Decreased sympathetic outflow |              |
| Vasodilators         | 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 successfully 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 SvO₂ (LoE I) 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].

**Vaspressors**
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 vasodilation 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 II 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
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 CO₂ 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 oncolytic 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.
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].

| 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                     |                | Fibrothorax           |
| Dopamine agonists             |                |                                  |                | ARDS                  |
| 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           |                | Bronchospasm                     |                | NCPE                  |
| Latex                         |                | Bronchospasm                     |                |                       |
| Minocycline                   |                | EP                               |                |                       |
| Nitrofurantoin                |                | Acute pneumonitis/ILD, subacute pneumonitis/ILD, PF | Acute pleuritis |                       |
| NSAIDS                        |                | Bronchospasm                     |                | NCPE                  |
| Salicylate                    |                | Bronchospasm                     |                |                       |

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)
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 ($\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg or P/F} \leq 300$), moderate ($100 < \text{P/F} \leq 200$), and severe ($\text{P/F} \leq 100$) [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 nalmefone 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
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.

| 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, sulfonyleureas |
| 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)
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, ...

| 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)
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
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 radiopaque 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/non-ionic) [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

### 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   | Contrast, amphotericin B, ACEI, NSAIDs         |
| Prerenal/hemodynamic  | Acetaminophen, aminoglycosides, amphotericin B, cephalosporins, cocaine |
| Intrarenal ATN        | Penicillins, cephalosporins, cocaine, sulfonamides, NSAIDs |
| Intrarenal 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)
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 cephalixin 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
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. 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                        |
|                              | Hydromorphone    | 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)
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., methylenedioxyamphetamine 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 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,
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].

Fluoroquinolones’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

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**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)
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 epilepsies 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]. Extrapulating 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].

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