Therapeutic Approach to the Critically Poisoned Patient

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Aggressive supportive care is the mainstay of treatment provided to patients in the intensive care unit (ICU). Basic aspects of care must be reevaluated or adjusted to account for unique aspects in the pathophysiology of the critically ill poisoned patient. This may include the use of gastrointestinal (GI) decontamination or the administration of antidotes. This chapter discusses the initial management and resuscitation of the critically ill poisoned patient. Subsequent chapters describe therapeutic decisions unique to particular drugs and xenobiotics and discuss specific antidotes in greater detail.

General Approach to Patient Data for the Poisoned Patient

The organization of data may be problem based (e.g., phenytoin overdose or hydrocarbon aspiration) or system based (i.e., pulmonary, cardiovascular, renal, or hematologic). The system-based approach, typically used for critical care patients, better organizes large quantities of data (e.g., liver failure following acetaminophen ingestion causing coagulopathy, increased intracranial pressure, and hepatopulmonary syndrome). For the toxicology patient, substance-specific problems and therapies should also be noted. The system-based approach prevents important therapeutic and organizational issues from being overlooked (Table 1). The system-based approach clearly identifies the number of organ system failures, a

Table 1 System-based approach to the poisoned intensive care unit patient

General
Vital signs: current HR, BP, RR, temperature
Avoid giving vital sign ranges (e.g., "systolic BP ranging from 50–180"), as this can be misleading and counterinformative
State vital signs that are "abnormal" (e.g., fever spikes, hypotension)
Input and outputs; weight
Cardiovascular
Cardiac biomarkers and ECG
Inotropes and vasopressors: dopamine, dobutamine, norepinephrine, epinephrine, phenylephrine, glucagon, high-dose insulin euglycemia
Advanced monitoring: CVP, PAP, PCWP, CO, SVR, SvO$_2$, stroke volume, IVC diameter and collapse, carotid velocity time integral
Echocardiogram, MRI, CT
Pulmonary
Ventilator settings
Mode and rate, V$_T$ (tidal volume), PEEP, FiO$_2$
Pressure support, if added to SIMV or CPAP modes
Report the patient's actual RR, V$_T$, and V$_E$ (minute volume)
Airway peak and plateau pressures, auto-PEEP
Arterial blood gases: pH, PCO$_2$, PO$_2$, SaO$_2$
Liberation parameters: NIF (MIP), rapid shallow breathing index
Chest x-ray and CT findings
Gastrointestinal
Liver function tests, amylase and lipase, albumin
Abdominal ultrasound and CT findings
Bowel function/elimination
Renal
Electrolytes, BUN, creatinine, anion gap, osmolar gap
Infectious diseases
Maximum temperature (minimum temperature when low), antibiotics (day number), positive cultures, cultures outstanding
WBC and bands
Neurologic
Sedation and paralysis; analgesia
Electroencephalographic findings
Hematologic
Coagulation studies, platelet count, DIC information
Endocrine
Blood glucose
Corticosteroid levels and results of stimulation tests
ICU housekeeping
Stress ulcer and DVT prophylaxis
Nutritional support (tube feedings or TPN)

(*continued*)

Table 1 (continued)

Central venous and arterial catheters, intraosseous lines
Peripheral intravenous access
Toxicology
Toxin or drug exposed to and route of exposure
Ongoing diagnostic testing (e.g., follow-up renal function, ECG)
Current gastrointestinal decontamination (e.g., whole bowel irrigation)
Specific therapies or antidotes

BP blood pressure, *BUN* blood urea nitrogen, *CO* cardiac output, *CPAP* continuous positive airway pressure, *CT* computerized tomography, *CVP* central venous pressure, *DIC* disseminated intravascular coagulation, *DVT* deep venous thrombosis, *ECG* electrocardiogram, *FiO$_2$* fraction of inspired oxygen, *HR* heart rate, *ICU* intensive care unit, *IVC* inferior vena cava, *MIP* maximum inspiratory pressure, *MRI* magnetic resonance imaging, *NIF* negative inspiratory force, *PAP* pulmonary artery pressure, *PCO$_2$* partial pressure of carbon dioxide, *PCWP* pulmonary capillary wedge pressure, *PEEP* positive end-expiratory pressure, *PO$_2$* partial pressure of oxygen, *RR* respiratory rate, *SaO$_2$* oxygen saturation in arterial blood, *SIMV* synchronized intermittent mandatory ventilation, *SvO$_2$* mixed venous oxygen saturation, *SVR* systemic vascular resistance, *TPN* total parenteral nutrition, *WBC* white blood cell count

criterion used to determine the need for ICU admission and to predict ICU mortality [1].

Patients with Toxicologic Exposures Admitted to an Intensive Care Unit

The American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) reported 101,141 exposure-related ICU admissions (3.5% of all toxicant exposures and 16.5% of all exposures managed in a health-care facility) in 2014 [2]. Of all the patients included in the NPDS, 7% had medical outcomes classified as "moderate" and 1% were classified as "major." For patients 20 years of age or older, 15% had medical outcomes classified as "moderate" and 2% as "major." Presumably patients with moderate or major effects were more likely to require admissions to the ICU. Moderate effect is defined by AAPCC as the patient exhibiting signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more

systemic in nature than minor symptoms. Examples include acid–base disturbances, high fever, disorientation, hypotension responsive to treatment, and isolated brief seizures. Major effect is defined by AAPCC as the patient exhibiting signs or symptoms that were life-threatening or resulted in significant residual disability or disfigurement. Examples include repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia, hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation. Patients experienced major effects for less than 24 h 29% of the time, between 24 h and 3 days 34% of the time, and between 3 days and 1 week 19% of the time. Since 2000, cases with more serious outcomes increased by 4.29% (95% CI 3.87–4.72%) per year. Some patients with less pronounced effects were also admitted to the ICU due to hospital requirements to admit all suicidal patients to the ICU in order for them to be closely monitored.

Initial Assessment

As with any unstable or critically ill patient, the ABCs (airway, breathing, circulation) of basic life support take priority (Level III recommendation). In the poisoned patient, therapeutic interventions and diagnostic evaluation often are initiated simultaneously (see ▶ Chap. 2, "The Diagnostic Process in Medical Toxicology"). Findings on physical examination often guide the initial therapy. Airway patency and ventilatory drive frequently are compromised in patients with decreased mental status and may need immediate intervention. The decision to administer certain antidotes such as thiamine, glucose, naloxone, flumazenil, and physostigmine is made early in the diagnostic stage, generally before the patient is admitted to the ICU. Although naloxone and flumazenil may obviate the need for intubation in selected patients, flumazenil should only be cautiously administered to patients who may have long-term benzodiazepine use or to patients who have co-ingested a benzodiazepine and drugs that lower the seizure threshold. The risk of a

flumazenil-induced seizure must be weighed against complications occurring during intubation (Level I recommendation). Further discussions of benzodiazepine poisoning and the use of flumazenil are found in ▶ Chaps. 45, "Anxiolytics, Sedatives, and Hypnotics," and ▶ 148, "Flumazenil." For further discussion about the role of physostigmine, see ▶ Chaps. 23, "Anticholinergic Syndrome," and ▶ 161, "Physostigmine". Decisions regarding GI decontamination, if any, which may include administration of single-dose activated charcoal (AC) and whole bowel irrigation (WBI) are also made early in the patient's course, likely before the patient arrives in the ICU. Currently, there is no role for gastric lavage. Diagnostic tests often need to be repeated to follow the ongoing effects of the toxicant (e.g., acid–base status in ethylene glycol ingestion) or to determine effectiveness of treatment (e.g., electrocardiogram after administration of sodium bicarbonate in patients with signs of sodium channel blockade, such as after overdose of tricyclic antidepressants [TCAs] or Type 1a or 1c antiarrhythmics, or trending of transaminases following toxic ingestions of acetaminophen [paracetamol]). Various types of toxicology laboratory screening or quantitative testing often are performed, and proper interpretation of the results is essential to making appropriate therapeutic decisions. Further information related to this aspect of the care of poisoned patients can be found in ▶ Chap. 2, "The Diagnostic Process in Medical Toxicology." Although GI decontamination if used should be initiated in the emergency department, the decision to continue GI decontamination in the ICU is usually toxicant specific and discussed later in this chapter.

Supportive Care Decisions

Airway Maintenance

The loss of airway-protective reflexes and concern for aspiration or the presence of respiratory failure dictates the need to secure the airway. Securing the airway should be accomplished by tracheal intubation as noninvasive ventilation is relatively

contraindicated in patients with hemodynamic instability, patients with inability to protect their airway, and patients with a full stomach (including pregnancy and obesity) [3]. Orotracheal intubation, if possible, is preferred over nasotracheal intubation for many reasons. Nasotracheal intubation causes a statistically significant increase in sinusitis [4–7], purulent and serous otitis [8], ventilator-associated pneumonia [9], and sepsis [10] and is technically more difficult compared with orotracheal intubation. Typically only a 6.0- or 6.5-mm endotracheal tube is used for nasotracheal intubation. These narrow tubes have increased airflow resistance compared with the larger diameter tubes used for orotracheal intubation. Airflow resistance increases after several days of intubation as secretions harden inside the tube and decrease the tube's diameter [11]. Increased airflow resistance can increase respiratory workload significantly. Should bronchoscopy be required (e.g., new infiltrates on chest x-ray, mucus plugging, lung collapse), the narrower, longer nasotracheal tube makes it more difficult, if not impossible, to pass a flexible bronchoscope.

An exception may be in patients with significant caustic injuries and swelling where nasotracheal intubation may be more practical than orotracheal intubation. In addition in patients with anticipated difficult airways, either nasotracheal intubation or an "awake orotracheal intubation" should be considered (Level III recommendation). Ingestion of caustic agents, with concomitant injury to the respiratory tract and oropharynx, requires special consideration in airway maintenance. Although airway obstruction is rare in patients who ingest caustic agents [12], airway patency is more at risk with the ingestion of solid rather than liquid caustic agents [13]. Only 11 of 33 children (33%) with either acid or alkali ingestions required intubation [14]. Seven children required immediate intubation for respiratory distress or airway obstruction, and the other four had minimal or no respiratory symptoms but were intubated after endoscopic findings of supraglottic edema. Most intubations after caustic ingestion can be done under direct visualization using standard direct laryngoscopic

techniques. The equipment for alternative methods of securing the airway (e.g., cricothyrotomy) should be in place before any paralytic or induction agent is given, however, in case the normal visual landmarks are obscured and orotracheal intubation cannot be accomplished. In the 11 intubated pediatric patients described above, no adverse consequences occurred as a result of orotracheal intubation [14].

Most patients are successfully intubated using a rapid sequence intubation (RSI) strategy which includes a period of preoxygenation. Preoxygenation prior to intubation assists in avoiding hypoxemia during the apneic period of RSI and decreases peri-intubation morbidity and mortality [15] (Level II-3 recommendation). However either due to an inability to adequately preoxygenate the patient or concerns that the patient may be difficult to intubate, strategies aside from RSI should be considered (Level III recommendation). While these strategies are well described, they have not been studied in the poisoned patient.

Delayed sequence intubation (DSI) temporarily separates the administration of the induction agent from the muscle relaxant in order to allow adequate preintubation preparation and preoxygenation [16, 17]. In DSI, patients are sedated with ketamine which causes dissociation and sedation while allowing for adequate preoxygenation before the administration of a muscle relaxant. This strategy is particularly useful in the delirious or agitated patient that cannot otherwise be preoxygenated. In one observational study, patients were induced with ketamine (starting dose of 1 mg/kg titrated to adequate sedation) and then preoxygenated for 3 min with either a non-rebreather or positive pressure ventilation (NIPPV) prior to the administration of a muscle relaxant [16]. Saturations increased from 89.9% prior to DSI to 98.8% afterward with an average increase of 8.9% (95% CI 6.4–10.9%). There were no complications and all patients were successfully intubated, aside from two patients that significantly improved and no longer required intubation.

Another potential strategy is an "awake intubation," where the patient is given a light sedative

such as ketamine but is mainly anesthetized with local anesthetics prior to intubation [18, 19]. An awake intubation can be attempted via direct visualization or with the assistance of a fiberoptic scope. This intubation strategy can be considered in patients requiring urgent intubation, but that may have a contraindication to receiving a sedative and muscle relaxant that impairs their ability to breathe. Patients with caustic injuries requiring intubation due to concerns of airway deterioration may be candidates for an awake intubation (Level III recommendation).

Apneic oxygenation is used to extend the safe apnea period beyond the time which can be achieved with preoxygenation and should be considered regardless of the method of intubation [17, 20] (Level II-3 recommendation). Even without respiratory effort, the pharynx can be filled with oxygen using a high-flow nasal cannula and acts as a reservoir [21]. During intubation, the aveoli will continue to take up oxygen that then diffuses into the bloodstream and prevents hypoxia. Patients were preoxygenated, paralyzed, intubated, and placed on a ventilator in one study [22]. They continued to be oxygenated at 1.0 FiO$_2$ but were not given any ventilation; no patients developed saturations less than 98% despite being paralyzed and not ventilated.

Respiratory Function

Adequacy of respiratory function must be assessed immediately after the airway is secured. The causes of respiratory failure can be divided into four groups (Table 2), as follows [23]:

1. Hypoxemic (type I) respiratory failure arises from the flooding or collapse of alveoli, resulting in intrapulmonary shunting. Patients are hypoxic but have a low or normal CO$_2$ concentration.
2. Hypercapnic (type II) respiratory failure is caused by inadequate alveolar ventilation from either decreased respiratory drive or an imbalance between respiratory load and respiratory muscle strength. Patients will have elevated CO$_2$ concentrations and may be hypoxic.

3. Postoperative (type III) respiratory failure is caused by pain leading to shallow breathing, atelectasis, hypoxemia, and narcotic administration to control pain, which further decreases respiratory drive and worsens atelectasis.
4. Shock-related (type IV) respiratory failure is caused by a combination of inadequate oxygen delivery to respiratory muscles and increased total-body metabolic demands.

Type I respiratory failure in the overdose patient typically is caused by aspiration or agents that cause the acute respiratory distress syndrome (ARDS) (e.g., salicylates). Type II respiratory failure can be caused by ingestion of drugs that decrease respiratory drive (e.g., narcotic or other sedative overdose) or cause respiratory muscle weakness (e.g., botulism). Type IV respiratory failure can be associated with any drug ingestion that causes myocardial depression or shock, such as calcium channel antagonists. Type III respiratory failure is not applicable to the overdose patient. The type of respiratory failure may change during a patient's hospitalization. For instance, patients may initiallly present with type IV respiratory failure from cardiogenic shock. As the patient's hemodynamics improve, they may be difficult to wean from the ventilator due to the development of type II respiratory failure from the accumulation of sedatives and analgesics administered in the ICU.

The therapeutic approach to each type of respiratory failure is determined by the underlying pathophysiology. Type I respiratory failure is treated with a high fraction of inspired oxygen (FiO$_2$) and the judicious use of positive end-expiratory pressure (PEEP). Some focal lung lesions, such as lesions from hydrocarbon aspiration, may not be PEEP responsive, however. In these situations, high levels of PEEP ($>$10 cm H$_2$O) may worsen the patient's condition by decreasing venous return (preload) and causing hypotension. If patients have high FiO$_2$ and PEEP requirements and are developing ARDS, the use of high-frequency oscillatory ventilation (HFOV), while controversial, may be considered [24, 25]. HFOV is a mode of ventilation that delivers small tidal volumes at high frequences in order to

Table 2 Classification of respiratory failure

	Type I: acute hypoxemic respiratory failure	Type II: hypercapnic	Type III: postoperative	Type IV: shock
Pathophysiology	Alveolar flooding Alveolar collapse	Decreased respiratory drive Increased respiratory workload Decreased respiratory muscle strength	Atelectasis (pain) Decreased respiratory drive from analgesics (narcotics)	Inadequate respiratory muscle perfusion with increased metabolic demands
Therapy	High FiO_2 PEEP Decrease pulmonary edema Treat pneumonia	Wake up/allow drugs to wear off Bronchodilators and suctioning Increase respiratory muscle endurance Correct metabolic abnormalities Intubation or NIPPV	Pain control Chest physical therapy Elevate head of bed	Treat underlying cause of the shock state Ventilator support
Overdose scenarios	Hydrocarbon aspiration, salicylates	Sedative overdose including narcotic or benzodiazepine overdose Bronchospasm Botulism	Not applicable	BB or CCA overdose Sepsis Mitochondrial inhibition

BB β-adrenergic blocking agents, *CCA* calcium channel antagonists, *FiO₂* fraction of inspired oxygen, *NIPPV* noninvasive positive pressure ventilation, *PEEP* positive end-expiratory pressure

maintain alveolar recruitment while avoiding injury from barotrauma [26]. Further details regarding the pathophysiology and mangement of ARDS can be found in ▶ Chap. 16, "Treatment of Acute Respiratory Distress Syndrome in the Poisoned Patient".

When type II (hypercapnic) respiratory failure is caused by decreased respiratory drive, minute volume (V_E) provided by the ventilator must be sufficient to maintain alveolar ventilation. Respiratory load and respiratory muscle strength are connected inseparably. Bronchoconstriction and increased secretions increase respiratory load. Impaired neuromuscular transmission or respiratory muscle problems (e.g., botulism, myopathy, or overuse fatigue) decrease respiratory muscle strength. If respiratory load increases or strength decreases to the point at which load is greater than strength, type II respiratory failure ensues. Treatment of increased respiratory load includes the

use of bronchodilators and frequent suctioning. Muscle strength can be increased by treatment of underlying causes and ventilator support until respiratory muscle strength has returned. Therapy for type IV respiratory failure is to provide ventilatory assistance while treating the shock state.

The ventilator mode to be used is dictated by the type of respiratory failure. In general, patients with type I (hypoxemic) or type IV (shock) respiratory failure should be managed with an assist/control (A/C) or continuous mandatory ventilation (CMV) mode, which decreases the patient's work of breathing (Level III recommendation). Use of A/C or CMV decreases but does not eliminate respiratory muscle work and decreases the patient's oxygen and metabolic requirements. The decreased oxygen requirement is particularly important when oxygen transfer from the airways to the blood is impaired (aspiration) or there is inadequate oxygen delivery (shock). Type II

(hypercapnic) respiratory failure typically is seen with drug-induced coma or paralysis and is managed with either a CMV or a synchronized intermittent mandatory ventilation (SIMV) mode (Level III recommendation). If the drug-induced coma or respiratory depression is from narcotics or benzodiazepines, administration of naloxone or flumazenil, respectively, will improve the patient's ventilatory function and can prevent the need for intubation (Level II-3 recommendation). The risks and benefits of administering naloxone or flumazenil should be carefully weighed when administering them to patients with chronic use of either opioids or benzodiazepines. If the patient is already intubated, naloxone or flumazenil should generally be avoided. However in patients that were intubated but known to have ingested opioids or benzodiazepines, reversal agents may allow the patient to be extubated sooner. In addition, these agents may be useful to reverse iatrogenic sedation that prolongs the time that the patient is intubated. Decreasing the duration of time that the patient is intubated may decrease ventilator-associated complications.

Patient workload in a patient-triggered SIMV mode has been shown to range from 49% to 118% of the workload expected from a spontaneously breathing subject [27, 28]. This is important because if the patient's type II (hypercapnic) respiratory failure is from muscular weakness, the use of the SIMV mode can exacerbate the muscular weakness and prolong time on the ventilator. If there is increased respiratory load from bronchoconstriction, care must be taken to avoid air trapping within the lung. Commonly called *auto-PEEP*, this dynamic hyperinflation of the lung occurs when a breath is delivered to the patient before the previous breath is completely exhaled. Adverse effects of auto-PEEP include hypotension, pulmonary barotrauma (e.g., pneumothorax), and ARDS. Auto-PEEP can be minimized by decreasing inspiratory time and maximizing expiratory time (i.e., decreasing the I:E ratio) and use of small tidal volumes (V_T), slow respiratory rates, and increased flow rates. If the provider is concerned about air trapping and *auto-PEEP*, they should check the plateau pressure or the alveolar pressure; it should be below 30 cm H_2O. If air trapping is present, the patient should be immediately removed from the ventilator and have their chest manually decompressed before being placed back on the ventilator with new settings.

When the patient has been intubated and initial ventilator settings chosen, further information may be obtained from serial arterial blood gas measurements, bedside observations, and patient–ventilator interactions. Arterial blood gases (ABGs) assess the patient's acid–base status, arterial oxygenation, and ventilation. Venous blood gases (VBGs) can also assess the acid–base status and ventilation but not oxygenation. Initiation of mechanical ventilation may cause rapid deterioration in some poisoned patients if appropriate V_E, $PaCO_2$, and pH are not maintained. Intoxicants such as salicylates, methanol, and ethylene glycol produce severe, life-threatening acidosis for which the patient naturally compensates with a respiratory alkalosis. If the patient is well sedated, paralyzed, or fatigued, he or she may not be able to increase V_E to compensate for a metabolic acidosis. When the amount of V_E set on the ventilator is less than the V_E the patient was maintaining before intubation, significant acid–base changes may occur and precipitate disastrous events. Loss of compensatory respiratory alkalosis in salicylate intoxication causes acidemia and further movement of salicylate into the central nervous system that may precipitate seizures and death. While intubation may still be indicated, the physician must be vigilant in adjusting the ventilator settings to maintain appropriate ventilation. In the setting of salicylate intoxication, for instance, the rate should be set to match the patient's peak respiratory rate. It is important to monitor ABGs and make appropriate ventilator changes to keep pH, $PaCO_2$, and PaO_2 in the desired ranges.

When determining the ventilator settings, a lung protective strategy should be employed [29, 30]. Lung protective strategies prevent the development of ARDS from barotrauma and oxygen toxicity (Level II-2 recommendation). While these strategies are commonly used in the ICU, they have not been studied in the poisoned patient. Many intoxicated patients are intubated for

reasons other than for an acute lung injury (e.g., respiratory depression, altered mental status, delirium). In these situations, the FiO_2 should be titrated down as long as the PaO_2 remains greater than 90 mmHg. The patient's initial V_T should be set to 6 ml/kg and titrated based on their ABG and oxygen saturation in order to avoid barotrauma and toxicity from hyperoxygenation.

Frequent physical examination is necessary to evaluate the patient's comfort and interactions with the ventilator. If the patient is not synchronizing well with the ventilator, the cause of the patient's discomfort should be investigated. Ventilator settings must be adjusted to stabilize and comfort the patient rather than reflexively increasing sedation or paralyzing the patient. In addition, it should be ensured that the patient is receiving adequate analgesia. The endotracheal tube and ventilator are painful and most sedatives do not control pain. With adequate analgesia, most patients remain lightly sedated and synchronize well with the ventilator. In addition to improving patient comfort, proper administration of analgesics can decrease the patient's sedative requirement, preventing delirium and other complications. Much information can be obtained by observing the patient's pattern of breathing. Most ventilators display airway pressure versus time and flow versus time waveforms. Careful analysis of these waveforms yields important clues as to the cause of the patient's discomfort [31]. Waveform analysis is beyond the scope of this chapter and can be achieved best with the help of an experienced intensivist. Some maneuvers that can make the patient more comfortable on the ventilator include increasing V_E (by increasing V_T, respiratory rate, or both), decreasing triggering sensitivity or switching to flow triggering, and increasing flow rates [28]. Other maneuvers include treating pain, anxiety, and derangements of gas exchange or respiratory mechanics [31]. When these changes fail to match the ventilator to the patient, judicious use of sedation is required. Paralysis in poisoned patients usually is only reserved for specific indications (discussed later).

Circulation and Hemodynamics

After establishing an airway and supporting respiratory function, the next priority is assessment of circulatory status. In the poisoned patient, cardiovascular abnormalities commonly seen are hypertension, hypotension, cardiac arrhythmias, or conduction disturbances.

Hypertension

Elevated blood pressure in the poisoned patient may or may not be the result of exposure to any one of many substances (Table 3). Other causes of elevated blood pressure should be considered and include [1] withdrawal (i.e., benzodiazepine or ethanol withdrawal); [2] the discontinuation of a therapeutically prescribed medication, such as clonidine or minoxidil, causing rebound hypertension; and [3] inadequately treated or untreated underlying hypertension.

Treatment of hypertension is determined by its underlying cause. When hypertension is caused by overdoses of drugs with direct adrenergic activity, such as amphetamines, ephedrine, or pseudoephedrine, direct vasodilators, such as phentolamine or nitroprusside [32], may be required (Level III recommendation). Other commonly used agents include short-acting dihydropyridine calcium channel antagonists, such as nicardipine and clevidipine. When hypertension is caused by drugs with indirect adrenergic activity or by drug-of-abuse withdrawal, sedation with benzodiazepines [33, 34] may be the treatment of choice (Level II-2 recommendation). Pharmaceutical drug withdrawal can be treated by the reinstitution of the causative agent or use of another agent that attenuates the signs and symptoms. The physiology and treatment of withdrawal states are described in detail in ▶ Chap. 27, "Withdrawal Syndromes". Combining direct vasodilators, such as oral nifedipine or parenteral nitroprusside, and sedatives may be necessary in cases of severe hypertension resulting from any cause. For sympathomimetic-induced hypertension, such as seen with

Table 3 Common examples of toxicants causing hypertension

Direct adrenergic agonists
Albuterol
Epinephrine
Ergotamines
Methoxamine
Midodrine
Phenylephrine
Indirect adrenergic agonists
Amphetamine and derivatives
Cocaine
Fenfluramine
Ketamine
LSD
Methylphenidate
Monoamine oxidase inhibitors
Phencyclidine
Serotonergic agonists
Mixed direct and indirect adrenergic agonists
α-2 agonists (initially and only temporarily)
Ephedrine
Ergotamine derivatives
Oxymetazoline
Phenylpropanolamine
Pseudoephedrine
Tetrahydrozoline
Anticholinergic agents
Atropine and derivatives
First-generation antihistamines
Tricyclic antidepressants
Other agents
Nicotine
Scorpion venom
Drug-of-abuse withdrawal
Benzodiazepines
Ethanol
Other sedatives or hypnotics
Pharmaceutical drug withdrawal
Clonidine (and other α-2 agonists)
Minoxidil
Propranolol
Metoprolol
Methyldopa
Benzodiazepines

LSD lysergic acid diethylamide, *PCP* phenylcyclohexyl piperidine

cocaine or amphetamines, administration of a β-adrenergic blocker alone may cause unopposed α-adrenergic stimulation and worsen hypertension (Level III recommendation). Large ingestions of α-2 agonists can initially cause hypertension. However, this is temporary and the patient is at risk of becoming hypotensive. If hypertension from α-2 agonists is treated, only short-acting agents that can be rapidly removed (e.g., nicardipine, nitroglycerin) should be administered (Level III recommendation).

Hypotension and Shock

Shock is the inability to deliver oxygen at a cellular level where the consumption of oxygen (VO_2) is greater than the delivery of oxygen (DO_2) [35]. Clinically, it appears as the constellation of hypotension, tachycardia, decreased or altered mentation, and oliguria or anuria. Laboratory values consistent with dysfunction of aerobic metabolism include hyperlactatemia and metabolic acidosis. Of patients who receive fluid resuscitation for shock, 85% have inadequate oxygen delivery to the tissues despite normalization of vital signs and urine output, referred to as cryptogenic shock [36]. Cryptogenic shock is diagnosed by biomarkers such as serial lactic acid concentrations and either ABGs or VBGs. The goal of circulatory resuscitation is to return VO_2 and DO_2 to normal and not simply to "fix the vital signs."

The initial assessment of the poisoned patient in shock is to determine the physiologic cause of the inadequate DO_2. DO_2 is the product of arterial oxygen content (CaO_2) and cardiac output (Q_T):

$$DO_2 = CaO_2 \times Q_T$$

CaO_2 is determined primarily by hemoglobin concentration and saturation:

$$\begin{aligned} CaO_2 = &\ (1.39 \text{ mL O}_2/\text{g hemoglobin} \\ &\times \text{g hemoglobin/dL} \times SaO_2) \\ &+ (0.0031 \text{ mL/dL/mmHg} \times PaO_2) \end{aligned}$$

Cardiac output (Q_T) is the product of heart rate (HR) and stroke volume (SV):

$$Q_T = HR(beats/min) \times SV(mL/beat)$$

SV is determined by left ventricular preload, contractility, and afterload. Physiologic causes of inadequate DO_2 in the poisoned patient may be the result of decreased hemoglobin concentration or saturation, decreased left ventricular preload (hypovolemia), decreased afterload (vasodilation), or impaired cardiac contractility.

Interruption of oxygen use at the molecular level is another cause of inadequate DO_2 in the poisoned patient. Specifically, abnormal hemoglobins (i.e., methemoglobin, sulfhemoglobin, or carboxyhemoglobin [37–39]) and toxins that disrupt the mitochondrial electron transport chain (e.g., cyanide, hydrogen sulfide, or sodium azide [40–42]) prevent the use of oxygen at the molecular level. Ineffective oxygen use may also occur from the disruption of metabolic processes, such as the uncoupling of oxidative phosphorylation (e.g., salicylate and dinitrophenol ingestions). In addition, impairment of the redox potential (NAD:NADH) disrupts oxidative processes as can occur from ethanol. Elevated plasma lactate concentration accompanying a metabolic acidosis is often a marker of these toxicities. It is a by-product of anaerobic metabolism of glucose when pyruvate is shunted to lactic acid [43].

$$Pyruvate + NADH + H^+$$
$$\Leftrightarrow Lactate + NAD^+$$
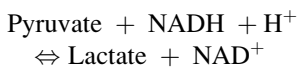
Lactic acidosis develops from an inequality between the production and breakdown of lactate, which is normally cleared by the liver and kidneys [44]. There are two forms of lactic acidosis as classified by Cohen and Woods in 1976 (Table 4) [45]. Type A lactic acidosis occurs from inadequate oxygen delivery [46]. While more common than Type B, both can be present at the same time. Carbon monoxide is an example of a toxicant producing a Type A lactic acidosis. Type B lactic acidosis occurs without evidence of poor tissue perfusion or oxygenation and is classifed into 3 subtypes [47, 48]. Subtype B1 occurs with systemic disease (e.g., malignancy, ketoacidosis); type B2 is from medications, drugs, or toxicants; and type B3 is from inborn errors of metabolism.

Table 4 Causes of lactic acidosis

Hypoxic (Type A)	Non-hypoxic (Type B)
Ischemia (e.g., cardiac arrest)	Delayed clearance (e.g., hepatic dysfunction)
Global hypoxia (e.g., carbon monoxide)	Pyruvate dehydrogenase dysfunction (e.g., thiamine depletion)
Respiratory failure (e.g., asthma)	Uncoupling of oxidative dysfunction (e.g., salicylates)
Regional hypoperfusion (e.g., mesenteric ischemia)	Accelerated aerobic glycolysis (e.g., seizures)

Examples of toxicants that produce a type B lactic acidosis include uncouplers (e.g., salicylates, dintirophenol), biguanides such as metformin, and methanol. The normal plasma lactate concentration is 0.5–1 mmol/L (4.5–9 mg/dl). Hyperlactatemia is defined as a concentration between 2 and 4 mmol/L (18–36 mg/dl) without a metabolic acidosis, while lactic acidosis is defined as a concentration greater than 5 mmol/L (45 mg/dl) with a metabolic acidosis [47]. Mortality is increased nearly threefold when lactic acidosis accompanies low-flow states with higher lactate concentrations associated with worse outcomes [49, 50]. A case–control study evaluated serum lactate concentraiton in drug overdoses at two urban teaching hospitals that were affiliated with a regional poison center [51]. Controls included consecutive drug overdoses admitted over a 1-year period surviving until hospital discharge. Cases were patients admitted over a 7-year period who died. The study consisted of 50 cases and 100 controls. The mean lactate concentration was 9.88 ± 6.7 mmol/L (89 mg/dl) for cases and 2.76 ± 2.9 mmol/L (25 mg/dl) for controls ($p < 0.001$). A lactate concentration of 3.0 mmol/L (27 mg/dl) conferred a 15.8-fold increase in odds of fatality ($p < 0.001$). Serum lactate concentrations were also evaluted in an 8-year retrospective review of all 110 β-adrenergic antagonist overdoses admitted to an ICU [52]. Serum lactate concentration (median 1.79 mmol/L; 10–90% percentiles 0.8–5.6) (19 mg/dl [7.2–50.5]) was the most significantly different parameter on admission between

survivors and fatalities (p = 0.0008). Six patients who presented with lactate concentrations >6 mmol/L (45 mg/dl) had prolonged prehospital cardiac arrests. Four patients died in the ICU despite lactate concentrations under 3.0 mmol/L (27 mg/dl). While a lactate >3 mmol/L (27 mg/dl) was associated with a 5.4-fold increased odd of mortality (OR 5.4, 95% CI 1.3–22.0), it only had a sensitivity of 55%, specificity of 80%, positive predictive value of 21%, negative predictive value of 95%, and an accuracy of 78%. The authors concluded that while serum lactate concentrations are useful, caution should be applied when using them to predict final outcome.

Decreased hemoglobin concentration may be the result of GI bleeding (e.g., gastric erosions from iron or nonsteroidal anti-inflammatory drug ingestion), intravascular hemolysis (e.g., arsine gas exposure), decreased production (e.g., benzene), or various chronic medical conditions (e.g., renal failure or cancer). Hemoglobin concentration is easily measured, and the administration of blood products may be indicated while the cause of the anemia is investigated. In acute bleeds, hemoglobin concentrations can be initially falsely elevated. While not studied in poisoned patients, recent studies advocate for conservative transfusion strategies in patients not in shock [53, 54]. When patients on anticoagulants are hemorrhaging, they should be reversed. Vitamin K antagonists (e.g., warfarin) can be reversed with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). Advantages of PCC include smaller volume and faster reversal. Unfortuantely, it is more expensive and is associated with thrombotic complications [55]. Patients on newer oral anticoagulants are more difficult to treat as it is unclear if they can be reversed. Dabigatran-related hemorrhage can be reversed with idarucizumab [56, 57]. Other potential reversal modalities include PCC and hemodialysis [58, 59]. While not currently approved, andexanet alfa is being studied to reverse hemorrhage from factor Xa inhibitors (e.g., apixaban and rivaroxaban) [60]. A full discussion of the management of significant bleeding from oral anticoagulants can be found in ▶ Chap. 68, "Oral Anticoagulants." Causes and treatment of decreased hemoglobin

saturation were addressed previously in the discussion of type I respiratory failure (see Table 2).

Hypovolemia in the poisoned patient may be caused by GI losses (e.g., organophosphates, cathartics, bleeding), renal losses (e.g., lithium or diuretics), redistribution (e.g., caustic burns or snake envenomations), or increased insensible losses (e.g., fever from sympathomimetics or salicylates). Signs of hypovolemia include dry mucous membranes, narrow pulse pressure, decreased urine output, and low cardiac output. Certain vasodilated shock states, such as liver failure from either acetaminophen overdose or *Amanita* mushroom poisoning or thyroid storm following thyroxine overdose, present with a clinical picture more consistent with sepsis: hypotension, warm extremities, a wide pulse pressure, and increased cardiac output.

Cardiac Dysrhythmias and Conduction Abnormalities

Cardiac depression, dysrhythmias, cardiac conduction abnormalities, or a combination of all three may cause shock from *impaired cardiac contractility.* Impaired cardiac contractility may be caused by β-adrenergic blocking agents or cocaine-induced myocardial ischemia and manifests as hypotension, narrow pulse pressure, low cardiac output, jugular venous distention, a gallop rhythm, and crackles in the lungs. Crackles are not present on examination with patients in right heart failure with preserved left ventricular function.

An electrocardiogram should be obtained in poisoned patients to assess for dysrhythmias, cardiac conduction defects, heart rate, and wave intervals (PR, QRS, QT), which may give clues as to the poison, the severity of the poisoning, and the treatment (Level III recommendation). The relationships between heart rate, QRS duration, and possible causes are listed in Table 5. Specific therapies are reviewed in ▶ Chaps. 21, "Cardiac Conduction and Rate Disturbances", and ▶ 22, "Toxicant-Induced Torsade de Pointes", and in chapters dealing with individual toxicants.

Torsades de Pointes, a form of ventricular tachycardia associated with a long QT interval, also may impair cardiac output. Although other causes such as electrolyte abnormalties exist,

Table 5 Examples of xenobiotic association between heart rate and QRS duration

Heart rate	Narrow QRS complex	Wide QRS complex
Tachycardia	α-Adrenergic agonists	Aberrant conduction
	Amphetamines	Antihistamines
	Anticholinergic agents	Cocaine
	Theophylline	Propoxyphene
		Sodium channel blockers
		Thioridazine
		Tricyclic antidepressants
Bradycardia	α-Adrenergic lytic agents	β-Adrenergic blocking agents
	β-Adrenergic blocking agents	Calcium channel antagonists
	Calcium channel antagonists	Hyperkalemia
	Cardiac glycosides	
	Ciguatoxin	
	Class Ia antiarrhythmics	
	Sodium channel blockers (open)	
	Tetrodotoxin	

torsades des pointes is often drug related. Medications that cause torsades des pointes, its pathophysiology, and its treatment are reviewed in ▶ Chap. 22, "Toxicant-Induced Torsade de Pointes" and in Table 6.

Fluid Resuscitation

Fluid resuscitation of the poisoned patient must be individualized. Many patients, especially patients found in coma many hours after their ingestion, are volume depleted (e.g., GI losses, fever, insensible losses). Volume depletion usually is not the acute cause of shock in poisoned patients but may be a contributing cause. Shock may be caused by vasodilation, myocardial depression, chemically induced hemoglobinopathy, or a combination of these. The usual approach of administering fluids until clinical improvement (e.g., improved blood pressure, mentation, adequate urine output) or development of a complication (i.e., pulmonary edema or worsening gas exchange) should be

Table 6 Examples of toxic causes of torsades des pointes

Antiarrhythmics
Amiodarone
Flecainide
Ibutilide
Moricizine
Procainamide
Quinidine
Sotalol
Antibiotics/antifungals
Azithromycin
Ciprofloxacin
Erythromycin
Fluconazole
Gemifloxacin
Itraconazole
Ketoconazole
Levofloxacin
Moxifloxacin
Antipsychotics
Chlorpromazine
Haloperidol
Olanzapine
Paliperidone
Perphenazine
Prochlorperazine
Promethazine
Quetiapine
Thioridazine
Thiothixene
Trifluoperazine
Ziprasidone
Cyclic antidepressants
Amitriptyline
Amoxapine
Desipramine
Doxepin
Imipramine
Nortriptyline
Serotonin reuptake inhibitors
Citalopram
Escitalopram
Fluoxetine
Mirtazapine
Paroxetine
Sertraline
Venlafaxine
Miscellaneous
Arsenic
Astemizole

(*continued*)

Table 6 (continued)

Chloroquine
Cisapride
Cocaine
Diphenhydramine
Erythromycin
Indapamide
Methadone
Ondansetron
Organophosphates
Pentamidine
Terfenadine
Thallium

modified in the poisoned patient (Level III recommendation). Initial resuscitation measures should include the administration of intravenous crystalloid fluid, but when appropriate, vasopressor infusion should be started early in the course of the resuscitation. Vasopressors or inotropes may be more appropriate than continued fluid administration in poisoned patients with a distributive shock (e.g., from vasodilators) or cardiogenic shock (e.g., from negative inotropes). Some patients require the placement of a central venous catheter to determine cardiac filling status and to optimize fluid and vasopressor therapy. In addition, bedside sonography is used to determine volume responsiveness and estimate cardiac contractility to further guide resuscitation [61, 62].

The debate regarding the most effective fluid to be used in the resuscitaiton of poisoned patients parallels the debate in critical care medicine in general [63–66]. The ideal fluid would have a chemical composition similar to that of extracellular fluid, would not accumulate in tissues, would not cause adverse metabolic effects, and is cost-effective [67]. Resuscitation fluids are broadly categorized as either colloid or crystalloid solutions. Colloids are suspensions of molecules within a carrier solution that are relatively incapable of crossing the capillary membrane, while crystalloids are ionic solutions that are freely permeable [67]. Fluids that provide oncotic pressure (e.g., albumin, fresh frozen plasma, hetastarch) and stay in the intravascular space longer than crystalloids theoretically are preferred

[68]. However, current evidence does not demonstrate improved clinical outcomes with colloids as opposed to crystalloids; as such, crystalloids should be used to resuscitate patients [69–71] (Level I recommendation). The infusion of packed red blood cells in patients with decreased hemoglobin concentrations increases plasma volume, CaO_2, and QO_2. As previously discussed, recent studies advocate for conservative transfusion strategies in patients not in shock [53, 54].

Colloids can be divided into albumin and semi-synthetic colloid solutions (hydroxyethyl starch [HES] and succinylated gelatin). Multiple trials have investigated albumin in the resuscitation of critically ill patients. A meta-analysis by the Cochrane Injuries Group compared albumin to crystalloid solutions or fluids without albumin in critically ill patients [66]. The analysis included 32 randomized controlled trials. In the study, albumin was associated with a significantly increased rate of death (relative risk [RR], 1.68; 95% CI 1.26–2.23; $p < 0.01$). An updated meta-analysis by the Cochrane Injuries Group in 2011 included 38 trials [72]. Albumin did not reduce mortality with a pooled RR of death of 1.05 (95% CI 0.95–1.16). The Saline versus Albumin Fluid Evaluation (SAFE) study was a blinded, randomized controlled study conducted in Australia and New Zealand [73]. Nearly 7,000 patients in ICUs in 16 different academic centers whom the treating physician judged to require fluid resuscitation were included. Mortality was compared in patients resuscitated with either 4% albumin or normal saline. Once again, albumin did not decrease mortality (RR 0.99; 95% CI 0.91–1.09; p = 0.87). In addition, the number of patients with new single-organ failure was similar between groups (P = 0.85 by Fisher's exact test). Albumin also did not decrease death at 28 days in the subgroups of patients with severe sepsis (RR 0.87; 95% CI 0.74–1.02; p = 0.09) or trauma without closed head injury (RR 1.00; 95% CI 0.56–1.79; p = 1.00). The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial was a multicenter, randomized clinical trial comparing crystalloids to colloids in patients with hypovolemic shock in the ICU [69]. The amount of fluid received and duration of treatment were at

the discretion of the treating physician. A total of 2,857 patients were enrolled. At 28 days, there were 359 deaths (25.4%) in the colloids group compared to 390 deaths (27%) in the crystalloids group (RR 0.96; 95% CI 0.88–1.04; $p = 0.26$).

Hydroxyethyl starch solutions are the most commonly used semisynthetic colloids and are produced by hydroxyethyl substituion of amylo-pectin obtained from sorghum, maize, or potatoes [67]. Reduced concentrations (6%) of HES are currently used due to safety concerns from con-centrated (10%) HES. In a blinded, randomized, controlled trial of 798 patients with severe sepsis in Scandinavia, HES was associated with an increase in mortality as compared to Ringer's acetate (RR 1.17; 95% CI 1.01–1.36; $p = 0.03$) [74]. More patients also required renal replace-ment therapy (RR 1.35; 95% CI 1.01–1.80; $p = 0.04$). A secondary analysis of this data dem-onstrated an increased rate of severe acute kidney injury and the use of renal replacement therapy within the first 5 days of treatment [75]. Given that colloids are more expensive and are not shown to improve outcomes, they cannot be recommended for the resuscitation of most critically ill patients (Level I recommendation). HES solutions should no longer be used in critically ill patients (Level I recommendation).

Crystalloids are used more frequently in poi-soned patients because they are readily available, are much cheaper, do not carry the risk of disease transmission seen with blood products, and are as effective as oncotic agents. While crystalloids should be used to resuscitate poisoned patients, practitioners should consider using a "balanced fluid" resuscitation strategy (Level II-2 recom-mendation). "Balanced fluids" contain organic anions such as lactate and have a lower chloride content more closely resembling the composition of normal plasma [76]. In "balanced fluids," the difference between the strong cations and the strong anions in the fluid will be between 24 and 28, which once dilutional changes are accounted for is similar to plasma. Examples of "balanced fluids" include lactated Ringer's and PlasmaLyte; chloride-rich solutions such as normal saline are not balanced. To determine if a solution is bal-anced, use the strong ion difference or SID and compare it to a patient's bicarbonate. If the SID is less than the patient's bicarbonate, the fluid will be acidotic; if the SID is greater than the patient's bicarbonate, the fluid will be alkalotic. As an example in normal saline, the difference between the Na and Cl is 0 (154-154 = 0). In a patient with a normal bicarbonate concentration (24 mEq/L), the bicarbonate is greater than the SID and so the fluid will essentially be acidotic [77]. This is the etiology of the non-anion gap metabolic acidosis in patients that receive normal saline. In compar-ison, lactated Ringer's has a SID of 21, which is much more similar to a patient's normal serum bicarbonate of 24 mEq/L and, therefore, much less likely to cause a metabolic acidosis. The topic of strong ion differences is reviewed in greater detail in ▶ Chap. 15, "Acid–Base Balance in the Poisoned Patient".

Recent literature indicates that patients that receive large volumes of "unbalanced solutions" have increased morbidity and mortality, although none of these trials have included poisoned patients. A large retrospective cohort study com-pared patients undergoing either elective or emer-gent open general surgical operations that received either NS or a balanced fluid the day of the procedure [78]. Unadjusted inhospital mortal-ity (5.6% CI 5.3–5.8 vs. 2.9% CI 2.0–4.2; $p < 0.001$) and the number of patients developing major complications (33.7 vs. 23%) were signifi-cantly greater in the group that received NS com-pared to the group that received balanced crystalloids. After using propensity scoring to correct for multiple variables, the difference in mortality was no longer significantly different; however, patients that received NS were 4.8 times more likely to require dialysis ($p < 0.001$). Additionally, patients requiring emergent general surgery showed an adjusted odds of death nearly 50% less in the cohort that received a balanced resuscitation compared to NS (OR 0.51 CI 0.28–0.95). In a prospective, open-label study of consecutive patients admitted to an ICU, those that received balanced crystalloids had a lower incidence of acute kidney injury (OR 0.52 CI 0.37–0.75; $p < 0.001$) and less need for renal replacement therapy (OR 0.52 CI0.33–0.81; $p = 0.004$) [79]. Septic patients also had a trend

toward lower mortality when resuscitated with balanced fluids as opposed to normal saline (OR 0.78; 95% credibility intervals 0.58–1.05) [80].

Current evidence indicates that balanced crystalloid fluids should be administered for rapid volume expansion during an acute resuscitation of a critically ill patient. However, different factors need to be considered in regard to the administration of maintenance fluids in these patients. While large amounts of crystalloid solution containing high chloride concentrations are associated with deleterious effects, this may not apply to maintenance fluids, where much less volume is administered. Maintenance fluids are used to preserve the extracellular volume while maintaining a normal electrolyte balance and preventing dehydration [81]. In this context, fluids are either isotonic (sodium concentration approximately equal to plasma sodium concentration) or hypotonic (sodium concentration is less than that of plasma). Dextrose-containing solutions, while they may be hyperosmolar, are not hypertonic as the glucose is rapidly metabolized.

Traditionally, hypotonic solutions were administered to both adults and children [82, 83]. Isotonic solutions were avoided due to concerns for the development of volume overload, hypernatremia, and hypertension. However, hypotonic solutions cause hyponatremia, which many critically ill patients are already at risk of developing due to either dysregulation of sodium and water homeostasis or medication-induced syndrome of inappropriate antidiuresis. In addition to normal triggers for the release of arginine vasopressin (AVP) such as hypovolemia and hypotension, pain, stress, nausea and vomiting, hypoxemia, hypercapnia, and hypoglycemia all stimulate the release of AVP, which impairs excretion of free water and causes hyponatremia [84]. Hyponatremia affects approximately 15–30% of hospitalized patients and is generally related to the administration of hypotonic fluids in patients with elevated AVP concentrations [85, 86]. The development of hyponatremia is linked to an increase in mortality [87].

Isotonic solutions are now recommended as maintenance fluids in both adults and children [88, 89] (Level I recommendation). While mainly investigated in pediatrics, more than 15 randomized, prospective trials involving more than 2000 patients have evaluated the safety and efficacy of isotonic fluids compared to hypotonic fluids as maintenance fluids [81]. A meta-analysis involving nearly 1000 children associated hypotonic fluids with a RR of 2.37 for the development of mild hyponatremia (<135 mmol per liter) and a RR of 6.2 for moderate hyponatremia (<130 mmol per liter) [90]. A Cochrane review compared the development of hyponatremia in patients receiving maintenance fluids composed of either isotonic or hypotonic solutions [91]. Ten studies with a total of 1106 patients were included in the review. Patients that received isotonic fluids had a lower risk of developing hyponatremia compared to those receiving hypotonic fluids (17% vs. 34%; RR 0.48; 95% CI 0.38–0.60). Importantly, many of the studies followed patients for less than 72 h, and patients with renal disease, heart disease, or cirrhosis were often excluded. In addition, the majority of patients were children. While little information exists regarding the most appropriate therapy in edematous states, isotonic fluids at a restricted rate are recommended in these patients [81].

Vasoactive Agents

The usual ICU approach to a patient with adequate fluid resuscitation and inadequate cardiac contractility is the administration of dobutamine or norepinephrine. However, the vasodilatory properties of dobutamine may worsen hypotension in a hypovolemic patient, which again stresses the need for optimal fluid resuscitation. Although norepinephrine increases mean arterial pressure, the increased afterload produced by infusion of norepinephrine may decrease cardiac output. Dopamine is considered to be a third-line agent for treating depressed cardiac contractility owing to its mixed α- and β-effects and indirect mechanism of action. However, it is still used in many pediatric intensive care units. Dopamine stimulates different adrenergic receptors at different infusion rates: dopaminergic at 1–3 μg/kg/min, β-adrenergic at 5–10 μg/kg/min, and α-adrenergic at 10–20 μg/kg/min. Further,

individual variability in response to dopamine infusions precludes the ability to predict which subset of adrenergic receptors is stimulated at a given dose of dopamine in a specific individual. Because part of dopamine's vasopressor effect is through the release of norepinephrine, dopamine has decreased efficacy in norepinephrine-depleted states, such as cyclic antidepressant toxicity [92]. Due to this mechanism, many medical toxicologists prefer the use of a direct-acting vasopressor such as norepinephrine as first-line treatment. If stimulation of β-receptors is desired, dobutamine is theoretically advisable. Norepinephrine is preferable to phenylephrine to stimulate α-receptors. Despite these considerations, the agent of choice is the one that works best for the individual patient and may not be predicted based on the abovementioned theoretical considerations. One multicenter, randomized trial compared norepinephrine to dopamine in patients with shock from multiple etiologies [93]. No difference in mortality was found between the two agents, although dopamine was associated with a greater incidence of arrhythmic events. No poisoned patients were included in the study.

There are very little data regarding the optimal adrenergic vasoactive agents in poisoned patients [94]. Case reports and retrospective case series imply that TCA-related hypotension may be more responsive to norepinephrine than dopamine [95, 96]. In a dog model, TCA-induced hypotension was equally responsive to dopamine and norepinephrine. Only high-dose dopamine infusions of 15 μg/kg/min or higher (α-range) were as effective, however, as low doses of norepinephrine (0.25 μg/kg/min) [97]. There is some evidence that norepinephrine may be the initial vasopressor of choice for TCA-induced hypotension [96]. In a retrospective analysis of 26 adults with TCA-associated hypotension, all patients responded to norepinephrine (n =11), while only 60% of patients adequately responded to dopamine (p-0.02). A single toxicology inpatient service retrospectively reviewed their management of 48 patients following an overdose of either verapamil or diltiazem; 33 (69%) received a vasopressor [98]. No patients died after vasopressors were initiated, even though many patients required high doses of vasopressors or multiple vasopressors (median 2; range 1–5). While direct comparisons between agents were not made, vasopressor use was associated with good outcomes with few ischemic complications.

Because of lack of data, the choice of pressor must be made on clinical and theoretical grounds. Contrary to some dogmatic beliefs, all vasopressors can initially be administered peripherally while central access is obtained [99]. Due to familiarity, traditional practice, and the belief that extravasation injuries from peripherally administered dopamine are less severe than from other vasopressors, dopamine is often the preferred agent in pediatric patients. Considerations for different xenobiotics or toxicants are reviewed in their respective chapters.

Nonadrenergic vasoactive drugs are an effective therapy for shock caused by β-adrenergic blocking agents and calcium channel antagonists (Level III recommendation). Glucagon stimulates adenyl cyclase, which increases intracellular cyclic adenosine monophosphate (cAMP) through a nonadrenergic mechanism. The increased cAMP causes an increase in intracellular calcium, which leads to positive chronotropic and inotropic actions. Glucagon improves cardiac index, urine output, and symptoms in patients with chronic congestive heart failure [100]. Numerous case reports and laboratory investigations describe glucagon's effectiveness in reversing hypotension caused by overdoses of β-adrenergic blocking agents and calcium channel antagonists, although its mechanism of action would seem to make its effectiveness in calcium channel antagonists less likely than in overdoses from β-adrenergic blocking agents [101–104]. There are also reports of glucagon reversing TCA-induced hypotension [105, 106]. In overdose patients, glucagon can be considered in hypotension unresponsive to the usual pressors (Level III recommendation). A glucagon dose of 5–10 mg administered intravenously over 10 min should be followed by a glucagon infusion (3–15 mg/h). An antiemetic should be provided with glucagon as it decreases lower esophageal tone which causes emesis. Inamrinone, a phosphodiesterase type III inhibitor formerly known

as amrinone, prevents the breakdown of intracellular cAMP. Inamrinone administration has been reported to reverse hypotension in overdoses of calcium channel antagonists [107], chloroquine [108], and propranolol [109]. It has also reversed hypotension in calcium channel antagonist overdoses in animals [110, 111]. Milrinone, another phosphodiesterase type III inhibitor, was used in the treatment of a patient with venlafaxine-associated cardiomyopathy; this patient required milrinone for 12 days in addition to multiple other therapies [112]. Milrinone was also studied in a dog model [113]. Because phosphodiesterase inhibitors have direct peripheral vasodilatory properties, however, further worsening of hypotension may occur if the decrease in blood pressure from vasodilation is greater than the increase in blood pressure from improved cardiac output. They should be used cautiously, if at all, with continuous bedside monitoring.

More recently, high-dose insulin euglycemia therapy (HIE) was used to treat hypotension and cardiac dysfunction from β-adrenergic blocking agents and calcium channel antagonists. In overdose, calcium channel antagonists decrease insulin release from pancreatic β-cells, cause insulin resistance in the myocardium, and change myocyte metabolism from fatty acids to carbohydrates [114]. Under stressful conditions such as in shock from both β-adrenergic blocking agents and calcium channel antagonists, the myocardium changes its preferred energy substrate from fatty acids to carbohydrates [114, 115]. High-dose insulin euglycemia therapy improves myocyte use of carbohydrates as an energy source and, therefore, increases cardiac contractility and improves perfusion. In the laboratory, insulin infusions increase myocardial contractility, possibly through increases in intracellular calcium [116]. Compared with calcium chloride, epinephrine, and glucagon, HIE decreased mortality in dogs poisoned with verapamil [114, 116, 117]. In a swine model, HIE was more effective than epinephrine and vasopressin, combined [118]. An increasing amount of data supports the efficacy of insulin in poisoning from β-adrenergic blockers and calcium channel antagonists. Insulin-glucose therapy improved hemodynamic parameters in five patients with calcium channel antagonist overdoses who were persistently hypotensive despite multiple therapies (calcium, atropine, glucagon, adrenergic agonists) [119]. All five patients survived. A 60-year-old male presented after ingesting 5.4 g of extended-release diltiazem [120]. His shock resolved after receiving HIE. One patient received 6 U/kg/h for 5 h with clinical improvement without experiencing an adverse event [121]. In a review of 78 patients with toxicity from either calcium channel antagonists or β-adrenergic blocking agents treated with HIE, 88% survived [115]. High-dose insulin euglycemia therapy was successfully used in another case series in 11 of 12 patients; the single fatality occurred in a patient 1 h after HIE was discontinued in favor of vasopressor therapy [122].

Based on current knowledge, insulin and glucose infusion should be used in shock caused by calcium channel antagonists and β-adrenergic blocking agents that is unresponsive to fluid resuscitation [123] (Level III recommendation). While glucagon can be considered in shock from β-adrenergic blocking agents in the author's opinion, many practicing medical toxicologists prefer HIE or vasopressors, instead. The dosing of HIE generally used is a bolus of 1 U/kg of regular insulin with 0.5 g/kg of dextrose, followed by an infusion of 1 U/kg/h of insulin titrated to effect. There are reports of patients receiving infusions as high as 22 U/kg/h [115]. To prevent hypoglycemia, glucose infusions should accompany insulin infusions. Plasma potassium concentrations should be closely monitored while the patient is receiving HIE. Consideration can be given to even initiating HIE prior to other therapies such as vasopressors. The clinical pharmacology of HIE is discussed in ► Chap. 147, "Euglycemic Insulin Therapy." Its clinical use is discussed in greater detail in chapters on specific agents.

Limited evidence also supports the use of methylene blue in the treatment of shock from calcium channel antagonists [124, 125]. In a single case report, methylene blue was successfully used in a mixed atenolol and amlodipine ingestion [126]. Amlodipine stimulates the release of nitric oxide, thereby causing vasodilation and

worsening hypotension. Methylene blue acts as a nitric oxide scavenger. In addition, it inhibits nitric oxide synthesis and decreases the production of cyclic guanosine monophosphate production, which is generated by nitric oxide and increases vasodilation. Given the limited experience with methylene blue, it should not be viewed as a therapy to be used routinely in calcium channel antagonist toxicity. Based on current evidence, the author recommends that it be used in cases of refractory circulatory shock due to amlodipine toxicity.

Calcium sensitizers (e.g., levosimendan) have been proposed to treat shock from calcium channel antagonists. They act as inotropic agents and increase the association of myosin and actin cross-bridges while slowing down their dissociation rate [127]. In patients with congestive heart failure, they decrease afterload while increasing cardiac contractility and output. Case reports describe levosimendan reversing shock from calcium channel antagonists [128–130]. However, the overall evidence is still limited and these agents are not currently available in the United States or in many other countries.

Lipid Emulsion Therapy

The administration of lipid emulsion therapy (LET) is one of the most recent advances in the care of the critically ill poisoned patient. Originally investigated as a treatment for patients with local anesthetic toxiciy, it has since been used in the management of toxicity from other xenobiotics [131]. Its mechanism of action is still not fully understood. The most accepted theory is that LET acts as a lipid sink and binds "lipid-soluble" xenobiotics removing them from their site of toxicity [132]. While there are multiple successful reports of LET reversing toxicity from lipophilic xenobiotics (e.g., calcium channel antagonists [133], tricyclic antidepressants [134]), there are also reports of its effectiveness in reversing toxicity from xenobiotics that are not lipophilic [135]. Other potential mechanisms of action include improving intracellular metabolism and ion channel activation.

Lipid emulsion therapy was first used in nonlocal anesthetic toxicity to resuscitate a 17-year-old with cardiovascular collapse following an ingestion of bupropion and lamotrigine [136]. Since then, there are many reports of LET successfully reversing toxicity from multiple agents (e.g., atenolol [135], diphenhydramine [137], quetiapine [138], cocaine [139], venlafaxine [140]). However, it is important to recognize that these anecdotal reports cannot be used to validate the efficacy of LET and are undoubtedly vulnerable to publication bias as unsuccessful use of LET in critically ill patients is unlikely to be reported.

A case series from the Toxicology Investigators' Consortium (ToxIC) identified nine patients with presumed non-survivable cardiac toxicity (either cardiac arrest or hypotension refractory to vasopressors) that received LET [141]. Five of the patients survived including two patients in cardiac arrest; eighty percent of survivors were neurologically intact. Adverse effects associated with LET include DVT, pancreatitis, and laboratory interferences [141, 142]. As such, there is still disagreement as to if and when to administer LET. The position of the American College of Medical Toxicology (ACMT) is that there is no standard of care in regard to the use of LET, but if and when it is administered, it should be as a 20% lipid emulsion as a 1.5 ml/kg bolus followed by an infusion of 0.25 ml/kg/min [143] (Level III recommendation). LET is further discussed in ▶ Chap. 152, "Lipid Resuscitation Therapy" and in chapters dealing with specific relevant agents.

Extracorporeal Membrane Oxygenation

In venoarterial extracorporeal membrane oxygenation (ECMO), either the right atrium or ventricle is cannulated. Hypoxic blood is pumped through an oxygenator and returned to the systemic circulation via a central arterial catheter. Extracorporeal membrane oxygenation is indicated in poisoned patients in refractory shock that are failing conventional treatment [144] (Level III recommendation). There are multiple reports of poisoned patients successfully resuscitated with ECMO [145, 146]. In a retrospective review of poisoned patients in arrest or shock, mortality was improved in those that received ECMO (12/14) compared to those that did not (23/48) (86%

vs. 48%, $p < 0.02$) [147]. In many cases, poisoned patients are ideal candidates for ECMO as they tend to be otherwise healthy and are suffering from a reversible illness. In these patients, ECMO serves as a bridge until the toxic xenobiotic is metabolized or eliminated, at which time the patient should regain normal cardiovascular function. While adverse events are associated with ECMO, recent advances in technology have made this a more practical alternative during emergency resuscitation of critically ill patients [148]. The use of ECMO in poisoned patients is further discussed in ▶ Chap. 4, "Extracorporeal Membrane Oxygenation and Cardiopulmonary Bypass in the Poisoned Patient."

Overdose and Cardiac Arrest

Few studies specifically address the issue of cardiac arrest as a direct consequence of poisoning. The AAPCC reported 1,835 exposure-related fatalities in 2014 [2]. The fatalities involved single substances in 42% of cases, two substances in 25% of cases, and three or more substances in the remainder of cases. There were 88 deaths in children (<20 years old), which was an 11.1% decrease from the previous year in that population; 16 deaths occurred in children less than 5 years old (1.4% of exposure-related fatalities). Nearly 66% of fatalities occurred in patients between 20 and 59 years of age. Only 2 deaths occurred in a pregnant patient. A recent analysis of data from the European Monitoring Centre for Drugs and Drug Addiction estimated that there were between 10,000 and 20,000 deaths a year in Europe from opioids [149]. In 2011, the average mortality rate due to overdoses in Europe was estimated at 18 deaths per million people aged 15–64 years old. Most countries reported an increase in overdose deaths from 2003 until 2009, when the number of deaths began to decline. Overall, there were approximately 6,500 overdose deaths reported in 2011. Over 19 years, there were 118 cases of cardiac arrest from intoxication at the Vienna General Hospital [150]. After resuscitation, 39 patients had a favorable outcome, defined as good neurologic function or moderate disability on the Pittsburgh Cerebral Performance Category. However nearly a quarter of patients were arrested from opioid intoxication and nearly a third of patients were deteriorated and arrested in the hospital, so the results may have limited external validity. Autopsy findings revealed that only 76% of older adults and 25% of young adults had atherosclerotic coronary artery disease as a cause of cardiac arrest. This finding should influence the medical management of drug-induced cardiac arrest. Advanced Cardiac Life Support (ACLS) algorithms [151] should be altered when cardiac arrest, ventricular tachycardia, or ventricular fibrillation is caused by drug overdose because the mechanisms for these arrests are significantly different from the cardiovascular events for which ACLS protocols were created. Specific therapies, such as sodium bicarbonate, glucagon, HIE, LET, and ECMO should be considered. Tox-ACLS was specifically developed to incorporate differences in the resuscitation of the critically ill, poisoned patient [152]. The management of acute coronary syndrome with cocaine toxicity, cocaine-associated dysrhythmias, and opioid-induced respiratory failure with naloxone are examples of important topics covered in Tox-ACLS. The post-arrest management of these patients is discussed in greater detail in ▶ Chap. 5, "Post-Resuscitation Management of the Poisoned Patient."

Invasive and Noninvasive Measurements of Hemodynamic Function

When patients are in shock, further information should be obtained to guide the resuscitation. Historically a pulmonary artery catheter (PAC), or Swan-Ganz catheter, was placed. Data obtained from a PAC includes central venous pressure, right ventricular pressure, pulmonary artery pressure, and left atrial pressure via the pulmonary capillary wedge pressure. Other data that can be obtained include oxygen saturation of mixed venous blood (SvO_2), thermodilution Q_T, systemic and pulmonary vascular resistance, QO_2, shunt fraction (Q_S/Q_T), and VO_2. However,

Table 7 Clinical uses of the pulmonary artery catheter

Determine etiology of shock state and assess efficacy of therapy
Assess intravascular volume
Renal failure, hypovolemia
Assess cardiac contractility
Cardiac output, mixed venous saturation (i.e., efficacy of therapy in CCA overdose)
Diagnosis of constrictive pericarditis or pericardial effusion
Waveform analysis
Measurement of pulmonary artery pressure
Pulmonary hypertension
Determine PCWP in the setting of pulmonary edema
High pressure (CHF) versus low pressure (ARDS) (i.e., hydrocarbon aspiration, toxic gas inhalation)

ARDS adult respiratory distress syndrome, *CCA* calcium channel antagonist, *CHF* congestive heart failure, *PCWP* pulmonary capillary wedge pressure

noninvasive monitoring techniques and a lack of an effect of PACs on outcome have sharply curtailed their use in poisoned patients. Some situations in which PACs may be useful are listed in Table 7. Because most overdose patients leave the ICU in 1–2 days, they rarely require a PAC and their use has not been studied in poisoned patients. The PAC may add useful data in some overdose situations such as [1] assessment of left heart filling pressures when persistent pulmonary edema is present (e.g., hydrocarbon aspiration or adult respiratory distress syndrome) and [2] assessment of myocardial contractility (cardiac output and stroke volume) to determine the severity of myocardial depression and efficacy of therapy (e.g., calcium channel antagonist overdose). Although several case reports describe the use of a PAC in a calcium channel antagonist overdose [101, 108, 153–155], no studies address either the indications for placement or whether the information obtained from the pulmonary catheter changes the outcome in these patients.

There are risks associated with the insertion of a PAC. Common complications include pulmonary artery injury, valvular injury, endocarditis, heparin-induced thrombocytopenia, catheter or balloon embolization, pulmonary infarction, ventricular arrhythmia, and cardiac perforation [156]. In addition, PACs are technically challenging to use [157–159]. Due to these limitations, there is a shift toward using less invasive and less challenging methods to monitor hemodynamic function [160] (Level III recommendation). As with PACs, these methods are not investigated in poisoned patients. Arterial pulse contour and pulse power analyses are less invasive alternatives to measure cardiac output [161]. Lithium dilution cardiac output (LiDCO Plus™) uses these principles to estimate cardiac output [162]. Isotonic lithium chloride is injected via a central or peripheral venous route to calculate cardiac output. The lithium doses used are too small to cause any pharmacologic effect. LiDCO was found to be an effective alternative to PAC [163]. Other noninvasive devices that provide similar information include the PiCCO Plus™ and FloTrac™ [164]. These devices use different calibration schemes to model the transfer of arterial pulse presure to stroke volume. Doppler cardiac monitoring devices are alternatives that require neither arterial or venous cannulation [165]. Esophageal or transthoracic Doppler probes measure flow in the descending aorta and estimate cardiac output. These products suffer from technical limitations, as probe position is crucial to obtaining accurate measurements. In addition, basic central venous catheters can measure central venous pressure and SvO_2 with fewer complications than PACs.

Bedside sonography is an even less invasive alternative used to guide resuscitation. The rapid ultrasound in shock (RUSH) protocol can determine the etiology of cardiovascular collapse [62]. The RUSH protocol is an easily learned technique that involves assessing the heart ("the pump"), inferior vena cava (IVC) and internal jugular (IJ) ("the tank"), and arterial vessels such as the aorta ("the pipes"). RUSH can exclude cardiac tamponade, decreased cardiac contractility, hypovolemia, hemothorax, pneumothorax, and aortic aneurysm as the cause of shock. In addition, a standard focused assessment in trauma (FAST) exam is included to exclude hemoperitoneum as the etiology of the hypotension.

Sonography also provides information about left and right ventricular function, central venous pressure, and fluid responsiveness. In addition to excluding tamponade, cardiac sonography is

useful to evaluate both left and right ventricular function. Ventricles with good contractility will have a large change in volume between systole and diastole [166]. Motion of the anterior leaflet of the mitral valve also assess contractility. In the parasternal long axis, the anterior leaflet should nearly touch the septum in diastole if the ventricle is contracting normally. The normal ratio of the left to right ventricle is 1:0.6. Right ventricular dilation indicates increased pressure within the pulmonary vascular circuit, such as with a large pulmonary embolism or pulmonary hypertension, as the cause of hypotension [167, 168]. Inferior vena cava measurement is used to determine volume status and fluid responsiveness; it also acts as a surrogate for central venous pressure (CVP) [169]. The size and change in size of the IVC during inspiration accurately estimates CVP [170]. An IVC with a diameter less than 2.1 cm that collapses more than 50% correlates with normal CVP and volume responsiveness [171]. Serial measurements as oppposed to a single measurment during the resuscitation are recommended to more accurately guide volume management [62]. The IJ can be used instead of the IVC [172]. Common carotid velocity time integral (VTi) with passive leg raise (PLR) also measures volume responsiveness. In PLR, a patient's legs are raised 45° while their upper body is kept horizontal, and the patient is assessed for changes in stroke volume or cardiac ouput [173]. Carotid artery flow velocity is measured with Doppler sonography to determine VTi. The common carotid artery's diameter is measured using Doppler to evaluate the flow [174]. Increases in VTi following PLR accurately predict volume responsiveness [175]. A 20% increase in VTi following PLR predicted volume responsiveness with a sensitivity of 94% and specificity of 86% [175]. This topic is further discussed in ▶ Chap. 14, "The Assessment and Management of Hypotension and Shock in the Poisoned Patient."

Sedation and Paralysis

When a patient is intubated and is in the ICU, sedation and analgesia are important to minimize discomfort. Some patients have vivid recall of events that occurred in the ICU [176]. These events (discomfort, being in unfamiliar surroundings, invasive procedures performed by total strangers) are terrifying because the patient's consciousness is clouded from illness and partial sedation; in fact, inadequate sedation and analgesia can lead to post-traumatic stress disorder (PTSD) [177]. At the same time, excess sedation causes delirium, with some literature associating it with distress and PTSD [178, 179]. Worse yet is being paralyzed without adequate sedation or analgesia and being unable to communicate [180]. For overdose patients, the patient's underlying emotional instability may complicate management further (see ▶ Chap. 6, "Psychiatric Issues in the Critically Poisoned Patient").

Patients intubated due to their toxicologic exposure may be agitated and require sedation. Until recently, this was typically achieved via benzodiazepine administration (continuous infusion or intermittent, around-the-clock dosing) or by continuous propofol infusion, with greater than 80% of critically ill patients sedated with one of these agents [181]. The α-2 agonist dexmedetomidine is now being used either in addition to these agents or replacement of them (Level I recommendation). A multicenter, randomized, double-blind trial compared midazolam or propofol to dexmedetomidine in intubated patients and was found to be non-inferior in maintaining light to moderate sedation [182]. It did reduce the duration of intubation compared to midazolam ($p = 0.03$) but not propofol ($P = .24$). As dexmedetomidine is unlikely to cause respiratory depression, it can be used with noninvasive positive pressure ventilation [183]. However, this is controversial and one randomized, double-blind, placebo-controlled pilot study did not find that it improved tolerance to noninvasive ventilation [184]. Recent trials in patients with sedative-hypnotic withdrawal indicate that dexmedetomidine may be a useful adjunct; however, more studies are required to determine its safety and efficacy in this population [185, 186]. Dexmedetomidine was administered to 22 poisoned patients who were intubated in an ICU [187]. Most patients (77%) required additional sedatives or analgesics and five patients

suffered adverse events. Further studies are needed to determine the role of dexmedetomidine in poisoned patients.

Continuous infusion provides a constant serum drug concentration and decreases the chance of the patient awakening or becoming agitated [188, 189]. Continuous sedative infusions of benzodiazepines and propofol, compared with intermittent dosing, prolong ventilator time and ICU time, however, as a result of overmedication [190]. For poisoned patients, as for all ICU patients, analgesia is as important as sedation. Neither benzodiazepines nor propofol provide analgesia, which is problematic as the endotracheal tube is a significant source of pain and discomfort [191]. Dexmedetomidine may provide analgesia in addition to sedation via receptors in the spinal cord [187]. Narcotic analgesics, such as fentanyl and morphine, may decrease the pain and discomfort patients experience from intubation, having invasive devices in place, and an inability to move. Combining narcotics with sedative-hypnotics decreases the amount of sedative-hypnotics required for comfort [192]. Simultaneous administration of opioids and propofol may cause hypotension, especially if large doses are used. Caution is warranted in patients who are poisoned by cardiovascular agents and therefore prone to hypotension.

Lorazepam and propofol are commonly used sedatives in the ICU. Continuous infusion of midazolam, compared with continuous infusion of propofol or lorazepam, lengthens time until the patient is awake and extubated after sedation has been stopped [193–195]. In critically ill patients, the midazolam half-life and volume of distribution are increased [196]. The half-life is prolonged further in renal failure [197]. In addition, sedation with midazolam may lead to higher rates of PTSD compared to other sedatives [179]. Benzodiazepines can also cause delirium [198], which is an independent predictor of death and prolonged ICU length of stay [199]. Infusions of propofol for greater than 48 h are associated with propofol infusion syndrome (PRIS) [200]. PRIS is a syndrome of refractory bradycardia, metabolic acidosis, rhabdomyolysis, hyperlipidemia, and fatty liver; patients can even

develop myocardial failure or cardiovascular collapse. Patients sedated with dexmedetomidine and other α-2 agonists develop bradycardia and hypotension. Haloperidol is also used as an adjunctive therapy for sedation. Independent of which sedative agents are used, daily interruption of sedation to assess the patient's neurologic status shortens the duration of mechanical ventilation and ICU length of stay [201].

Analgesia-based sedation or analgosedation is another option in the intubated patient [198, 202] (Level II-2 recommendation). Here, the primary objective is to control pain with an analgesic and only administer a sedative-hypnotic if necessary [203]. Analgosedation was demonstrated to be as effective as a sedative-hypnotic approach while reducing the dose of administered sedatives. Patients treated with analgosedation were able to be weaned from the ventilator sooner and had shorter ICU lengths of stay compared to standard management [204]. Just as with sedative-hypnotics, dosing of analgesics may need to be adjusted due to altered pharmacokinetics in critically ill patients [205].

In postoperative patients, the use of topical anesthetics to the pharyngeal, laryngeal, and tracheal mucosa statistically decreased the amount of sedation required [206]. As patients begin to regain consciousness and experience discomfort from the endotracheal tube, the use of topical anesthetics may relieve discomfort without requiring consciousness-altering medications. This may also be true of nonsurgical, intubated patients. Topical anesthetics must be administered judiciously because overzealous administration may cause significant methemoglobinemia and local anesthetic systemic toxicity.

In the overdose patient, sedation is often less problematic as patients are often intubated due to taking central nervous system depressants and can usually be extubated within 24 h. Overdose patients with depressed mental status may not require sedation if they were intubated due to their depressed mental status and inability to protect their airway. When the clinical effects of the overdose begin to resolve, either further sedation or ventilator liberation must be performed. In these situations if additional sedation is required,

intermittent administration of fentanyl (or another short acting opioid) or an infusion of dexmedetomidine, combined with the use of topical anesthetics, may be the best choice (Level III recommendation). This combination avoids oversedation and allows for continuous assessment of the patient's mental status and other clinical signs and symptoms indicating that the patient is ready to be liberated from the ventilator. Benzodiazepines, propofol, or dexmedetomidine can always be added to opioids if further sedation is required. Many patients, especially those presenting following polypharmacy overdoses, are delirious or have a fluctuating level of alertness. They may benefit from small amounts of sedation, until enough of the substances have worn off for them to be extubated. In general if the patient is sufficiently awake and can protect their airway, rapid ventilator liberation and extubation is appropriate. For otherwise healthy overdose patients, extubation usually can be accomplished safely without a "wean from the ventilator."

Neuromuscular blocking agents (NMBAs) should be used in only two circumstances in the poisoned patient: [1] in patients who, despite adequate sedation, still have a high oxygen demand owing to the work of respiratory muscles and [2] in patients poisoned with xenobiotics such as strychnine (Level III recommendation). Normally, about 5% of oxygen consumed by the body (VO_2) is used by the respiratory muscles. In critically ill patients, this can be 25% or greater [207]. Although therapeutic paralysis decreases VO_2, it has been shown that administering an NMBA to patients who are adequately sedated does not decrease VO_2 further [208]. Critically ill patients who have received NMBAs may develop persistent muscular weakness after discontinuation of the NMBA [209–211], even after short-term or intermittent NMBA administration [212]. The effect may last for weeks or months. The presence of renal dysfunction allows for the accumulation of active metabolites from some NMBAs (e.g., vecuronium). Addition of steroids (e.g., in patients with either upper airway obstruction or lower airway bronchospasm) increases the risk and severity of prolonged muscular weakness

[209]. NMBAs should be administered only if the patient can benefit from decreasing VO_2 requirements. NMBAs should never be used to control an agitated patient. The cause should be investigated and treated (e.g., increase sedation or analgesia, change the vent settings), which will likely improve the agitation without the need for NMBAs. Paralysis should not be used as a punitive intervention or to absolve the physician from the need to sedate an agitated patient. A poisoned patient seldom requires the use of an NMBA, unless adult respiratory distress syndrome, sepsis, hyperthermia from severe neuromuscular agitation (e.g., severe serotonin syndrome), or a toxicant such as strychnine is part of the clinical picture.

Ventilator Liberation

When the patient begins to show improvement, the issue of ventilator liberation arises. *Liberation* is a more desirable term, and a better mind set, than *weaning* for discontinuing ventilatory support. Weaning implies a gradual withdrawal of ventilator support, and most poisoned patients do not need to be "weaned" from the ventilator. Of 456 patients evaluated for participation in a trial designed to compare ventilator modes during liberation, 347 (76%) were liberated after an initial 2-h, spontaneous-breathing T-piece trial [213]. These findings have been confirmed in other studies [214]. As many overdose patients are intubated due to agitation or decreased mental status, most can be extubated as soon as their mental status improves and do not require a formal wean (Level III recommendation).

The conditions that led to the patient's being intubated and ventilated need to be resolved. In the case of overdoses, most respiratory failure is type II (hypercapnic) from decreased mental status and respiratory drive. When the patient regains his or her respiratory drive and the ability to protect their airway, ventilator liberation should proceed rapidly. If type I (hypoxemic) respiratory failure was involved, adequate oxygenation on 40% FiO_2 and PEEP of less than 5 cm H_2O should be present before liberation is attempted [215]. In

type IV (shock) respiratory failure, the patient should be hemodynamically stable and metabolic abnormalities corrected. If type II (hypercapnic) respiratory failure from respiratory muscle weakness has complicated the clinical course, liberation may require a more thoughtful approach, which is outlined subsequently.

Indices previously used to determine whether respiratory muscle strength was adequate for liberation have included a negative inspiratory force less than -20 cm H_2O, respiratory rate less than 35 breaths/min, V_T greater than 5 mL/kg, V_E less than 10 L, and forced vital capacity greater than 10 mL/kg [216, 217]. All of these parameters are moderately sensitive but poorly specific [218]. Their utility in the overdose or poisoned patient population has not been evaluated.

The rapid shallow breathing index (RSBI) was developed to assist in the bedside assessment of patients who are potentially ready for ventilator liberation [219]. The RSBI quantifies what we intuitively know about patients' breathing patterns: patients who take deep breaths at a slow rate are ready for ventilator liberation, whereas patients breathing rapidly are unlikely to be successfully liberated. The RSBI is performed while the patient is spontaneously breathing for 1 min without any ventilator assistance. The respiratory rate is divided by the spontaneous V_T in liters. Patients with an RSBI greater than 105 are at risk of failing ventilator liberation. The RSBI is highly sensitive (0.97) and moderately specific (0.64) in medical ICU patients [219]. Further studies have shown a sensitivity and specificity equal to the original study when the RSBI is performed after 30 min of spontaneous breathing [220]. The RSBI is valid in surgical patients, as well [221]. Analysis of patients failing liberation with RSBIs less than 100 found that most fail due to new problems unrelated to the original process that caused them to be intubated, such as new-onset congestive heart failure, upper airway obstruction, and aspiration [222]. The utility of the RSBI in overdose or poisoned patients has not been studied.

Questions may arise about which ventilator mode to use during ventilator liberation. As mentioned previously, the SIMV mode can increase the work of breathing. For the general ICU population, once-daily trials of spontaneous breathing lead to extubation three times faster than SIMV and two times faster than pressure support ventilation [214]. It is not known whether this applies to toxicology patients.

If there is concern that the patient may not be ready for ventilator liberation, a simple five-step procedure can be followed:[218].

1. Ensure all underlying abnormalities that led to intubation are corrected.
2. Assess the RSBI. If the RSBI is greater than 105, therapy to decrease respiratory workload and increase respiratory muscle strength should be employed.
3. For patients with an RSBI less than 105, perform a 2-h spontaneous breathing trial (SBT). This is accomplished by placing the patient on a T-piece or on continuous positive airway pressure with minimal or no pressure support.
4. Evaluate the patient during the SBT. Failure of a SBT manifests as diaphoresis, tachypnea, desaturation, tachycardia, hypotension, or arrhythmias.
5. If the patient tolerates a 2-h SBT, he or she is ready to be liberated from the ventilator.

Ventilator liberation does not imply that extubation should be performed, just as an inability to protect the airway does not imply respiratory failure. Other factors need to be considered, especially in cases of upper airway injury such as following a caustic injury. Bedside assessment of airway adequacy may be determined by endotracheal tube "cuff leak." The cuff-leak test can be performed in one of two ways. The first is to disconnect the patient from the ventilator, deflate the endotracheal tube's cuff while it is still in place, occlude the end of the tube, and listen for air passing around the tube. The second is to leave the endotracheal tube connected to the ventilator, deflate the cuff, and measure the difference between the V_T delivered by the ventilator and the V_T returned to the ventilator. If there is a leak, the delivered V_T will be greater than the returned V_T. Prospective evaluation of 72 patients with upper airway obstructions using the first method led to successful extubation in 89% of patients

with a cuff leak [223]. Using the second method, patients who did not develop stridor on extubation averaged 360 mL cuff leak with average V_T of 650 mL [224]. Patients who did develop stridor, given the same average V_T, had cuff leaks of only 180 mL. These data, along with direct visualization of the upper airway, can assist the clinician in deciding whether patients with upper airway obstruction are ready for extubation.

Ancillary Issues in the Intensive Care Unit Management of Poisoned Patients

Certain management issues need to be addressed in all patients who enter the ICU. Any patient who is critically ill, is intubated, or has a PAC requires a daily chest x-ray. New findings are discovered in 15–45% of daily chest x-rays [225–228], 8% had findings of "major" clinical significance (e.g., pneumothorax, improperly positioned endotracheal tube), and 42% of these findings (3.3% of total) were not suspected previously from bedside assessment [229].

Critically ill, poisoned patients are at increased risk of GI bleeding. Of ICU patients, 75% have endoscopic evidence of gastric mucosal injury by 18 h after admission, with 5% of patients developing overt bleeding [230]. GI bleeding prophylaxis should be started on admission to the ICU and can be achieved best through the use of histamine$_2$-receptor antagonists or proton-pump inhibitors [231] (Level I recommendation).

Poisoned ICU patients are at risk for venous thromboembolic disease if they have a prolonged course requiring them to remain in bed. Approximately 33% of all ICU patients develop ultrasonographically detectable DVTs despite receiving prophylaxis. Meta-analyses show that the use of heparin or pneumatic compression stockings decreases the incidence of DVT by at least 50% [232]. DVT prophylaxis should be initiated with unfractionated heparin, low-molecular-weight heparin, or compression devices as soon as the patient is admitted to the ICU if a prolonged stay is anticipated (Level I recommendation).

The goal of nutritional support is to meet the patient's nutritional needs without overfeeding. This may be difficult because critically ill patients can be catabolic with a negative nitrogen balance. Exact caloric requirements can be determined through indirect calorimetry ("metabolic cart"). Overfeeding should be avoided because excess carbohydrates can lead to increased carbon dioxide production, which leads to higher minute ventilation needs. The increased ventilation needed to blow off the excess carbon dioxide may prevent liberation from the ventilator. Enteral feedings, which help maintain integrity of the gut's mucosal barrier, are preferred over the parenteral route. If a prolonged stay is anticipated, feedings optimally should be initiated within the first 24 h after admission. If ventilator liberation is anticipated within the first 24–48 h, as is typical of many poisoned patients, enteral feedings are not necessary.

Gastrointestinal Decontamination

Gastrointestinal decontamination, once a mainstay in the management of the intoxicated patient, has greatly fallen out of favor. It is generally relegated to patients that present very early (less than an hour after their ingestion) or for those patients who took a very large or dangerous overdose, where an antidote does not exist (e.g., verapamil) (Level III recommendation). While once common, the administration of syrup of ipecac or the performance of gastric lavage should not be done, and administration of even single-dose activated charcoal (AC) is now rare. Intuitively GI decontamination should decrease absorption of many xenobiotics. However, its use is not associated with improved patient-centered outcomes (e.g., mortality, length of stay) [233–235].

If GI decontamination is attempted, it should be done as early as possible in the patient's treatment to have any chance of being beneficial. If it is preformed, this should occur in the emergency department, shortly after the patient arrives; the patient is very unlikely to benefit from decontamination started in a delayed fashion, such as in the ICU. However, patients who ingest sustained

release preparations, have heavy metals in their GI tract, or are body packers may benefit from whole bowel irrigation (WBI) (Level II-3 recommendation). In addition if the patient has a bezoar, GI decontamination may be beneficial.

Activated charcoal is produced in a two-step process, starting with pyrolysis of various carbonaceous materials. It is then treated at high temperatures with oxidizing agents such as steam or carbon dioxide that "activate" it and increase its adsorptive capacity. Activated charcoal adsorbs many xenobiotics but does not adsorb metals or strongly ionized substances. In addition, it should not be administered to patients with caustic injuries, as it will obscure landmarks during the endoscopy. Serious adverse events include chemical pneumonitis following aspiration, peritonitis if it is administered to a patient with perforation of their GI tract, and pseudo-obstruction in patients with an ileus or obstruction. In their most recent position statement, the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) compared 122 studies in human volunteers [235]. There was a large amount of variability in the types of xenobiotics ingested, the amount of xenobiotic ingested, and the amount of charcoal administered. While absorption was decreased when AC was administered within 30 min, the mean reduction was only 16% when administered two hours after the ingestion. Studies of AC in patients with ingestions are difficult to interpret as they include patients receiving multiple types of decontamination in addition to AC or have serious methodological or statistical flaws. Merigian et al. investigated the outcome of 451 asymptomatic patients who received either 50 g of AC or no treatment and did not find a statistically significant change in clinical outcomes between the groups [236]. Buckley et al. conducted a retrospective, non-randomized study on 981 consecutive patients admitted following acetaminophen overdoses [237]. Activated charcoal was administered in 36% of patients and 39% of patients were not decontaminated. Patients that received AC were significantly less likely (odds ratio 0.36) to have acetaminophen concentrations in the probable or high-risk portion

of the nomogram. However, the mean time to presentation in the no treatment group was 385 min versus 135 min in the treatment group. If AC is administered, it should be dosed at 1 g/kg if the dose is unknown or in a 10:1 ratio of AC to xenobiotic if known; most adults receive approximately 100 g of AC. Administration of a cathartic with AC is controversial. The current position of the AACT does not support the routine use of activated charcoal, even though benefit cannot be excluded if AC is administered more than one hour after the ingestion [235] (Level I recommendation). AC may be considered in patients that present within one hour of a toxic ingestion, which would still exclude its use in patients after they are admitted to the ICU. Multidose activated charcoal (MDAC) is used to enhance the elimination of various xenobiotics. Multidose activated charcoal may benefit patients at risk from delayed absorption due to ingesting delayed release products or if they ingested xenobiotics that cause pylorospasm or bezoar formation, such as salicylates [238]. In these scenarios, MDAC prevents absorption of the xenobiotic. Patients that ingest xenobiotics that undergo enteroenteric or enterohepatic circulation may also benefit from MDAC. In enterohepatic circulation, absorbed substances are secreted into the bile and then into the small intestine before being reabsorbed. In enteroenteric circulation, absorbed substances are secreted into the intestine before being reabsorbed. By administering MDAC, charcoal can adsorb xenobiotics that are secreted into the intestine before being reabsorbed, thereby enhancing elimination. In these scenarios, the xenobiotic has already been absorbed so MDAC is not being used for the purpose of decontamination but as an adjunct to increase elimination by preventing reabsorption. Both animal and human data demonstrate that MDAC increases xenobiotic elimination [239–241]. However, MDAC has not been shown to decrease morbidity or mortality [242]. MDAC is generally administered at a dose of ½ gram/kg following the initial standard dose of charcoal. In pediatric patients, the dose may need to be decreased. Cathartics should not be administered with MDAC as repeated dosing causes electrolyte disturbances and dehydration.

Multidose activated charcoal may be administered every four hours. However, the timing of MDAC administration is patient and provider specific. Multidose activated charcoal should be withheld in patients with altered mental status and an unprotected airway, GI tract obstruction or disruption, and an ileus. Currently, the AACT/EAPCCT only recommends the administration of MDAC in patients who have ingested life-threatening amounts of either carbamazepine, dapsone, phenobarbital, quinine, or theophylline [243] (Level II-3 recommendation). Xenobiotics whose elimination may be increased by MDAC are discussed in their respective chapters.

Over the last 10–20 years, the use of gastric lavage has drastically decreased due to concerns that complications from the procedure outweigh any benefit. Given the real risks associated with it, the AACT and EAPCCT do not recommend the use of gastric lavage [234]; in situations where a clinician believes lavage may be appropriate, either AC or supportive care should be considered instead (Level II-2 recommendation).

Whole bowel irrigation prevents absorption by attempting to enhance the flow of xenobiotics through the gut. In order to achieve this, a nasogastric or orogastric tube must be placed. Large amounts, approximately 1–2 l/h, of osmotically balanced polyethylene glycol solution (PEG) are administered until the patient has at least two clear, liquid stools. Unlike other forms of GI decontamination, WBI may be started or continued in the ICU. Patients that have ingested sustained release preparations may be candidates for WBI in order to prevent delayed absorption; this is also why WBI may be considered in patients with bezoars. If patients are suspected of ingesting metals and have radiopaque foreign bodies on imaging, WBI may prevent absorption, as AC will not adsorb metal. Lastly, body packers are traditionally treated with WBI. Body packers internally smuggle large amounts of packets in order to smuggle narcotics. Should a packet leak, each one has a potentially lethal amount of drug in it. There are multiple retrospective case studies and cohorts in body packers that received WBI [244–246]. Interpretation of some of the literature is limited due to patients either refusing to drink the PEG solution or WBI not recorded as being completed. While efficacy of WBI is difficult to interpret, no adverse events were reported in these studies; however, aspiration has been reported with WBI [247, 248]. In body packers, WBI should be initiated in order to remove the packets as soon as possible, given the life-threatening risk associated with even a single packet leaking. Contraindications include patients with an ileus or obstruction or an injury to their GI tract. While there are multiple reports suggesting that WBI can assist with the passage of tablets or packets, there is no evidence to support that WBI improves clinical outcomes [249]. The AACT and EAPCCT do not routinely recommend the use of WBI, but it can be considered in select situations (Level II-2 recommendation).

Antidotes

Most poisoned patients can be treated with standard supportive care, as detailed earlier. In certain instances specific therapy or antidotes are required. Specific therapies are described in subsequent chapters dealing with specific substances. Properties of specific antidotes are described in chapters at the end of the book. Some antidotes that may be administered in the ICU are listed in Table 8.

Table 8 Examples of antidotes that may be used in the ICU

Toxin/poison	Antidotes
α-2 agonist (clonidine, guanfacine, guanabenz, tizanidine, methyldopa)	Naloxone
Acetaminophen	N-acetylcysteine
Anticholinergic agents	Physostigmine
Benzodiazepines	Flumazenil (with caution)
β-Adrenergic blocking agents	Glucagon
	Lipid emulsion therapy
Black widow envenomation	Latrodectus antivenin
Botulism	Botulin antitoxin
Calcium channel antagonists	Calcium
	Glucagon

(*continued*)

Table 8 (continued)

Toxin/poison	Antidotes
	Insulin and glucose
	Methylene blue (amlodipine)
	Lipid emulsion therapy
Carbamate insecticides	Atropine
Carbon monoxide	Oxygen or hyperbaric oxygen
Cyanide	Amyl and sodium nitrites
	Hydroxocobalamin
	Sodium thiosulfate
Digoxin/digitoxin	Antidigoxin antibodies
Dystonic reactions	Diphenhydramine
	Benztropine
Ethylene glycol	Ethanol
	Fomepizole
	Thiamine and pyridoxine
Fluoride	Calcium salts
Heparin	Protamine
Heavy metals	Dimercaprol (BAL)
	Penicillamine
	Dimercaptosuccinic acid (DMSA)
	Calcium ethylenediaminetetraacetic acid (EDTA)
	Dimercaptopropanesulfonic acid (DMPS)
Isoniazid/hydrazines (*Gyromitra*)	Pyridoxine
Iron	Deferoxamine
Methanol	Ethanol
	Fomepizole
	Folate or folinic acid
Methemoglobinemia	Methylene blue
Methotrexate, trimethoprim, pyrimethamine	Folinic acid
	Glucarpidase
New oral anticoagulants Opiates	Prothrombin complex concentrates (Xa inhibitors)
	Hemodialysis (dabigatran)
	Idarucizumab (dabigatran) Naloxone (methylnaltrexone only reverses opioid induced constipation)
Oral hypoglycemics	Glucose infusion
	Octreotide
Organophosphate insecticides	Atropine
	Pralidoxime/obidoxime
Rattlesnake envenomation	*Crotalidae antivenin*

(*continued*)

Table 8 (continued)

Toxin/poison	Antidotes
Scorpion envenomation	Anascorp® antivenin
Sodium channel blockade (TCAs, type I antiarrhythmics)	Sodium bicarbonate
	Hypertonic saline
Warfarin	Vitamin K
	Fresh frozen plasma

Subspecialty Care

In the United States, medical toxicology is a recognized subspecialty by the American Board of Medical Specialties. There are currently 500–600 board-certified practicing medical toxicologists in the United States. These individuals have the greatest experience in the care of critically poisoned patients. When available, on-site or telemedical consultation is recommended. In some areas highly specialized regional poison treatment centers have been established to which critically poisoned patients might be transferred.

References

1. Zimmerman JE, Knaus WA, Wagner DP, Sun X, Hakim RB, Nystrom PO. A comparison of risks and outcomes for patients with organ system failure: 1982–1990. Crit Care Med. 1996;24(10):1633–41.
2. Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 annual report of the American association of poison control centers' national poison data system (NPDS): 32nd annual report. Clin Toxicol (Phila). 2015;53(10):962–1147.
3. O'Connor MFHJ, Schmidt GA, Wod LDH. Acute hypoxemic respiratory failure. In: Hall JBSG, Wood LDH, editors. Principles of critical care. 2nd ed. New York: McGraw-Hill; 1998.
4. Gabbott DA, Baskett PJ. Management of the airway and ventilation during resuscitation. Br J Anaesth. 1997;79(2):159–71.
5. Bach A, Boehrer H, Schmidt H, Geiss HK. Nosocomial sinusitis in ventilated patients. Nasotracheal versus orotracheal intubation. Anaesthesia. 1992;47(4):335–9.
6. Michelson A, Schuster B, Kamp HD. Paranasal sinusitis associated with nasotracheal and orotracheal long-

term intubation. Arch Otolaryngol Head Neck Surg. 1992;118(9):937–9.

7. Salord F, Gaussorgues P, Marti-Flich J, Sirodot M, Allimant C, Lyonnet D, et al. Nosocomial maxillary sinusitis during mechanical ventilation: a prospective comparison of orotracheal versus the nasotracheal route for intubation. Intensive Care Med. 1990; 16(6):390–3.

8. O'connor MFKM, Hall JB. Airway management. In: Hall JBSG, Wood LDH, editors. Principles of critical care. 2nd ed. New York: Mc-Graw Hill; 1998.

9. Holzapfel L, Chevret S, Madinier G, Ohen F, Demingeon G, Coupry A, et al. Influence of long-term oro- or nasotracheal intubation on nosocomial maxillary sinusitis and pneumonia: results of a pro-spective, randomized, clinical trial. Crit Care Med. 1993;21(8):1132–8.

10. Aebert H, Hunefeld G, Regel G. Paranasal sinusitis and sepsis in ICU patients with nasotracheal intuba-tion. Intensive Care Med. 1988;15(1):27–30.

11. Wright PE, Marini JJ, Bernard GR. In vitro versus in vivo comparison of endotracheal tube airflow resis-tance. Am Rev Respir Dis. 1989;140(1):10–6.

12. Friedman EM, Lovejoy Jr FH. The emergency man-agement of caustic ingestions. Emerg Med Clin North Am. 1984;2(1):77–86.

13. Howell JM. Alkaline ingestions. Ann Emerg Med. 1986;15(7):820–5.

14. Moulin D, Bertrand JM, Buts JP, Nyakabasa M, Otte JB. Upper airway lesions in children after accidental ingestion of caustic substances. J Pediatr. 1985; 106(3):408–10.

15. Heffner AC, Swords DS, Neale MN, Jones AE. Incidence and factors associated with cardiac arrest complicating emergency airway management. Resuscitation. 2013;84(11):1500–4.

16. Weingart SD, Trueger NS, Wong N, Scofi J, Singh N, Rudolph SS. Delayed sequence intubation: a prospec-tive observational study. Ann Emerg Med. 2015; 65(4):349–55.

17. Weingart SD. Preoxygenation, reoxygenation, and delayed sequence intubation in the emergency depart-ment. J Emerg Med. 2011;40(6):661–7.

18. Ramkumar V. Preparation of the patient and the air-way for awake intubation. Indian J Anaesth. 2011; 55(5):442–7.

19. Simmons ST, Schleich AR. Airway regional anesthe-sia for awake fiberoptic intubation. Reg Anesth Pain Med. 2002;27(2):180–92.

20. Roppolo LP, Wigginton JG. Preventing severe hyp-oxia during emergent intubation: is nasopharyngeal oxygenation the answer? Crit Care. 2010;14(6):1005.

21. Weingart SD, Levitan RM. Preoxygenation and pre-vention of desaturation during emergency airway man-agement. Ann Emerg Med. 2012;59(3):165–75. e1.

22. Frumin MJ, Epstein RM, Cohen G. Apneic oxygena-tion in man. Anesthesiology. 1959;20:789–98.

23. Wood LDHSG, Hall JB. Principles of critical care of respiratory failure. In: Murray JF, Nadal JA, editors.

Textbook of respiratory medicine. 3rd ed. Philadelphia: WB Saunders; 2000.

24. Fessler HE, Derdak S, Ferguson ND, Hager DN, Kacmarek RM, Thompson BT, et al. A protocol for high-frequency oscillatory ventilation in adults: results from a roundtable discussion. Crit Care Med. 2007;35(7):1649–54.

25. Taki K, Huang DT. High-frequency oscillation in early adult respiratory distress syndrome. Crit Care. 2014;18(3):310.

26. Malhotra A, Drazen JM. High-frequency oscillatory ventilation on shaky ground. N Engl J Med. 2013; 368(9):863–5.

27. Marini JJ, Rodriguez RM, Lamb V. The inspiratory workload of patient-initiated mechanical ventilation. Am Rev Respir Dis. 1986;134(5):902–9.

28. Marini JJ, Capps JS, Culver BH. The inspiratory work of breathing during assisted mechanical ventilation. Chest. 1985;87(5):612–8.

29. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Esposito DC, Pasqualucci Mde O, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308(16):1651–9.

30. Fuller BM, Mohr NM, Drewry AM, Carpenter CR. Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respira-tory distress syndrome: a systematic review. Crit Care. 2013;17(1):R11.

31. Schmidt GA, Hall JB. Management of the ventilated patient. In: Hall JB, Schmidt GA, Wood LDH, editors. Principles of critical care. 2nd ed. New York: McGraw-Hill; 1998.

32. Murphy C. Hypertensive emergencies. Emerg Med Clin North Am. 1995;13(4):973–1007.

33. Grossman E, Messerli FH. High blood pressure. A side effect of drugs, poisons, and food. Arch Intern Med. 1995;155(5):450–60.

34. Olmedo R, Hoffman RS. Withdrawal syndromes. Emerg Med Clin North Am. 2000;18(2):273–88.

35. Walley KR, Wood L. Shock. In: Hall JB, Schmidt G, Wood LDH, editors. Principles of critical care. 2nd ed. New York: McGraw-Hill; 1998.

36. Porter JM, Ivatury RR. In search of the optimal end points of resuscitation in trauma patients: a review. J Trauma. 1998;44(5):908–14.

37. Griffin JP. Methaemoglobinaemia. Adverse Drug React Toxicol Rev. 1997;16(1):45–63.

38. Park CM, Nagel RL, Blumberg WE, Peisach J, Magliozzo RS. Sulfhemoglobin. Properties of par-tially sulfurated tetramers. J Biol Chem. 1986; 261(19):8805–10.

39. Hardy KR, Thom SR. Pathophysiology and treatment of carbon monoxide poisoning. J Toxicol Clin Toxicol. 1994;32(6):613–29.

40. Cyanide toxicity. Agency for Toxic Substances and Disease Registry. Am Fam Physician. 1993;48(1): 107–14.

41. Smith RP, Gosselin RE. Hydrogen sulfide poisoning. J Occup Med. 1979;21(2):93–7.

42. Abrams J, el-Mallakh RS, Meyer R. Suicidal sodium azide ingestion. Ann Emerg Med. 1987;16(12):1378–80.

43. Kraut JA, Madias NE. Lactic acidosis. N Engl J Med. 2014;371(24):2309–19.

44. Ruiz JP, Singh AK, Hart P. Type B lactic acidosis secondary to malignancy: case report, review of published cases, insights into pathogenesis, and prospects for therapy. Sci World J. 2011;11:1316–24.

45. Cohen RD, Woods HF. Clinical and biochemical aspects of lactic acidosis. J Clin Pathol. 1976;30(1):92.

46. Luft FC. Lactic acidosis update for critical care clinicians. J Am Soc Nephrol. 2001;12 Suppl 17:S15–9.

47. Sia P, Plumb TJ, Fillaus JA. Type B lactic acidosis associated with multiple myeloma. Am J Kidney Dis. 2013;62(3):633–7.

48. Megarbane B, Brivet F, Guerin JM, Baud FJ. Lactic acidosis and multi-organ failure secondary to antiretroviral therapy in HIV-infected patients. Presse Med. 1999;28(40):2257–64.

49. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care. 2006;10(1):R22.

50. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Crit Care. 2010;14(1):R25.

51. Manini AF, Kumar A, Olsen D, Vlahov D, Hoffman RS. Utility of serum lactate to predict drug-overdose fatality. Clin Toxicol (Phila). 2010;48(7):730–6.

52. Megarbane B, Deye N, Malissin I, Baud FJ. Usefulness of the serum lactate concentration for predicting mortality in acute beta-blocker poisoning. Clin Toxicol (Phila). 2010;48(10):974–8.

53. Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368(1):11–21.

54. Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, Kuhn L, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA. 2014;311(13):1317–26.

55. Franchini M, Lippi G. Prothrombin complex concentrates: an update. Blood Transfus. 2010;8(3):149–54.

56. Pollack Jr CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373(6):511–20.

57. Pollack Jr CV, Reilly PA, Bernstein R, Dubiel R, Eikelboom J, Glund S, et al. Design and rationale for RE-VERSE AD: a phase 3 study of idarucizumab, a specific reversal agent for dabigatran. Thromb Haemost. 2015;114(1):198–205.

58. Chang DN, Dager WE, Chin AI. Removal of dabigatran by hemodialysis. Am J Kidney Dis. 2013;61(3):487–9.

59. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011;124(14):1573–9.

60. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373(25):2413–24.

61. Jones AE, Tayal VS, Sullivan DM, Kline JA. Randomized, controlled trial of immediate versus delayed goal-directed ultrasound to identify the cause of nontraumatic hypotension in emergency department patients. Crit Care Med. 2004;32(8):1703–8.

62. Seif D, Perera P, Mailhot T, Riley D, Mandavia D. Bedside ultrasound in resuscitation and the rapid ultrasound in shock protocol. Crit Care Res Pract. 2012;2012:503254.

63. Velanovich V. Crystalloid versus colloid fluid resuscitation: a meta-analysis of mortality. Surgery. 1989;105(1):65–71.

64. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. BMJ. 1998;316(7136):961–4.

65. Shoemaker WC, Monson DO. The effect of whole blood and plasma expanders on volume-flow relationships in critically ill patients. Surg Gynecol Obstet. 1973;137(3):453–7.

66. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ. 1998;317(7153):235–40.

67. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med. 2013;369(13):1243–51.

68. Shoemaker WC. Comparison of the relative effectiveness of whole blood transfusions and various types of fluid therapy in resuscitation. Crit Care Med. 1976;4(2):71–8.

69. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declere AD, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809–17.

70. Jiang L, Jiang S, Zhang M, Zheng Z, Ma Y. Albumin versus other fluids for fluid resuscitation in patients with sepsis: a meta-analysis. PLoS One. 2014;9(12), e114666.

71. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2013;2:CD000567.

72. Albumin R. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2011;10:CD001208.

73. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247–56.

74. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124–34.

75. Muller RB, Haase N, Lange T, Wetterslev J, Perner A. Acute kidney injury with hydroxyethyl starch 130/0.42 in severe sepsis. Acta Anaesthesiol Scand. 2015;59(3):329–36.

76. Santi M, Lava SA, Camozzi P, Giannini O, Milani GP, Simonetti GD, et al. The great fluid debate: saline or so-called "balanced" salt solutions? Ital J Pediatr. 2015;41:47.

77. Carlesso E, Maiocchi G, Tallarini F, Polli F, Valenza F, Cadringher P, et al. The rule regulating pH changes during crystalloid infusion. Intensive Care Med. 2011;37(3):461–8.

78. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to plasma-Lyte. Ann Surg. 2012;255(5):821–9.

79. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566–72.

80. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014;161(5):347–55.

81. Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely Ill patients. N Engl J Med. 2015;373(14):1350–60.

82. Freeman MA, Ayus JC, Moritz ML. Maintenance intravenous fluid prescribing practices among paediatric residents. Acta Paediatr. 2012;101(10):e465–8.

83. Padhi S, Bullock I, Li L, Stroud M, National Institute for Health, Care Excellence Guideline Development Group. Intravenous fluid therapy for adults in hospital: summary of NICE guidance. BMJ. 2013;347:f7073.

84. Danziger J, Zeidel ML. Osmotic homeostasis. Clin J Am Soc Nephrol. 2015;10(5):852–62.

85. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006;119(7 Suppl 1):S30–5.

86. DeVita MV, Gardenswartz MH, Konecky A, Zabetakis PM. Incidence and etiology of hyponatremia in an intensive care unit. Clin Nephrol. 1990;34(4):163–6.

87. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med. 2009;122(9):857–65.

88. Moritz ML, Ayus JC. Hospital-acquired hyponatremia–why are hypotonic parenteral fluids still being used? Nat Clin Pract Nephrol. 2007;3(7):374–82.

89. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. Pediatrics. 2003;111(2):227–30.

90. Foster BA, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. J Pediatr. 2014;165(1):163–9. e2.

91. McNab S, Ware RS, Neville KA, Choong K, Coulthard MG, Duke T, et al. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. Cochrane Database Syst Rev. 2014;12:CD009457.

92. Murray P, Wylam ME. Dopamine, dobutamine, and dopexamine. In: Leff AR, editor. Pulmonary and critical care pharmacology and therapeutics. New York: McGraw-Hill; 1996. p. 242.

93. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362(9):779–89.

94. Hannemann L, Reinhart K, Grenzer O, Meier-Hellmann A, Bredle DL. Comparison of dopamine to dobutamine and norepinephrine for oxygen delivery and uptake in septic shock. Crit Care Med. 1995;23(12):1962–70.

95. Teba L, Schiebel F, Dedhia HV, Lazzell VA. Beneficial effect of norepinephrine in the treatment of circulatory shock caused by tricyclic antidepressant overdose. Am J Emerg Med. 1988;6(6):566–8.

96. Tran TP, Panacek EA, Rhee KJ, Foulke GE. Response to dopamine vs norepinephrine in tricyclic antidepressant-induced hypotension. Acad Emerg Med. 1997;4(9):864–8.

97. Vernon DD, Banner Jr W, Garrett JS, Dean JM. Efficacy of dopamine and norepinephrine for treatment of hemodynamic compromise in amitriptyline intoxication. Crit Care Med. 1991;19(4):544–9.

98. Levine M, Curry SC, Padilla-Jones A, Ruha AM. Critical care management of verapamil and diltiazem overdose with a focus on vasopressors: a 25-year experience at a single center. Ann Emerg Med. 2013;62(3):252–8.

99. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care. 2015;30(3):653 e9–17.

100. White CM. A review of potential cardiovascular uses of intravenous glucagon administration. J Clin Pharmacol. 1999;39(5):442–7.

101. Doyon S, Roberts JR. The use of glucagon in a case of calcium channel blocker overdose. Ann Emerg Med. 1993;22(7):1229–33.

102. Walter FG, Frye G, Mullen JT, Ekins BR, Khasigian PA. Amelioration of nifedipine poisoning associated with glucagon therapy. Ann Emerg Med. 1993;22(7):1234–7.

103. Stone CK, May WA, Carroll R. Treatment of verapamil overdose with glucagon in dogs. Ann Emerg Med. 1995;25(3):369–74.

104. Salzberg MR, Gallagher EJ. Propranolol overdose. Ann Emerg Med. 1980;9(1):26–7.

105. Sensky PR, Olczak SA. High-dose intravenous glucagon in severe tricyclic poisoning. Postgrad Med J. 1999;75(888):611–2.

106. Sener EK, Gabe S, Henry JA. Response to glucagon in imipramine overdose. J Toxicol Clin Toxicol. 1995;33(1):51–3.

107. Wolf LR, Spadafora MP, Otten EJ. Use of amrinone and glucagon in a case of calcium channel blocker overdose. Ann Emerg Med. 1993;22(7):1225–8.

108. Hantson P, Ronveau JL, De Coninck B, Horn JL, Mahieu P, Hassoun A. Amrinone for refractory cardiogenic shock following chloroquine poisoning. Intensive Care Med. 1991;17(7):430–1.

109. Whitehurst VE, Vick JA, Alleva FR, Zhang J, Joseph X, Balazs T. Reversal of propranolol blockade of adrenergic receptors and related toxicity with drugs that increase cyclic AMP. Proc Soc Exp Biol Med. 1999;221(4):382–5.

110. Koury SI, Stone CK, Thomas SH. Amrinone as an antidote in experimental verapamil overdose. Acad Emerg Med. 1996;3(8):762–7.

111. Tuncok Y, Apaydin S, Gidener S, Guven H, Oto O, Ates M, et al. The effects of amrinone and glucagon on verapamil-induced myocardial depression in a rat isolated heart model. Gen Pharmacol. 1997; 28(5):773–6.

112. Vinetti M, Haufroid V, Capron A, Classen JF, Marchandise S, Hantson P. Severe acute cardiomyopathy associated with venlafaxine overdose and possible role of CYP2D6 and CYP2C19 polymorphisms. Clin Toxicol (Phila). 2011;49(9):865–9.

113. Lee KC, Canniff PC, Hamel DW, Pagani ED, Ezrin AM. Cardiovascular and renal effects of milrinone in beta-adrenoreceptor blocked and non-blocked anaesthetized dogs. Drugs Exp Clin Res. 1991; 17(3):145–58.

114. Kline JA, Leonova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. Crit Care Med. 1995;23(7):1251–63.

115. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol (Phila). 2011;49(4):277–83.

116. Kline JA, Tomaszewski CA, Schroeder JD, Raymond RM. Insulin is a superior antidote for cardiovascular toxicity induced by verapamil in the anesthetized canine. J Pharmacol Exp Ther. 1993;267(2):744–50.

117. Kline JA, Raymond RM, Leonova ED, Williams TC, Watts JA. Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. Cardiovasc Res. 1997;34(2):289–98.

118. Holger JS, Engebretsen KM, Fritzlar SJ, Patten LC, Harris CR, Flottemesch TJ. Insulin versus vasopressin and epinephrine to treat beta-blocker toxicity. Clin Toxicol (Phila). 2007;45(4):396–401.

119. Yuan TH, Kerns 2nd WP, Tomaszewski CA, Ford MD, Kline JA. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. J Toxicol Clin Toxicol. 1999;37(4):463–74.

120. Agarwal A, Yu SW, Rehman A, Henkle JQ. Hyperinsulinemia euglycemia therapy for calcium channel blocker overdose: a case report. Tex Heart Inst J. 2012;39(4):575–8.

121. Holger JS, Engebretsen KM, Marini JJ. High dose insulin in toxic cardiogenic shock. Clin Toxicol (Phila). 2009;47(4):303–7.

122. Holger JS, Stellpflug SJ, Cole JB, Harris CR, Engebretsen KM. High-dose insulin: a consecutive case series in toxin-induced cardiogenic shock. Clin Toxicol (Phila). 2011;49(7):653–8.

123. Jang DH, Spyres MB, Fox L, Manini AF. Toxin-induced cardiovascular failure. Emerg Med Clin North Am. 2014;32(1):79–102.

124. Jang DH, Donovan S, Nelson LS, Bania TC, Hoffman RS, Chu J. Efficacy of methylene blue in an experimental model of calcium channel blocker-induced shock. Ann Emerg Med. 2015;65(4):410–5.

125. Jang DH, Nelson LS, Hoffman RS. Methylene blue in the treatment of refractory shock from an amlodipine overdose. Ann Emerg Med. 2011; 58(6):565–7.

126. Aggarwal N, Kupfer Y, Seneviratne C, Tessler S. Methylene blue reverses recalcitrant shock in beta-blocker and calcium channel blocker overdose. BMJ Case Rep. 2013;2013.

127. Haikala H, Linden IB. Mechanisms of action of calcium-sensitizing drugs. J Cardiovasc Pharmacol. 1995;26 Suppl 1:S10–9.

128. Osthoff M, Bernsmeier C, Marsch SC, Hunziker PR. Levosimendan as treatment option in severe verapamil intoxication: a case report and review of the literature. Case Rep Med. 2010;2010:3.

129. Varpula T, Rapola J, Sallisalmi M, Kurola J. Treatment of serious calcium channel blocker overdose with levosimendan, a calcium sensitizer. Anesth Analg. 2009;108(3):790–2.

130. Teker MG, Ozdemir H, Saidoglu L, Erkalp K, Basaranoglu G. Levosimendan as a rescue adjunct in amlodipine intoxication–a case report. Middle East J Anaesthesiol. 2010;20(6):869–72.

131. Cave G, Harvey M, Willers J, Uncles D, Meek T, Picard J, et al. LIPAEMIC report: results of clinical use of intravenous lipid emulsion in drug toxicity reported to an online lipid registry. J Med Toxicol. 2014;10(2):133–42.

132. Weinberg G. Lipid rescue resuscitation from local anaesthetic cardiac toxicity. Toxicol Rev. 2006; 25(3):139–45.

133. Young AC, Velez LI, Kleinschmidt KC. Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. Resuscitation. 2009;80(5): 591–3.

134. Blaber MS, Khan JN, Brebner JA, McColm R. "Lipid rescue" for tricyclic antidepressant cardiotoxicity. J Emerg Med. 2012;43(3):465–7.

135. Cao D, Heard K, Foran M, Koyfman A. Intravenous lipid emulsion in the emergency department: a systematic review of recent literature. J Emerg Med. 2015;48(3):387–97.

136. Sirianni AJ, Osterhoudt KC, Calello DP, Muller AA, Waterhouse MR, Goodkin MB, et al. Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. Ann Emerg Med. 2008;51(4):412-5–5 e1.

137. Abdelmalek D, Schwarz ES, Sampson C, Halcomb SE, McCammon C, Arroyo-Plasencia A, et al. Life-threatening diphenhydramine toxicity presenting with seizures and a wide complex tachycardia improved with intravenous fat emulsion. Am J Ther. 2014; 21(6):542–4.

138. Finn SD, Uncles DR, Willers J, Sable N. Early treatment of a quetiapine and sertraline overdose with Intralipid. Anaesthesia. 2009;64(2):191–4.

139. Jakkala-Saibaba R, Morgan PG, Morton GL. Treatment of cocaine overdose with lipid emulsion. Anaesthesia. 2011;66(12):1168–70.

140. Dagtekin O, Marcus H, Muller C, Bottiger BW, Spohr F. Lipid therapy for serotonin syndrome after intoxication with venlafaxine, lamotrigine and diazepam. Minerva Anestesiol. 2011;77(1):93–5.

141. Geib AJ, Liebelt E, Manini AF, Toxicology IC. Clinical experience with intravenous lipid emulsion for drug-induced cardiovascular collapse. J Med Toxicol. 2012;8(1):10–4.

142. Levine M, Skolnik AB, Ruha AM, Bosak A, Menke N, Pizon AF. Complications following antidotal use of intravenous lipid emulsion therapy. J Med Toxicol. 2014;10(1):10–4.

143. American College of Medical Toxicology. ACMT position statement: interim guidance for the use of lipid resuscitation therapy. J Med Toxicol. 2011;7(1):81–2.

144. de Lange DW, Sikma MA, Meulenbelt J. Extracorporeal membrane oxygenation in the treatment of poisoned patients. Clin Toxicol (Phila). 2013;51(5):385–93.

145. Shenoi AN, Gertz SJ, Mikkilineni S, Kalyanaraman M. Refractory hypotension from massive bupropion overdose successfully treated with extracorporeal membrane oxygenation. Pediatr Emerg Care. 2011; 27(1):43–5.

146. Weinberg RL, Bouchard NC, Abrams DC, Bacchetta M, Dzierba AL, Burkart KM, et al. Venoarterial extracorporeal membrane oxygenation for the management of massive amlodipine overdose. Perfusion. 2014;29(1):53–6.

147. Masson R, Colas V, Parienti JJ, Lehoux P, Massetti M, Charbonneau P, et al. A comparison of survival with and without extracorporeal life support treatment for severe poisoning due to drug intoxication. Resuscitation. 2012;83(11):1413–7.

148. Palatinus JA, Lieber SB, Joyce KE, Richards JB. Extracorporeal membrane oxygenation support for hypokalemia-induced cardiac arrest: a case report and review of the literature. J Emerg Med. 2015; 49(2):159–64.

149. Eurosurveillance editorial team. The European Monitoring Centre for Drugs and Drug Addiction publishes the European Drug Report 2013: trends and developments. Euro Surveill. 2013;18(22):1–80.

150. Horburger D, Kurkciyan I, Sterz F, Schober A, Stockl M, Stratil P, et al. Cardiac arrest caused by acute intoxication-insight from a registry. Am J Emerg Med. 2013;31(10):1443–7.

151. Richman PB, Nashed AH. The etiology of cardiac arrest in children and young adults: special considerations for ED management. Am J Emerg Med. 1999;17(3):264–70.

152. Albertson TE, Dawson A, de Latorre F, Hoffman RS, Hollander JE, Jaeger A, et al. TOX-ACLS: toxicologic-oriented advanced cardiac life support. Ann Emerg Med. 2001;37(4 Suppl):S78–90.

153. Proano L, Chiang WK, Wang RY. Calcium channel blocker overdose. Am J Emerg Med. 1995;13(4): 444–50.

154. Quezado Z, Lippmann M, Wertheimer J. Severe cardiac, respiratory, and metabolic complications of massive verapamil overdose. Crit Care Med. 1991; 19(3):436–8.

155. Brass BJ, Winchester-Penny S, Lipper BL. Massive verapamil overdose complicated by noncardiogenic pulmonary edema. Am J Emerg Med. 1996; 14(5):459–61.

156. Coulter TD, Wiedemann HP. Complications of hemodynamic monitoring. Clin Chest Med. 1999; 20(2):249–67. vii.

157. Morris AH, Chapman RH, Gardner RM. Frequency of wedge pressure errors in the ICU. Crit Care Med. 1985;13(9):705–8.

158. Gnaegi A, Feihl F, Perret C. Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: time to act? Crit Care Med. 1997; 25(2):213–20.

159. Iberti TJ, Fischer EP, Leibowitz AB, Panacek EA, Silverstein JH, Albertson TE. A multicenter study of physicians' knowledge of the pulmonary artery catheter. Pulmonary Artery Catheter Study Group. JAMA. 1990;264(22):2928–32.

160. Yamada T, Tsutsui M, Sugo Y, Sato T, Akazawa T, Sato N, et al. Multicenter study verifying a method of noninvasive continuous cardiac output measurement using pulse wave transit time: a comparison with intermittent bolus thermodilution cardiac output. Anesth Analg. 2012;115(1):82–7.

161. Montenij LJ, de Waal EE, Buhre WF. Arterial waveform analysis in anesthesia and critical care. Curr Opin Anaesthesiol. 2011;24(6):651–6.

162. Linton RA, Band DM, Haire KM. A new method of measuring cardiac output in man using lithium dilution. Br J Anaesth. 1993;71(2):262–6.

163. Mora B, Ince I, Birkenberg B, Skhirtladze K, Pernicka E, Ankersmit HJ, et al. Validation of cardiac output measurement with the LiDCO pulse contour system in patients with impaired left ventricular function after cardiac surgery. Anaesthesia. 2011; 66(8):675–81.

164. Hadian M, Kim HK, Severyn DA, Pinsky MR. Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters. Crit Care. 2010;14(6):R212.

165. Alhashemi JA, Cecconi M, Hofer CK. Cardiac output monitoring: an integrative perspective. Crit Care. 2011;15(2):214.

166. Jones AE, Craddock PA, Tayal VS, Kline JA. Diagnostic accuracy of left ventricular function for identifying sepsis among emergency department patients with nontraumatic symptomatic undifferentiated hypotension. Shock. 2005;24(6):513–7.

167. Vieillard-Baron A, Page B, Augarde R, Prin S, Qanadli S, Beauchet A, et al. Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. Intensive Care Med. 2001;27(9):1481–6.

168. Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, et al. Utility of an integrated clinical, echocardiographic, and venous ultrasonographic approach for triage of patients with suspected pulmonary embolism. Am J Cardiol. 1998;82(10):1230–5.

169. Randazzo MR, Snoey ER, Levitt MA, Binder K. Accuracy of emergency physician assessment of left ventricular ejection fraction and central venous pressure using echocardiography. Acad Emerg Med. 2003;10(9):973–7.

170. Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. Am J Cardiol. 1990;66(4):493–6.

171. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685–713. quiz 86–8.

172. Jang T, Aubin C, Naunheim R, Lewis LM, Kaji AH. Jugular venous distension on ultrasound: sensitivity and specificity for heart failure in patients with dyspnea. Am J Emerg Med. 2011;29(9):1198–202.

173. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, et al. Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med. 2006;34(5):1402–7.

174. Evans D, Ferraioli G, Snellings J, Levitov A. Volume responsiveness in critically ill patients: use of sonography to guide management. J Ultrasound Med. 2014;33(1):3–7.

175. Marik PE, Levitov A, Young A, Andrews L. The use of bioreactance and carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. Chest. 2013;143(2):364–70.

176. Schelling G, Stoll C, Haller M, Briegel J, Manert W, Hummel T, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med. 1998;26(4):651–9.

177. Devlin JW. The pharmacology of oversedation in mechanically ventilated adults. Curr Opin Crit Care. 2008;14(4):403–7.

178. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med. 2003;168(12):1457–61.

179. Rock LF. Sedation and its association with posttraumatic stress disorder after intensive care. Crit Care Nurse. 2014;34(1):30–7. quiz 9.

180. Jones JG. Perception and memory during general anaesthesia. Br J Anaesth. 1994;73(1):31–7.

181. Rhoney DH, Murry KR. National survey of the use of sedating drugs, neuromuscular blocking agents, and reversal agents in the intensive care unit. J Intensive Care Med. 2003;18(3):139–45.

182. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA. 2012;307(11):1151–60.

183. Demuro JP, Mongelli MN, Hanna AF. Use of dexmedetomidine to facilitate non-invasive ventilation. Int J Crit Illn Inj Sci. 2013;3(4):274–5.

184. Devlin JW, Al-Qadheeb NS, Chi A, Roberts RJ, Qawi I, Garpestad E, et al. Efficacy and safety of early dexmedetomidine during noninvasive ventilation for patients with acute respiratory failure: a randomized, double-blind, placebo-controlled pilot study. Chest. 2014;145(6):1204–12.

185. Rayner SG, Weinert CR, Peng H, Jepsen S, Broccard AF, Study I. Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. Ann Intensive Care. 2012;2(1):12.

186. Ludtke KA, Stanley KS, Yount NL, Gerkin RD. Retrospective review of critically ill patients experiencing alcohol withdrawal: dexmedetomidine versus propofol and/or lorazepam continuous infusions. Hosp Pharm. 2015;50(3):208–13.

187. Mohorn PL, Vakkalanka JP, Rushton W, Hardison L, Woloszyn A, Holstege C, et al. Evaluation of dexmedetomidine therapy for sedation in patients with toxicological events at an academic medical center. Clin Toxicol (Phila). 2014;52(5): 525–30.

188. Shapiro BA, Warren J, Egol AB, Greenbaum DM, Jacobi J, Nasraway SA, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary.

Society of Critical Care Medicine. Crit Care Med. 1995;23(9):1596–600.

189. Young C, Knudsen N, Hilton A, Reves JG. Sedation in the intensive care unit. Crit Care Med. 2000; 28(3):854–66.

190. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest. 1998;114(2):541–8.

191. Kress JP, Hall JB. Sedation in the mechanically ventilated patient. Crit Care Med. 2006;34(10):2541–6.

192. Wheeler AP. Sedation, analgesia, and paralysis in the intensive care unit. Chest. 1993;104(2):566–77.

193. Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. Crit Care Med. 1997;25(1):33–40.

194. Kress JP, O'Connor MF, Pohlman AS, Olson D, Lavoie A, Toledano A, et al. Sedation of critically ill patients during mechanical ventilation. A comparison of propofol and midazolam. Am J Respir Crit Care Med. 1996;153(3):1012–8.

195. Pohlman AS, Simpson KP, Hall JB. Continuous intravenous infusions of lorazepam versus midazolam for sedation during mechanical ventilatory support: a prospective, randomized study. Crit Care Med. 1994;22(8):1241–7.

196. Malacrida R, Fritz ME, Suter PM, Crevoisier C. Pharmacokinetics of midazolam administered by continuous intravenous infusion to intensive care patients. Crit Care Med. 1992;20(8):1123–6.

197. Fragen RJ. Pharmacokinetics and pharmacodynamics of midazolam given via continuous intravenous infusion in intensive care units. Clin Ther. 1997; 19(3):405–19. discussion 367–8.

198. Sessler CN, Varney K. Patient-focused sedation and analgesia in the ICU. Chest. 2008;133(2):552–65.

199. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med. 2010; 38(12):2311–8.

200. Kam PC, Cardone D. Propofol infusion syndrome. Anaesthesia. 2007;62(7):690–701.

201. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med. 2000;342(20):1471–7.

202. Mattia C, Savoia G, Paoletti F, Piazza O, Albanese D, Amantea B, et al. SIAARTI recommendations for analgo-sedation in intensive care unit. Minerva Anestesiol. 2006;72(10):769–805.

203. Park G, Lane M, Rogers S, Bassett P. A comparison of hypnotic and analgesic based sedation in a general intensive care unit. Br J Anaesth. 2007;98(1):76–82.

204. Breen D, Karabinis A, Malbrain M, Morais R, Albrecht S, Jarnvig IL, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. Crit Care. 2005;9(3):R200–10.

205. Devabhakthuni S, Armahizer MJ, Dasta JF, Kane-Gill SL. Analgosedation: a paradigm shift in intensive care unit sedation practice. Ann Pharmacother. 2012; 46(4):530–40.

206. Mallick ASS, Bodenham AR. Local anaesthesia to the airway reduces sedation requirements in patients undergoing artificial ventilation. Br J Anaesth. 1966;77:731–4.

207. Marik PE, Kaufman D. The effects of neuromuscular paralysis on systemic and splanchnic oxygen utilization in mechanically ventilated patients. Chest. 1996;109(4):1038–42.

208. Pohlman AOCM, Olsen D, et al. Sedation with propofol lowers VO2 in critically ill patients. Am J Respir Crit Care Med. 1995;151:A325.

209. Hansen-Flaschen J, Cowen J, Raps EC. Neuromuscular blockade in the intensive care unit. More than we bargained for. Am Rev Respir Dis. 1993;147(1):234–6.

210. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med. 1992;327(8):524–8.

211. Shapiro BA, Warren J, Egol AB, Greenbaum DM, Jacobi J, Nasraway SA, et al. Practice parameters for sustained neuromuscular blockade in the adult critically ill patient: an executive summary. Society of Critical Care Medicine. Crit Care Med. 1995;23(9):1601–5.

212. Watling SM, Dasta JF. Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: a review of the literature. Crit Care Med. 1994;22(5):884–93.

213. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med. 1994;150(4):896–903.

214. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med. 1995;332(6):345–50.

215. Hall JB, Wood LD. Liberation of the patient from mechanical ventilation. JAMA. 1987;257(12):1621–8.

216. Millbern SM, Downs JB, Jumper LC, Modell JH. Evaluation of criteria for discontinuing mechanical ventilatory support. Arch Surg. 1978;113(12):1441–3.

217. Sahn SA, Lakshminarayan S. Bedside criteria for discontinuation of mechanical ventilation. Chest. 1973;63(6):1002–5.

218. Manthous CA, Schmidt GA, Hall JB. Liberation from mechanical ventilation: a decade of progress. Chest. 1998;114(3):886–901.

219. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from

mechanical ventilation. N Engl J Med. 1991; 324(21):1445–50.

220. Chatila W, Jacob B, Guaglionone D, Manthous CA. The unassisted respiratory rate-tidal volume ratio accurately predicts weaning outcome. Am J Med. 1996;101(1):61–7.

221. Jacob B, Chatila W, Manthous CA. The unassisted respiratory rate/tidal volume ratio accurately predicts weaning outcome in postoperative patients. Crit Care Med. 1997;25(2):253–7.

222. Esteban A, Alia I. Clinical management of weaning from mechanical ventilation. Intensive Care Med. 1998;24(10):999–1008.

223. Fisher MM, Raper RF. The 'cuff-leak' test for extubation. Anaesthesia. 1992;47(1):10–2.

224. Miller RL, Cole RP. Association between reduced cuff leak volume and postextubation stridor. Chest. 1996;110(4):1035–40.

225. Brainsky A, Fletcher RH, Glick HA, Lanken PN, Williams SV, Kundel HL. Routine portable chest radiographs in the medical intensive care unit: effects and costs. Crit Care Med. 1997;25(5):801–5.

226. Strain DS, Kinasewitz GT, Vereen LE, George RB. Value of routine daily chest x-rays in the medical intensive care unit. Crit Care Med. 1985;13(7):534–6.

227. Greenbaum DM, Marschall KE. The value of routine daily chest x-rays in intubated patients in the medical intensive care unit. Crit Care Med. 1982;10(1):29–30.

228. Bekemeyer WB, Crapo RO, Calhoon S, Cannon CY, Clayton PD. Efficacy of chest radiography in a respiratory intensive care unit. A prospective study. Chest. 1985;88(5):691–6.

229. Hall JB, White SR, Karrison T. Efficacy of daily routine chest radiographs in intubated, mechanically ventilated patients. Crit Care Med. 1991;19(5):689–93.

230. Liolios A, Oropello JM, Benjamin E. Gastrointestinal complications in the intensive care unit. Clin Chest Med. 1999;20(2):329–45. viii.

231. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. N Engl J Med. 1998;338(12):791–7.

232. Legere BM, Dweik RA, Arroliga AC. Venous thromboembolism in the intensive care unit. Clin Chest Med. 1999;20(2):367–84. ix.

233. Hojer J, Troutman WG, Hoppu K, Erdman A, Benson BE, Megarbane B, et al. Position paper update: ipecac syrup for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):134–9.

234. Benson BE, Hoppu K, Troutman WG, Bedry R, Erdman A, Hojer J, et al. Position paper update: gastric lavage for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):140–6.

235. Chyka PA, Seger D, Krenzelok EP, Vale JA, American Academy of Clinical Toxicology, European Association of Poisons Centre, et al. Position paper: single-dose activated charcoal. Clin Toxicol (Phila). 2005; 43(2):61–87.

236. Merigian KS, Woodard M, Hedges JR, Roberts JR, Stuebing R, Rashkin MC. Prospective evaluation of gastric emptying in the self-poisoned patient. Am J Emerg Med. 1990;8(6):479–83.

237. Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. J Toxicol Clin Toxicol. 1999;37(6):753–7.

238. Hillman RJ, Prescott LF. Treatment of salicylate poisoning with repeated oral charcoal. Br Med J (Clin Res Ed). 1985;291(6507):1472.

239. Chyka PA, Holley JE, Mandrell TD, Sugathan P. Correlation of drug pharmacokinetics and effectiveness of multiple-dose activated charcoal therapy. Ann Emerg Med. 1995;25(3):356–62.

240. Arimori K, Nakano M. Accelerated clearance of intravenously administered theophylline and phenobarbital by oral doses of activated charcoal in rats. A possibility of the intestinal dialysis. J Pharmacobiodyn. 1986;9(5):437–41.

241. Neuvonen PJ, Elonen E. Effect of activated charcoal on absorption and elimination of phenobarbitone, carbamazepine and phenylbutazone in man. Eur J Clin Pharmacol. 1980;17(1):51–7.

242. Wason S, Baker RC, Carolan P, Seigel R, Druckenbrod RW. Carbamazepine overdose–the effects of multiple dose activated charcoal. J Toxicol Clin Toxicol. 1992;30(1):39–48.

243. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. J Toxicol Clin Toxicol. 1999;37(6):731–51.

244. Beckley I, Ansari NA, Khwaja HA, Mohsen Y. Clinical management of cocaine body packers: the Hillingdon experience. Can J Surg. 2009;52(5):417–21.

245. Farmer JW, Chan SB. Whole body irrigation for contraband bodypackers. J Clin Gastroenterol. 2003; 37(2):147–50.

246. Hoffman RS, Smilkstein MJ, Goldfrank LR. Whole bowel irrigation and the cocaine body-packer: a new approach to a common problem. Am J Emerg Med. 1990;8(6):523–7.

247. Givens ML, Gabrysch J. Cardiotoxicity associated with accidental bupropion ingestion in a child. Pediatr Emerg Care. 2007;23(4):234–7.

248. Narsinghani U, Chadha M, Farrar HC, Anand KS. Life-threatening respiratory failure following accidental infusion of polyethylene glycol electrolyte solution into the lung. J Toxicol Clin Toxicol. 2001;39(1):105–7.

249. Thanacoody R, Caravati EM, Troutman B, Hojer J, Benson B, Hoppu K, et al. Position paper update: whole bowel irrigation for gastrointestinal decontamination of overdose patients. Clin Toxicol (Phila). 2015;53(1):5–12.