The Crashing Toxicology Patient

Aaron Skolnik, MD[a,b,*], Jessica Monas, MD[b]

KEYWORDS

• Toxicology • Poisoning • Overdose • Critical care • Intensive care • ECMO • Kidney injury • Hemodialysis

KEY POINTS

- Conventional antiepileptics are typically ineffective at terminating drug-induced seizures or status epilepticus.
- Drug-induced cardiogenic shock treatment differs from conventional shock therapy in the use of antidotes, such as hyperinsulinemic-euglycemic therapy for calcium-channel blocker or beta-blocker toxicity, among first-line treatments.
- Poisoned patients who require extracorporeal life support (ECLS) for refractory drug-induced acute respiratory distress syndrome, cardiogenic shock, or cardiac arrest may have improved survival compared with those with other indications and should be considered for emergent ECLS.
- Drugs are the leading cause of acute liver failure in the United States and Europe. Treatment with N-acetylcysteine should be started for all patients with suspected drug-induced liver failure and such patients should be referred to a transplant-capable center.
- Many critically poisoned patients have a conventional indication for renal replacement therapy. If drug or toxin removal is desired, intermittent hemodialysis provides superior clearance to continuous therapies.

INTRODUCTION

Emergency physicians are well equipped to deal with routine drug- and toxin-related visits to the emergency department (ED). Recently, poisoning-related ED visits have been increasing, and with them, lengths of stay, patient complexity, resource utilization, and likelihood of hospital admission.[1] In 2017, the Centers for Disease Control and Prevention reported 75,354 poisoning deaths in the United States.[2] Patients are often sickest in the first few hours of their illness. Therefore, emergency physicians

[a] Department of Critical Care Medicine, Mayo Clinic Hospital, 5777 East Mayo Boulevard, Phoenix, AZ 85054, USA; [b] Department of Emergency Medicine, Mayo Clinic Alix School of Medicine, Mayo Clinic Hospital, 5777 East Mayo Boulevard, Phoenix, AZ 85054, USA
* Corresponding author. Department of Critical Care Medicine, Mayo Clinic Hospital, 5777 East Mayo Boulevard, Phoenix, AZ 85054, USA.
E-mail address: Skolnik.aaron@mayo.edu
Twitter: @ToxCCM (A.S.)

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and intensivists bear the primary responsibility for the diagnosis and management of the crashing toxicology patient. Diagnostic testing and specific antidotes are secondary to the immediate resuscitation and stabilization of these patients with multiple organ failure.

NEUROLOGIC TOXICITY

Seizures and Status Epilepticus

Drug-induced seizures are common, responsible for up to 9% of status epilepticus cases and 6% of new-onset seizures in some series.[3] Status epilepticus may develop more frequently in drug-induced seizures, complicating up to 10% of cases.[3] Compared with non–drug-induced seizures, seizures due to drug ingestion have a higher rate of complications, including hypoxia, hypercapnia, rhabdomyolysis, metabolic acidosis, elevated lactate, and brain injury from excessive metabolic demand,[4] as well as mortality. Unlike most epilepsy, drug-induced seizures begin as a generalized brain process, often resulting from an acute imbalance in inhibitory (gamma aminobutyric acid [GABA]) and excitatory (acetylcholine, glutamate, dopamine, norepinephrine, and serotonin) transmission. This may be related to $GABA_A$ receptor antagonism or modulation, withdrawal from chronic use of $GABA_A$ or $GABA_B$ agonists, or excessive excitatory transmission (**Table 1**). For this reason, conventional antiepileptic drugs, notably phenytoin, are typically ineffective in terminating them.[5]

Treatment of drug-induced seizures is focused on immediate stabilization and restoration of inhibitory neurotransmission. Although assessing and managing the patient's airway, point-of-care (POC) glucose and sodium should be tested or empirical dextrose administered if testing is unavailable. Hypotension may be treated with empirical administration of balanced crystalloid solution or vasopressors if fluid-nonresponsive. Core temperature should be measured and hyperthermia treated with active cooling measures. The first-line agents in the treatment of drug-induced seizures are the $GABA_A$ agonists and benzodiazepines, listed in **Table 2**.[6] If isoniazid or hydrazine (ie, *Gyromitra esculenta* [false morel] mushroom poisoning) is suspected, pyridoxine should be administered.[7] If the patient remains in status epilepticus, second-line agents should be used. Second-line agents include phenobarbital, high-dose midazolam infusion, and propofol. The dose of propofol required to achieve burst suppression is higher than typically used for intensive care unit (ICU) sedation.[8] Ketamine shows promise, but a lack of randomized controlled trials prohibits its recommendation as part of algorithmic treatment.[9]

Table 1
Seizures related to poisonings

Mechanism	Common Agents
$GABA_A$ receptor antagonism or modulation	Flumazenil, ciprofloxacin, clozapine, cicutoxin
Withdrawal from chronic use of $GABA_A$ or $GABA_B$ agonists	Ethanol, benzodiazepines, barbiturates, baclofen, gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL)
Excessive excitatory transmission	Sympathomimetics, serotonin syndrome, monoamine oxidase inhibitors
Inhibition of GABA generation	Isoniazid, hydrazines, *Gyromitra* mushrooms
Adenosine antagonism	Carbamazepine, caffeine, theophylline

Table 2
Treatment of drug-induced seizures

Initial Stabilization	• Provide supportive care ◦ Assess and manage the airway ◦ Manage hypotension ■ Give balanced crystalloid solution ■ Give vasopressors if fluid-unresponsive ◦ Check for and manage hyperthermia • Check point-of-care laboratories (glucose, basic metabolic panel) ◦ Give empirical dextrose, 25 grams, IV if unable to assess
First-line Treatment	• Give first-line medication ◦ Benzodiazepines ■ Lorazepam, 4 mg, IV q4–5 min or ■ Midazolam, 5 mg, IM ◦ If isoniazid or hydrazine suspected ■ Pyridoxine • Gram-for-gram based on ingested isoniazid amount or • 25 mg/kg IV over 15–30 min up to 5 g
Second-line Treatment	• Secure the airway if not already done • Give second-line medication ◦ Phenobarbital IV or ◦ High-dose midazolam or ◦ Propofol, 80 mcg/kg/min
Diagnostic Considerations	• Send urine drug screen, acetaminophen, and salicylate levels • Send antiepileptic drug levels as indicated • Obtain head CT scan ◦ If status epilepticus, head trauma, or prolonged postictal state • Obtain continuous EEG monitoring ◦ If status epilepticus
Disposition	• Admit to ICU

Diagnostic Considerations: Neurotoxicity

Patients with underlying epilepsy may experience drug-induced seizures, even while taking medications as prescribed. In addition, some antiepileptic drugs, such as carbamazepine, may induce seizures at supratherapeutic concentrations.[10] Patients with antiepileptic drug exposure should have drug levels tested. A urine or serum drugs of abuse screen is of limited utility, but a positive result may be helpful if subsequent workup is otherwise negative. Blood levels of common poisons, including acetaminophen and salicylate, should be tested, as salicylates may cause fatal neurotoxicity. Patients with status epilepticus, a prolonged postictal period, or signs or history concerning for head trauma should undergo noncontrast computed tomography (CT) scan of the head. Regardless of the use of neuromuscular blockers for intubation, patients who presented with status epilepticus should undergo continuous electroencephalography monitoring, as 14% of treated generalized convulsive status epilepticus may evolve into nonconvulsive status epilepticus.[11] All patients with drug-induced status epilepticus or complicated seizures should be admitted to the ICU.

RESPIRATORY FAILURE

A large number of drugs are capable of causing acute respiratory failure through multiple mechanisms. Numerous central nervous system depressants cause central

hypoventilation. In the current era, opioids are one of the most commonly encountered causes of drug-induced respiratory failure by the emergency physician.[12] If opioid intoxication is on the differential in a patient with hypoventilation, trial administration of naloxone is warranted. Naloxone has proved to be relatively safe but can rarely cause serious pulmonary and cardiac complications.[13] These may be due to a rapid increase in catecholamine levels associated with acute opioid antagonism and seem to increase in incidence with higher initial (>0.4 mg) and total (>4.4 mg) doses of naloxone.[14] Unfortunately, multiple administrations and higher initial doses of naloxone may be required to reverse overdoses of fentanyl analogues or other novel synthetics.[15] Many sedating agents can also cause or exacerbate hypercapnic respiratory failure or lead to loss of airway protective reflexes.

Toxins that cause neuromuscular weakness, such as organophosphate pesticides or nerve agents, can cause hypoventilation, failure of secretion clearance, and respiratory arrest. Many drugs can cause acute respiratory distress syndrome (ARDS) in overdose (ie, salicylate, calcium channel blockers).[16] Cardiogenic (ie, beta blockers, cocaine) and neurogenic (ie, naloxone) pulmonary edema are also well described.

All causes of respiratory failure are initially managed supportively with endotracheal intubation and lung-protective mechanical ventilation strategies. Toxicology patients may have suffered prolonged immobilization, and acute kidney injury is common, so nondepolarizing neuromuscular blockers are recommended for rapid sequence intubation. For refractory hypoxic or hypercapnic respiratory failure, venovenous extracorporeal membrane oxygenation (V-V ECMO) has also been used with relatively high survival rates (see the later discussion *Mechanical Circulatory Support*).[17]

CARDIOVASCULAR TOXICITY

Drug-Induced Tachycardia and Malignant Dysrhythmias

Sympathomimetic or anticholinergic poisoning may produce sinus tachycardia. Classically, these entities are distinguished by dry mucous membranes and axillary skin in the anticholinergic patient.[18] Reflex tachycardia in response to peripheral vasodilation can occur but is relatively rare, with the exception of dihydropyridine calcium channel blocker poisoning. Many drugs are associated with increased risk for malignant tachydysrhythmias. Common mechanisms include sodium channel blockade resulting in QRS widening, potassium efflux blockade resulting in QTc prolongation and torsades de pointes, sympathomimesis leading to increased myocardial irritability, and sensitization of the myocardium to endogenous catecholamines.[19] The agents associated with tachydysrhythmias in a retrospective review of poison control data are listed in **Table 3**.[20] Initial treatment of pulseless dysrhythmias of unknown cause should follow Advanced Cardiac Life Support (ACLS) guidelines, in an attempt to restore spontaneous circulation.

Drug-Induced Bradycardia

Drug-induced bradycardia, including atrioventricular conduction blocks of varying degree, can be attributed to several drug classes. Most notorious are calcium channel antagonists and beta-adrenergic antagonists, the 2 classes responsible for most of the fatalities among cardiac drug poisoning. In nondiabetic patients, a markedly elevated glucose in the presence of hypotension and bradycardia or conduction blocks directs suspicion to calcium channel blocker poisoning.[21] **Table 3** lists agents known to cause significant bradycardia.[22] Drug-induced symptomatic bradycardia is treated according to ACLS and may respond to atropine. Calcium administered via IV bolus or infusion may improve inotropy and blood pressure but fails to improve

Table 3
Dysrhythmias related to poisonings

Cardiac Disturbance	Common Agents
Sinus tachycardia	Sympathomimetics, anticholinergics
Wide-complex tachycardia	Tricyclic antidepressants, stimulants (cocaine), diphenhydramine, citalopram, propoxyphene, bupropion, lithium, lamotrigine, and antiarrhythmic drugs
Torsades de pointes	Cyclic antidepressants, methadone, antipsychotics, and antiarrhythmics
Bradycardia/heart block	Calcium channel antagonists, beta adrenergic antagonists, cardiac glycosides (ie, digoxin), organophosphorous or carbamate compounds (ie, nerve agents, malathion, pyridostigmine, central alpha-2 agonists (ie, clonidine, guanfacine)

bradycardia in animal models; effects in human case reports have been mixed.[23] Treatment of toxicologic bradycardia has included transcutaneous and transvenous cardiac pacing, but electrical capture may not occur reliably.[23] For patients with significant dysrhythmia, hyperkalemia (>6 mmol/L), or hemodynamic instability following known or suspected cardiac glycoside poisoning, digoxin Fab fragments may be administered as described in **Table 4**.[24]

Sodium Bicarbonate

Drug-induced sodium channel blockade and resulting wide complex tachycardia have been reported across a wide variety of drugs (see **Table 3**). The first-line antidote of choice is sodium bicarbonate, although the exact mechanism by which sodium bicarbonate reverses blockade is incompletely understood. Traditional treatment thresholds for sodium bicarbonate administration have been based on QRS duration, although there is variability on when to begin treatment.[25] Because a normal QRS duration varies from 80 to 100 msec, in wide complex tachycardia suspected to be drug related, it is reasonable to administer a trial dose of sodium bicarbonate if QRS duration is greater than 120 msec and promptly reexamine the ECG for QRS narrowing. If the QRS narrows, an infusion of sodium bicarbonate should be administered to maintain a target blood pH of 7.45 to 7.55. Patients should be monitored with serial arterial blood gases to control pH and serial electrolyte testing because of the risk of hypokalemia due to transcellular potassium shifts.[26]

Lipid Emulsion

Antidotal intravenous lipid emulsion (ILE) first emerged as a treatment of local anesthetic toxicity. Administration of large amounts of concentrated lipid (typically a 20% solution) reversed cardiovascular toxicity of local anesthetics in animal models and human case reports.[27] Thereafter, rescue use of ILE was reported across a wide variety of overdoses including cyclic antidepressants, calcium channel blockers, and beta blockers. Several mechanisms have been proposed for lipid emulsion's reported salutary effects on hemodynamics: a "lipid sink" into which soluble drugs preferentially distribute, supply of free fatty acids for cardiac metabolism in the stunned heart, and inhibition of endothelial nitric oxide synthase.[28] Use of ILE to treat overdose patients has expanded to include non–life-threatening overdoses, but a recent systematic review found the effects in these cases to be heterogeneous.[28] Multiple complications have been reported including lipemic laboratory interference, acute kidney

Table 4
Dosing for common antidotes

Antidote	Indications	Bolus	Infusion
Intravenous NAC	Acetaminophen poisoning (based on >4-h level and nomogram) Acute liver failure	150 mg/kg loading dose over 1 h, followed by:	12.5 mg/kg/h for 4 h, followed by 6.25 mg/kg/h at least 16 h (see text for termination criteria)
Glucagon	Beta blocker overdose with myocardial dysfunction	50–150 μg/kg, up to 10 mg IV	Start infusion at same dose in mg required for response. For example, 5 mg effective bolus dose followed by a 5 mg/h infusion
Insulin	Calcium channel or beta blocker overdose with myocardial dysfunction	1 U/kg IV bolus, followed by:	1–2 U/kg/h titrated every 15 min, up to a maximum rate of 10 U/kg/h
Sodium bicarbonate	Wide QRS dysrhythmia (QRS duration >120 msec) Urine alkalization	1–2 mEq/kg of 8.4% sodium bicarbonate IV	150 mEq/L of sodium bicarbonate in 1 L of dextrose 5% water or 8.4% sodium bicarbonate solution (1mEq/mL)
Digoxin fab fragments	Life-threatening dysrhythmia, hemodynamic instability, or hyperkalemia >5 mEq/L associated with digoxin or cardiac glycoside poisoning	May be administered at an initial empirical dose of 400 mg (10 vials) in cases of imminent cardiac arrest or 80 mg (2 vials) otherwise	Can consider half-molar reversal in patients at risk of cardiac deterioration due to underlying heart disease
Lorazepam	Drug-induced status epilepticus (first-line agent)	4 mg IV every 4–5 min until seizures abate	
Pyridoxine	Isoniazid poisoning Hydrazine or *Gyromitra mushroom poisoning* Intractable drug-induced seizures	Administer on a gram-for-gram basis to the amount of isoniazid ingested OR 25 mg/kg IV over 15–30 min, up to 5 g in adult patients	
Propofol	Drug-induced status epilepticus		Propofol titration is required to achieve EEG burst suppression (typically >80 mcg/kg/min).
Naloxone	Opioid poisoning	In hospital settings where oxygenation and ventilation are supported, titration of 0.04 mg IV every 1–2 min until respiratory rate is >10 may avoid rapidly precipitated	For patients with recurrent respiratory depression or resedation after naloxone, start IV infusion at 2/3 of the dose required

		withdrawal Can also be given 0.4–2 mg IM OR 4 mg intranasal if no IV access. Initial dosing may be repeated if fails to respond. Higher doses (>10 mg) may be required for novel or highly potent opioids	for reversal, given hourly (ie, if 1 mg reversed, start infusion at 0.66 mg/h)
Hydroxo-cobalamin	Cyanide poisoning Refractory vasoplegia	5 g IV over 15 min	5 g dose may be repeated, infused intravenously over 15 min to 2 h, based on clinical status, for a total dose of 10 g

injury, cardiac arrest, ventilation/perfusion mismatch, ARDS, venous thromboembolism, hypersensitivity, fat embolism or overload syndrome, pancreatitis, allergic reaction, and increased susceptibility to infection.[29] In patients on venoarterial extracorporeal membrane oxygenation (VA-ECMO), fat emulsion has been reported to cause agglutination in the circuit, cracking of stopcocks, oxygenator dysfunction, and an increase in circuit thrombosis.[30]

The American Academy of Clinical Toxicology's evidence-based recommendations support ILE use for cardiac arrest resulting from bupivacaine toxicity but recommend *against* using ILE as first-line therapy for most other poisonings. If other therapies fail, they recommend ILE for bupivacaine toxicity and suggest ILE for toxicity due to other local anesthetics, amitriptyline, and bupropion, but their recommendations are neutral for all other toxins.[31] Lipid emulsion may be considered for drug-induced cardiac arrest when other antidotes have failed, and advanced therapies such as mechanical circulatory support are not immediately available.

CARDIOGENIC AND VASODILATORY SHOCK

Vasopressors and Inotropes

Emergency physicians commonly use intravenous fluids and vasopressors in the initial resuscitation of patients with hypotension or shock of unknown cause, including patients with drug-induced shock. With the advent of ED POC ultrasonography, distinguishing between vasodilatory, cardiogenic, and mixed shock should guide empirical therapy with respect to fluid tolerance, vasopressors, and inotropes. For example, dihydropyridine calcium channel antagonists may initially produce vasodilatory shock that may respond to calcium and vasopressors alone. Other calcium channel antagonists, or dihydropyridines taken in sufficient quantity such that receptor specificity is lost, may produce cardiogenic shock with myocardial depression, favoring the use of inotropes.

Concerns around the use of vasopressors to treat drug-induced shock have centered around ischemic complications and adverse effects on cardiac metabolism and cardiac output, primarily based on animal models.[32] A single-center retrospective review of verapamil and diltiazem overdoses managed with high doses of vasopressors and inotropes reported high survival with a low rate of ischemic complications.[33] In a systematic review of vasopressors in the treatment of toxin-induced cardiogenic shock, the investigators reported a lack of detrimental effects of vasopressors and high survival among the patients included in their study.[32] Although the investigators note that treatment failures of vasopressors are likely underreported, it is also likely that treatment successes are underreported, as the reversal of hypotension with vasopressors is not a case-reportable event. A systematic review of the treatment of calcium channel blocker poisoning found that dopamine and norepinephrine improved hemodynamic parameters and survival without documented severe side effects, although evidence quality was very low.[34] It is therefore reasonable, after optimizing volume status, to administer vasopressors or inotropes to support hemodynamic parameters in patients with cardiovascular drug toxicity. Ideally, this should be guided by invasive (pulmonary artery catheterization) or noninvasive (echocardiography, pulse contour analysis) hemodynamic monitoring.

Hyperinsulinemic-Euglycemic Therapy

Hyperinsulinemic-euglycemic therapy (HIET), primarily used for calcium channel blocker and beta blocker poisoning, consists of administration of very high doses of insulin, often coadministered with concentrated dextrose infusions to maintain

euglycemia. Cardiac myocytes stunned by drug toxicity alter their metabolism from primarily free fatty acid utilization to favor carbohydrate metabolism.[35] In animal models of drug-induced cardiogenic shock, insulin administration has been shown to improve both systolic and diastolic cardiac function[36] and seems to have independent positive inotropic effects on failing human myocardium.[37] Calcium channel blocker poisoning causes insulin resistance, and antagonism of pancreatic L-type calcium channels inhibits calcium-mediated insulin release.[3] These effects, combined with the physiologic stress response, lead to hyperglycemia and relative hypoinsulinemia.[38] In one retrospective study of verapamil and diltiazem overdose, the degree of hyperglycemia was a better predictor of illness severity than hemodynamics.[21] The mechanism of HIET as an antidote relies on meeting altered cardiac metabolic demands, improving inotropy, and peripheral vasodilation, improving organ perfusion. Therefore, HIET is best used in cases of calcium channel blocker– or beta blocker–induced cardiogenic shock with impaired myocardial contractility.

Recent consensus guidelines on treatment of calcium channel blocker poisoning recommend HIET as part of first-line therapies.[39] Once initiated, insulin infusion rates can be titrated to clinical effect.[40,41] A concentrated dextrose infusion, often dextrose 50% at 25 g/h, is used to maintain euglycemia. All infusions should be concentrated to avoid pulmonary edema resulting from drug effect, volume overload, or acute left ventricular dysfunction. Hypokalemia, hyponatremia, and hypoglycemia are common, even with poison center or toxicologist oversight, and must be carefully monitored during treatment.[42]

Glucagon

The pancreatic hormone glucagon circumvents poisoning of the β1 adrenergic receptor via agonism at the G-protein coupled glucagon receptor. The downstream result is similar to stimulation of adenylate cyclase and increase in cellular cyclic AMP. Pharmacologic effects include increased inotropy and chronotropy, supported by animal models of beta blocker poisoning.[43] Use of glucagon in the treatment of human beta blocker overdose has shown mixed results, however.[23] In animal models of propranolol and verapamil toxicity, glucagon was inferior to HIET as an antidote.[44] The side effect profile of glucagon is favorable, with dose-dependent nausea, vomiting, and hyperglycemia. In patients with appropriate level of consciousness and intact airway protective reflexes, or a protected airway, glucagon may be used for known or suspected beta antagonist poisoning with myocardial dysfunction or cardiogenic shock. If a favorable clinical response is observed after a bolus, an infusion can then be started at the same dose in milligram required for response per hour.[23]

Methylene Blue

Methylene blue is proposed to treat refractory vasodilatory shock through inhibition of soluble guanylyl cyclase and nitric oxide synthase in the nitric oxide pathway, with a downstream decrease in vasodilation and concomitant increase in systemic vascular resistance.[45] A systematic review of methylene blue for drug-induced shock found only case reports and abstracts, with variable effects on hemodynamics. These data being subject to lack of randomization, publication bias, confounding by other therapies, and incomplete reporting, the investigators concluded there is insufficient evidence to recommend methylene blue for drug-induced shock.[46] Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency due to risk of hemolysis.[47] Although no serious adverse effects were reported in any of the cases reviewed earlier, it should be noted that methylene blue has been

reported to precipitate serotonin syndrome in patients taking other serotonergic medications.[48]

Hydroxocobalamin

Hydroxocobalamin is well established as a cyanide antidote. In cases of severe cyanide exposure, defined by unconsciousness, seizure, and cardiac or respiratory compromise, there is little downside to empirical treatment with hydroxocobalamin. For patients with smoke inhalation and possible cyanide exposure, one evidence-based algorithm for cyanide treatment based on ED POC testing recommends immediate empirical treatment of any severe exposure.[49]

Hydroxocobalamin has also been used as a rescue therapy for refractory vasodilatory shock, based on its ability to scavenge nitric oxide (NO) and reverse NO-mediated vasoplegia.[50] This effect was noted as a hypertensive response in volunteer studies of the drug and later followed by its successful use in cardiac surgery to reverse postcardiopulmonary bypass vasoplegic syndrome.[51] There are no reports of hydroxocobalamin treatment of shock resulting from noncyanide overdoses. In a large (greater than 5-fold) iatrogenic overdose of hydroxocobalamin, the only clinically significant effect was erythroderma, which resolved.[52] Hydroxocobalamin, administered at the cyanide treatment dose, has a favorable side-effect profile and can be considered a last-line treatment of refractory drug-induced vasoplegia, although evidence is limited.[53]

Mechanical Circulatory Support in Toxicology Patients

Critically poisoned patients may be ideal candidates for extracorporeal life support (ECLS). Overdose patients tend to be younger and have fewer comorbid conditions than those with cardiac indications. If these patients can be supported until toxicity wanes, excellent recovery is anticipated. Despite this, the use of ECLS in poisoned patients remains rare.[54] The use of mechanical circulatory supports including the intra-aortic balloon pump and the Impella (Abiomed, Danvers, MA, USA) percutaneous left ventricular assist device has been reported in poisoned patients, but the evidence for these devices is sparse.

Although still uncommon, ECMO is the most reported mechanical support modality for poisoned patients. In a series of patients undergoing emergent percutaneous ECMO, outcomes were superior in the poisoned cohort to those with primary cardiac indications.[55] Another series compared 12 patients treated with ECMO for poisoning-related shock with 5 patients with cardiovascular indications. All patients required continuous CPR for greater than 45 minutes at the time of cannulation for VA-ECMO. Three of 12 poisoned patients survived, whereas none of the nonpoisoned patients survived.[56] Masson and colleagues[57] examined 62 poisoned patients in persistent shock or cardiac arrest, of whom 14 were treated with VA-ECMO. In the ECMO cohort, 86% survived compared with 48% of the conventionally treated cohort. Notably, the number of included patients is small and the results fragile. An analysis of the Extracorporeal Life Support Organization registry showed that use of ECMO for poisoned patients continues to increase dramatically, and survival was 59% overall and 89% for the subgroup undergoing V-V ECMO for inhalational or aspiration injury.[17] Poisoned patients with severe refractory hypoxia failing conventional treatment, persistent cardiogenic shock, or cardiac arrest should be evaluated for ECMO, if available. If an ECMO retrieval service is available at a non-ECMO capable center, they should be consulted urgently for the critically ill poisoned patients described earlier, based on high predicted mortality with conventional treatment and high rates of ECLS survival in this population.

Drug-Induced Liver Failure

Acute liver failure (ALF), also referred to as acute fulminant hepatic failure, is defined by an acute (<26 weeks) insult with liver injury, encephalopathy, and synthetic dysfunction (elevated international normalized ratio >1.5), in a patient without underlying liver disease.[58] Drugs are the leading cause of ALF in the United States and Europe, with acetaminophen (APAP) comprising most of the cases and nonacetaminophen–induced ALF (11%) of all cases in the United States Acute Liver Failure Study Group registry.[59] Patients who present with ALF from APAP are already late in the course of their illness because of the time required to develop liver injury from its toxic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI). Patients who present in ALF with marked transaminitis, low bilirubin, and elevated INR are most likely to have APAP-induced ALF.

N-acetylcysteine (NAC), which works by replenishing hepatic glutathione stores, detoxification of NAPQI, and antiinflammatory properties, has been shown to improve survival from APAP overdose.[60] NAC has a favorable safety profile when dosed correctly. All adult patients with ALF should be started on NAC according to the acetaminophen antidote dosing, until APAP level is undetectable, with improving aminotransferases and improving clinical biomarkers such as creatinine, lactate, pH, prothrombin time/INR, and phosphate. Pre-bolusing NAC or infusions at higher rates may be warranted in some cases and should be guided by toxicology consultation.[61] Reversal of coagulopathy is not recommended unless clinically significant bleeding occurs or it is required for invasive procedures, as degree of coagulopathy influences all predictive models for liver transplantation.

Hyperammonemia can cause cerebral edema and elevated intracranial pressure (ICP) via its conversion to glutamine in astrocytes. There is no evidence for the utility of lactulose or rifaximin to lower ammonia in ALF. For refractory hyperammonemia (>100 μmol/L) or high-grade encephalopathy in which the prevalence of intracranial hypertension is high, continuous renal replacement therapy can be used to reduce ammonia levels, although outcomes-based evidence is limited.[58] There is no accepted consensus on the risks versus benefits of invasive ICP monitoring in patients with ALF, and institutional practice varies.[62,63]

The only other treatment proved to improve survival for ALF is emergency liver transplantation, although survival is lower than in those undergoing elective liver transplant.[64] Multiple prognostic criteria exist for both APAP and all-cause ALF. Two of the most widely used are the King's College Criteria (composed of one set of criteria for APAP and another for non-APAP patients) and the Model for End-Stage Liver Disease (MELD) score.[65,66] King's College Criteria are more specific and MELD score more sensitive with respect to the need for liver transplant in cases of drug-induced ALF.[67] In cases of suspected drug-induced ALF, urgent hepatology consultation and transfer to a liver transplant center are recommended.

Enhanced Elimination

Although many drugs' elimination can be enhanced by urinary alkalization, the most clinically relevant are salicylate, methotrexate, and phenobarbital.[18] By using sodium bicarbonate and targeting a urinary pH of 8, renal elimination of these toxins can be enhanced. In the case of salicylate, alkalization of blood and urine also helps to minimize the volume of distribution of salicylate and central nervous system toxicity.[68]

Extracorporeal Toxin Removal

Many crashing toxicology patients will have acute kidney injury with conventional indications for hemodialysis, such as metabolic acidosis, electrolyte derangements,

volume overload, or uremia. In those cases, nephrology should be consulted early, and toxin removal is a secondary consideration. Extracorporeal toxin removal (ECTR) can be achieved via hemodialysis or continuous renal replacement therapy (CRRT).[69] Technical advances in renal replacement therapy and an enhanced understanding of toxicokinetics have changed the classic criteria for ECTR.[18] High-efficiency, high-flux dialysis membranes allow for enhanced clearance of substances up to 15,000 Da. Larger hemodialysis catheters and improved hemodialysis machines permit higher blood flows during dialysis.[70] Several drugs with high protein binding, such as salicylate, valproic acid, phenytoin, and carbamazepine, are amenable to ECTR in overdose, as protein binding becomes saturated, and free drug is then removed by hemodialysis.

Extracorporeal clearance of a poison must also comprise a significant portion of total clearance to render ECTR effective treatment, and there must not be an effective antidote for the poison that renders the risk/benefit ratio of ECTR unfavorable.[69] For example, insulin is dialyzable via high-flux membranes, but concentrated dextrose therapy is easily instituted.

CRRT is often used in ICU patients too hemodynamically unstable to undergo hemodialysis, but clearance of drugs and toxins by these methods is too low for effective toxin removal.[71] CRRT may be helpful, however, in permitting greater net fluid removal over time and preserving cerebral perfusion pressure in patients with ALF.[72] In general, the decision to perform ECTR should not be based on a single drug level, as this is often a poor surrogate measure of drug concentration at the target organ of toxicity. Rather, patients with severe organ dysfunction or life-threatening poisoning by toxins amenable to ECTR should have urgent nephrology consultation and consideration of hemodialysis.

SUMMARY

The crashing toxicology patient presents a unique critical care challenge for the emergency physician. Patients may present in extremis, requiring a unique set of antidotes and treatments for clinical entities associated with poisoning with which emergency physicians are otherwise familiar, such as status epilepticus, cardiogenic shock, kidney injury, or liver failure. The brunt of resuscitation of the crashing poisoned patient falls to the ED, although all of these patients will ultimately require ICU management. Frequently, critical decisions regarding emergent mechanical circulatory support, consideration for organ transplant, or extracorporeal toxin removal and renal replacement therapy will be made in the ED, by emergency physicians. Rapid diagnostic evaluation, hemodynamic stabilization, and application of drug- and class-specific antidotes as outlined earlier are therefore crucial for improved patient survival and clinical outcomes.

DISCLOSURE

The authors have nothing to disclose.

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