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AHA FOCUSED UPDATE

2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Endorsed by the American Academy of Pediatrics

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ABSTRACT: In this focused update, the American Heart Association provides updated guidance for resuscitation of patients with cardiac arrest, respiratory arrest, and refractory shock due to poisoning. Based on structured evidence reviews, guidelines are provided for the treatment of critical poisoning from benzodiazepines, β-adrenergic receptor antagonists (also known as β-blockers), L-type calcium channel antagonists (commonly called calcium channel blockers), cocaine, cyanide, digoxin and related cardiac glycosides, local anesthetics, methemoglobinemia, opioids, organophosphates and carbamates, sodium channel antagonists (also called sodium channel blockers), and sympathomimetics. Recommendations are also provided for the use of venoarterial extracorporeal membrane oxygenation. These guidelines discuss the role of atropine, benzodiazepines, calcium, digoxin-specific immune antibody fragments, electrical pacing, flumazenil, glucagon, hemodialysis, hydroxocobalamin, hyperbaric oxygen, insulin, intravenous lipid emulsion, lidocaine, methylene blue, naloxone, pralidoxime, sodium bicarbonate, sodium nitrite, sodium thiosulfate, vasodilators, and vasopressors for the management of specific critical poisonings.

Key Words: AHA Scientific Statements ■ advanced cardiac life support ■ American Heart Association ■ antidotes ■ drug overdose ■ heart arrest ■ poisoning ■ resuscitation

TOP 10 TAKE-HOME MESSAGES FOR MANAGEMENT OF PATIENTS WITH CARDIAC ARREST OR LIFE-THREATENING TOXICITY DUE TO POISONING

1. Treatment of cardiac arrest and life-threatening toxicity due to poisoning often requires specialized treatments that most clinicians do not use frequently such as antidotes and venoarterial extracorporeal membrane oxygenation, in addition to effective basic and advanced life support. Timely consultation with a medical toxicologist, clinical toxicologist, or regional poison center facilitates rapid and effective therapy.
2. Opioid overdose remains the leading cause of cardiac arrest due to poisoning in North America. Naloxone administration may reverse respiratory arrest, preventing progression to cardiac arrest.

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3. High-dose insulin therapy is recommended early in the treatment of patients with life-threatening β-blocker and calcium channel blocker poisoning.
4. Standard advanced life support with the addition of administration of sodium bicarbonate is appropriate for the treatment of life-threatening dysrhythmias caused by cocaine or other sodium channel blockers.
5. If cyanide poisoning is suspected, do not wait for confirmatory testing. Treat immediately with hydroxocobalamin (preferred) or sodium nitrite plus sodium thiosulfate.
6. Administration of digoxin-specific immune antibody fragments can reverse life-threatening dysrhythmias from digoxin poisoning.
7. Use of 20% intravenous lipid emulsion can be efficacious in the resuscitation of life-threatening local anesthetic toxicity, especially from bupivacaine.
8. Patients with severe agitation from sympathomimetic poisoning require sedation to manage hyperthermia and acidosis, to prevent rhabdomyolysis and injury, and to allow evaluation for other life-threatening conditions.
9. Flumazenil reverses central nervous system and respiratory depression from benzodiazepine poisoning, but important risks and contraindications limit its use.
10. Venoarterial extracorporeal membrane oxygenation can be lifesaving for patients with cardiogenic shock or dysrhythmias that are refractory to other treatment measures. Because venoarterial extracorporeal membrane oxygenation implementation takes time, the process should be started early in patients who are not responding well to other therapies.

PREAMBLE

In the 12-month period ending in April 2021, more than 100 000 people in the United States died of poisoning and drug overdose, an increase of 28.5% from the prior year.[1] Ninety percent of these deaths were unintentional. Although the majority of these deaths (75 673) were attributed to opioid overdose, poisoning from other toxins continues to claim a significant number of lives.

Management of patients with critical poisoning, defined as those in cardiac arrest, refractory shock, or other conditions posing an imminent threat of cardiac arrest, often differs from standard resuscitation. For example, patients may develop hypotension from β-adrenergic receptor antagonist (aka β-blocker) or calcium channel antagonist (aka calcium channel blocker [CCB]) poisoning that does not respond to atropine, standard vasopressors, or cardiac pacing but is amenable to targeted therapies such as high-dose insulin. Mitochondrial inhibition from cyanide poisoning requires specific antidotes such as hydroxocobalamin to restore cellular adenosine triphosphate concentrations in the heart and brain. Poisoned patients are ideal candidates for extracorporeal life support techniques such as venoarterial extracorporeal membrane oxygenation (VA-ECMO) because temporary circulatory support is a bridge to survival until the poison can be removed by renal elimination, hepatic elimination, or extracorporeal elimination techniques such as hemodialysis or resin hemoperfusion.[2–4]

Abbreviations

Abbreviation	Meaning/Phrase
AHA	American Heart Association
ALS	advanced life support
β-blocker	β-adrenergic receptor antagonist
BLS	basic life support
CCB	calcium channel antagonist, aka calcium channel blocker
CNS	central nervous system
COR	Class of Recommendation
CPR	cardiopulmonary resuscitation
Fab	fragment antigen binding
ILE	intravenous lipid emulsion
LA	local anesthetic
LAST	local anesthetic systemic toxicity
LOE	Level of Evidence
PICO	population, intervention, comparison, outcome
RCT	randomized controlled trial
TCA	tricyclic or tetracyclic antidepressant
VA-ECMO	venoarterial extracorporeal membrane oxygenation

1. INTRODUCTION

Scope of the Guidelines

These guidelines are designed primarily for North American health care professionals treating adults and children who are critically ill due to poisoning, including intentional and unintentional drug overdose, chemical exposure, and drug-drug interactions. Although there is no one best term, for consistency of language, we use poisoning throughout these guidelines except in the opioids section, in which overdose is the generally accepted term. In addition to recommendations for the management of patients in cardiac arrest, these guidelines include recommendations for patients with respiratory arrest, refractory hypotension, critical metabolic acidosis, and other conditions caused by poisoning that, if not effectively addressed, can lead rapidly to cardiac arrest.

These guidelines contain recommendations for basic life support (BLS) and advanced life support (ALS) for both adult and pediatric patients. Unless otherwise specified, the interventions recommended here are intended for use in addition to standard BLS and ALS resuscitation. Although many of these treatments are impractical outside of the hospital setting, several can be initiated by emergency medical services, and some (eg, naloxone for opioid overdose) are incorporated into standard BLS training and may be relevant to lay rescuers. These guidelines are intended to be used in conjunction with topic-specific references and advice from local and regional experts in the treatment of poisoning.

Organization of the Writing Group

The Resuscitation From Critical Poisoning Writing Group included a diverse group of experts with backgrounds in emergency medicine, pediatrics, medical toxicology, pharmacology, critical care, emergency medical services, education, research, and nursing. Group members were appointed by the American Heart Association (AHA) Emergency Cardiovascular Care Science Subcommittee and approved by the AHA Manuscript Oversight Committee.

The AHA has rigorous conflict-of-interest policies and procedures to minimize the risk of bias or improper influence during the development of guidelines. Before appointment, writing group members disclosed all relevant commercial relationships and other potential (including intellectual) conflicts. These procedures are described more fully in "Part 2: Evidence Evaluation and Guidelines Development" in the "2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care."[5] Appendix 1 of this document lists the writing group members' relevant relationships with industry.

METHODOLOGY AND EVIDENCE REVIEW

The writing group members first created and approved a list of population, intervention, comparison, outcome (PICO) questions considered important to resuscitation of poisoned patients. Specific poisons and classes of poisons were considered for PICO development if poisonings from these agents are common causes of cardiac arrest or if they have unique antidotes and other treatment interventions that can be administered in a timely manner in the context of active resuscitation. In addition, because the use of VA-ECMO is relevant to resuscitation from many critical poisonings and a consistent approach is desirable, a non-PICO clinical question was created as the basis for recommendations about VA-ECMO. For each clinical question, the writing group chairs and a member assigned to each topic created a search strategy, which was internally peer reviewed. This search was executed in Medline and the Excerpta Medica Database (Embase), using the Ovid search interface, and the Cochrane Central Register of Controlled Trials. The search strategies and details about article selection are provided in the Supplemental Appendix. Final searches were executed in February 2022. Search results were not limited by language or year. Search results were imported into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; https://covidence.org). Two writing group members performed dual screening of the titles and abstracts of all articles identified from each search and identified articles for full-text review. Screening conflicts were resolved between the 2 writing group members and writing group leadership before full-text review. Two writing group members reviewed the full text of all selected articles and applied the information contained to develop treatment recommendations appropriate for each clinical question. Each draft recommendation was created by a group of 2 writing group members and then reviewed and refined by all writing group members during regular virtual meetings. The final manuscript was reviewed and approved by all writing group members.

Class of Recommendation and Level of Evidence

As with all AHA guidelines, each recommendation in this focused update is assigned a Class of Recommendation (COR) that is based on the strength and consistency of the evidence, alternative treatment options, and impact on patients and society (Table 1). Recommendation wording flows in a structured manner based on the COR determination. The Level of Evidence (LOE) is based on the quality, quantity, relevance, and consistency of the available evidence. For each recommendation, the writing group discussed and approved specific recommendation wording and the COR and LOE assignments. In determining the COR, the writing group considered the LOE and other factors, including systems issues, economic factors, and ethical factors such as equity, acceptability, and feasibility. These evidence-review methods, including specific criteria used to determine COR and LOE, are described more fully in "Part 2: Evidence Evaluation and Guidelines Development" of the "2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care."[5] The writing group members had final authority over and formally approved these recommendations.

Unfortunately, despite improvements in the design and funding support for resuscitation research, the overall certainty of the evidence base for resuscitation science and management of critical poisoning is low. Of the 73 recommendations in these guidelines, only 2 recommendations

Table 1. Applying the American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated May 2019)

CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only)	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

are supported by Level A evidence (high-quality evidence from more than 1 randomized controlled trial [RCT] or 1 or more RCTs corroborated by high-quality registry studies). Three recommendations are supported by Level B–randomized evidence (moderate evidence from 1 or more RCTs) and 12 by Level B–nonrandomized evidence. The majority of recommendations are based on Level C evidence, including those based on limited data (46 recommendations) and expert opinion (10 recommendations). Accordingly, the strength of recommendations is weaker than optimal: 23 Class 1 (strong) recommendations, 26 Class 2a (moderate) recommendations, and 15 Class 2b (weak) recommendations are included in these guidelines. In addition, 7 recommendations are designated Class 3: No Benefit, and 2 recommendations are Class 3: Harm. Clinical trials in resuscitation and the management of critical poisoning are sorely needed.

Guideline Structure

These guidelines are organized into knowledge chunks, grouped into discrete modules of information on specific topics or management issues.[6] Each modular knowledge chunk includes a table of recommendations that uses standard AHA nomenclature of COR and LOE. A brief introduction is provided to put the recommendations into context with important background information and overarching management or treatment concepts. Recommendation-specific

supportive text clarifies the rationale and key study data supporting the recommendations. When appropriate, flow diagrams or additional tables are included. Hyperlinked references are provided to facilitate quick access and review.

Document Review and Approval

These guidelines were submitted for blinded peer review to subject-matter experts nominated by the AHA and the American Academy of Pediatrics. The American College of Medical Toxicology, the American Academy of Clinical Toxicology, and America's Poison Centers were also invited to suggest reviewers. Before appointment, all peer reviewers were required to disclose relationships with industry and any other conflicts of interest, and all disclosures were reviewed by AHA staff. Peer reviewer feedback was provided for guidelines in draft format and again in final format. All guidelines were reviewed and approved for publication by the AHA Science Advisory and Coordinating Committee and the AHA Executive Committee. Comprehensive disclosure information for peer reviewers is listed in Appendix 2.

These recommendations supersede the last full set of AHA recommendations for critical poisoning, made in 2010,[7] and the 2015 recommendations pertaining to the role of intravenous lipid emulsion (ILE).[8] After reviewing new literature published since 2020, including an AHA scientific statement published in 2021,[9] the writing group reaffirms the AHA's 2020 recommendations for the management of resuscitation emergencies associated with opioid overdose,[10,11] which are included in these guidelines with additional explanatory text.

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2. MAJOR CONCEPTS

Overview: Concepts of Resuscitation From Critical Poisoning

Poisoning can be defined as an injury that results from being exposed to an exogenous substance that causes cellular injury or death.[1] Specific poisons impair a specific molecular mechanism of cellular function. Treatment of poisoning includes prevention of additional exposure, removal of the poison (when possible), provision of supportive care, and administration of medications that reverse or bypass the effect of the poison on its molecular target (antidotes). Some toxins produce cell death; others interfere with cellular function transiently in a way that threatens survival of the patient. In some cases, extracorporeal therapies for drug removal (eg, hemodialysis) or cardiovascular support (eg, VA-ECMO) may be required for survival and recovery.

Treatment and stabilization of critically poisoned patients often must be performed before the poison involved is known. Timely and effective supportive care, including airway management, hemodynamic support, and correction of critical vital sign and metabolic derangements, is essential to the care of the poisoned patient and takes priority over identification of the toxicant and antidotal therapy. Rapid laboratory identification of a specific poison is not available for most potential poisons in most hospitals. Often, a combination

of signs and symptoms (toxidrome) can be identified to provisionally identify a likely class of poison and to allow treatment to proceed while collateral information is gathered. For example, a patient with central nervous system (CNS) depression, miosis, and apnea may have opioid poisoning, whereas a patient removed from a house fire with CNS depression, bradycardia, and elevated plasma lactate concentration may have cyanide poisoning. Toxidrome tables can be found in many readily available sources,[2–7] although they are rarely exhaustive, and the sensitivity and specificity of any given toxidrome are often unknown.

Many of the recommendations presented in these guidelines involve administration of antidotes. Few antidotes have been evaluated with RCTs or dose-finding studies. Instead, the dosing strategies for most antidotes have been extrapolated from animal studies or physiological rationale and found to be effective in human observational studies. Table 2 provides a list of selected antidotes used in resuscitation from critical poisoning, along with dosing regimens commonly used in the literature. The ideal dose is rarely known, and in many cases, equally well-supported alternative dosing strategies exist.

In the United States, Canada, and much of the rest of the world, regional poison centers can provide expert treatment guidance for the management of specific poisoning cases. Each of the 55 poison centers operating in the United States is supported by board-certified medical and clinical toxicologists with specialized training in poisoning resuscitation. In the United States, a single telephone number (1-800-222-1222) exists to reach a poison center in any state or territory. In Canada, the dedicated poison center for each province can be called directly; a list is available at https://infopoison.ca.

These guidelines provide and evaluate specific treatment options meant to be provided in addition to, and alongside, traditional resuscitation care. Unless otherwise specified, all patients should receive standard airway management, support of breathing, and treatment of hypotension, dysrhythmias, or cardiac arrest, consistent with local guidelines and the resources available at the site of treatment.

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3. BENZODIAZEPINES

Introduction

Benzodiazepines are commonly used sedative-hypnotics used to treat anxiety, insomnia, seizures, and withdrawal syndromes and as a component of general anesthesia and procedural sedation. Benzodiazepines are implicated in a large number of poisoning-related deaths, usually in combination with other CNS depressants such as opioids or alcohol.[1]

Benzodiazepine overdose causes CNS depression through agonist effects at the GABA-A (gamma aminobutyric acid-A) receptor with resultant respiratory compromise through loss of protective airway reflexes. The subsequent hypoxemia and hypercarbia cause tissue injury and death. Patients with benzodiazepine poisoning can be readily managed with standard life support measures. Immediate treatment includes establishing an open airway and providing bag-mask ventilation, followed by endotracheal intubation when appropriate.

Flumazenil, a competitive antagonist at the benzodiazepine binding site on the GABA-A receptor, reverses CNS and respiratory depression, potentially preventing the need for intubation and mechanical ventilation. However, flumazenil administration may precipitate refractory benzodiazepine withdrawal and seizures in patients with benzodiazepine tolerance.[2] Flumazenil-provoked seizures are reported in patients with preexisting seizure disorder, even in the absence of other risk factors.[3] Flumazenil removes benzodiazepine-mediated suppression of sympathetic tone and may precipitate dysrhythmias, including supraventricular tachycardia, ventricular dysrhythmias, and asystole, particularly in the presence of dysrhythmogenic drugs (such as cyclic antidepressants) or hypoxia.[2,4–7] Flumazenil may not fully reverse respiratory depression, particularly in mixed overdoses.[8] At the time the RCTs of flumazenil in undifferentiated overdose were performed, tricyclic or tetracyclic antidepressant (TCA) overdose was common; recent data about flumazenil safety are lacking.

Overdose with multiple drugs is common. Benzodiazepine overdose should not preclude the timely administration of naloxone when opioid overdose is suspected. This is particularly important given the presence of opioid-adulterated illicit drugs.

Table 2. Commonly Used Doses of Antidotes for Resuscitation in Critical Poisoning

Antidote	Indication	Initial Dose (Adult)*	Initial Dose (Pediatric)*	Maintenance Infusion	Notes
Atropine	β-Blockers CCBs Digoxin Local anesthetics	0.5–1.0 mg every 3–5 min up to 3 mg	0.02 mg/kg	None	
Atropine	Organophosphates Carbamates	1–2 mg, doubled every 5 min	0.02 mg/kg, doubled every 5 min	10%–20% of the total loading dose per hour up to 2 mg/h (adults)	Titrate to reversal of bronchorrhea, bronchospasm, bradycardia, and hypotension.
Calcium chloride	CCBs	2000 mg 28 mEq Ca^{2+} 20 mL 100 mg/mL solution	20 mg/kg 0.28 mEq Ca^{2+}/kg 0.2 mL/kg 100 mg/mL solution	20–40 mg·kg^{-1}·h^{-1} 0.28–0.56 mEq Ca^{2+}·kg^{-1}·h^{-1} 0.2–0.4 mL·kg^{-1}·h^{-1} 100 mg/mL solution	Titrate to blood pressure. Do not exceed serum ionized calcium concentration 1.5–2 times the upper limits of normal. Administer through central line, especially in children.
Calcium gluconate	CCBs	6000 mg 28 mEq Ca^{2+} 60 mL 100 mg/mL solution	60 mg/kg 0.28 mEq/kg Ca^{2+} 0.6 mL/kg 100 mg/mL solution	60–120 mg·kg^{-1}·h^{-1} 0.28–0.56 mEq Ca^{2+}·kg^{-1}·h^{-1} 0.6–1.2 mL·kg^{-1}·h^{-1} 100 mg/mL solution	Titrate to blood pressure. Do not exceed serum ionized calcium concentration 1.5–2 times the upper limits of normal.
Digoxin immune Fab	Digoxin	Acute overdose: 1 vial for every 0.5 mg digoxin ingested Chronic poisoning: Use formula: dose in vials=serum digoxin concentration (ng/mL)×weight (kg)/100 Acute overdose, critically ill, ingested dose unknown: 10–20 vials	Same as adult	None	1 vial contains 40 mg Fab. Lower doses may be equally effective.[8]
Digoxin immune Fab	Yellow oleander *Bufo* toad venom	1200 mg (30 vials)	Unknown	None	
Glucagon	β-Blockers CCBs	2–10 mg	0.05–0.15 mg/kg	1–15 mg/h (adult)	Anticipate vomiting.
Flumazenil	Benzodiazepines	0.2 mg, titrated up to 1 mg	0.01 mg/kg	None	Many contraindications
Hydroxocobalamin	Cyanide	5 g	70 mg/kg	None	
Insulin	β-Blockers CCBs	1 U/kg	Same as adult	1–10 U·kg^{-1}·h^{-1}	Regular human insulin. Monitor for hypoglycemia, hypokalemia, volume overload.
ILE	Local anesthetics	1.5 mL/kg up to 100 mL	Same as adult	0.25 mL·kg^{-1}·min^{-1} for up to 30 min	All studies use 20% lipid emulsion.
Methylene blue	CCBs Methemoglobinemia	1–2 mg/kg, repeated every hour if needed	Same as adult	1 mg·kg^{-1}·h^{-1} (for vasodilatory shock)	Maximum 5–7 mg/kg
Naloxone	Opioids	0.2–2 mg IV/IO/IM 2–4 mg intranasal Repeat every 2–3 min as needed	0.1 mg/kg	Two-thirds of the waking dose per hour	Titrate to reversal of respiratory depression and restoration of protective airway reflexes.
Pralidoxime	Organophosphates	1–2 g	20–50 mg/kg	400–600 mg/h (adult) 10–20 mg·kg^{-1}·h^{-1} (pediatric)	
Sodium bicarbonate†	Sodium channel blockers Cocaine	50–150 mEq	1–3 mEq/kg	Prepare 150 mEq/L solution, infuse at 1–3 mL·kg^{-1}·h^{-1}	Watch for hypernatremia, alkalemia, hypokalemia, hypochloremia.
Sodium nitrite	Cyanide	300 mg	6 mg/kg	None	Watch for hypotension.
Sodium thiosulfate	Cyanide	12.5 g	250 mg/kg	None	

β-blocker indicates β-adrenergic receptor antagonist; CCB, calcium channel blocker; Fab, fragment antigen binding; ILE, intravenous lipid emulsion; IM, intramuscular; IO, intraosseous; and IV, intravenous.

*Unless otherwise stated, the route of administration should be intravenous or intraosseous. Maximum pediatric dose should not exceed adult dose. Most antidotes should be repeated frequently and titrated to achieve control of critical signs and symptoms. The ideal dose of most antidotes is not known and is often controversial. Large doses are sometimes required to overcome competitive inhibition of molecular targets such as adrenergic receptors and ion channels. Consult a medical or clinical toxicologist, regional poison center, or topic-specific reference for detailed dosing and administration instructions.

†Different sodium bicarbonate solutions are typically used for adults (1 mEq/mL) and children (0.5 mEq/mL). Both formulations are hypertonic.

Recommendations for the Management of Patients With Life-Threatening Benzodiazepine Poisoning		
COR	**LOE**	**Recommendations**
2a	B-NR	1. If combined opioid and benzodiazepine poisoning is suspected, it is reasonable to administer naloxone first (before other antidotes) for respiratory depression/respiratory arrest.
2a	B-NR	2. Flumazenil can be effective in select patients with respiratory depression/respiratory arrest caused by pure benzodiazepine poisoning who do not have contraindications to flumazenil.
3: No Benefit	C-EO	3. Flumazenil has no role in cardiac arrest related to benzodiazepine poisoning.
3: Harm	B-R	4. Flumazenil administration is associated with harm in patients who are at increased risk for seizures or dysrhythmias.

Recommendation-Specific Supportive Text

1. Isolated benzodiazepine poisoning rarely causes life-threatening hypoventilation or hemodynamic instability.[1,9] Consider the presence of concomitant opioid, ethanol, or other CNS depressant poisoning in these presentations. Opioid poisoning is more common and causes more significant respiratory depression than benzodiazepine poisoning, and naloxone has a better safety profile than flumazenil.
2. Flumazenil is safe in some low-risk presentations (eg, pediatric exploratory ingestions and iatrogenic overdoses during procedural sedation) and when high-risk conditions (eg, chronic benzodiazepine dependence and coingestion of other dangerous substances) can be reliably excluded.[10]
3. Flumazenil does not directly affect cardiac rhythm or restore spontaneous circulation.
4. In a meta-analysis of randomized clinical trials in patients with presumed benzodiazepine overdose, higher rates of serious adverse effects, including seizures and dysrhythmias, occurred with flumazenil compared with standard care alone.[2] Harms from flumazenil were uncommon and, in most cases, readily managed. The risks of flumazenil likely exceed the benefit in patients with undifferentiated coma for whom medical history, substance use history, and the potential poison(s) involved are unknown.

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4. β-BLOCKERS

Introduction

β-Blockers are a leading cause of poisoning mortality.[1] Patients with severe β-blocker poisoning develop hypotension due to bradycardia and reduced cardiac contractility.[2]

Some β-blockers also cause dysrhythmias from sodium or potassium channel blockade. Bradycardia is due to direct effects on the β_1-adrenergic receptor. Hypotension, which can be cardiogenic, vasodilatory from α_1-adrenergic receptor antagonism, or multifactorial, is often refractory to vasopressor therapy. β-Blocker poisoning is sometimes associated with hypoglycemia,[3,4] although this relationship is complex.[5,6] Hypoglycemia is treated with supplemental dextrose as part of standard care.

Commonly used treatment modalities include atropine, glucagon, calcium, vasopressors, high-dose insulin, and ILE therapy. In some refractory cases, VA-ECMO has been used. No studies have evaluated the use of these therapies for cardiac arrest due to β-blocker poisoning. Therefore, recommendations are derived from studies in poisoned patients with severe β-blocker–induced shock. Other nonadrenergic vasopressors such as vasopressin, angiotensin II, amrinone, milrinone, methylene blue, and hydroxocobalamin are not supported by sufficient evidence to support a recommendation.

The treatment of patients with life-threatening sodium channel blockade due to severe poisoning is discussed in Section 13 of this focused update, and specific recommendations about the use of VA-ECMO for critical poisoning are provided in Section 15. Recommendations about the management of patients with long QT syndromes and torsade de pointes were last updated by the AHA in 2020.[7]

Recommendations for the Management of Patients With Life-Threatening Beta Blocker Poisoning		
COR	**LOE**	**Recommendations**
1	B-NR	1. We recommend that high-dose insulin be administered for hypotension due to β-blocker poisoning refractory to or in conjunction with vasopressor therapy.
1	C-LD	2. We recommend that vasopressors be administered for hypotension due to β-blocker poisoning.
2a	C-LD	3. It is reasonable to use a bolus of glucagon, followed by a continuous infusion, for bradycardia or hypotension due to β-blocker poisoning.
2a	C-LD	4. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO for life-threatening β-blocker poisoning with cardiogenic shock refractory to pharmacological interventions.
2b	C-LD	5. It may be reasonable to administer atropine for β-blocker–induced bradycardia.
2b	C-LD	6. It may be reasonable to attempt electrical pacing for β-blocker–induced bradycardia.
2b	C-LD	7. It may be reasonable to use hemodialysis for life-threatening atenolol or sotalol poisoning.
3: No Benefit	C-LD	8. Intravenous lipid emulsion therapy is not likely to be beneficial for life-threatening β-blocker poisoning.

Recommendation-Specific Supportive Text

1. High-dose insulin improves inotropy in cardiogenic shock from β-blocker poisoning.[8,9] One large cohort study reports favorable outcomes with lower rates of vasoconstrictive complications than vasopressor-only therapy.[10] In some cases, high-dose insulin therapy appears to be vasopressor sparing, with recurrence of vasopressor-resistant hypotension after insulin therapy was reduced or stopped,[8,11] although this is not reported consistently.[12] Protocolized care with supplemental dextrose reduces the risk of hypoglycemia.[13] Hypokalemia and volume overload are additional concerns.[9,10]
2. Successful use of inotropes and vasopressors is described in a recent systematic review of case reports, case series, and animal studies.[12] Because they are readily available and act quickly, vasopressors are almost always the initial therapy for β-blocker–induced hypotension.
3. Intravenous glucagon increased contractility and improved hemodynamics in case reports,[14,15] a human trial involving a nontoxic dose of esmolol,[16] and some case series of β-blocker poisoning[12] but not others.[17] The doses used are larger than those used to treat hypoglycemia. Vomiting is common with the bolus, and rapid tachyphylaxis is described.[12,18]
4. On the basis of case reports,[19] case series,[20] and observational studies,[21,22] VA-ECMO may be lifesaving for patients with persistent cardiogenic shock (pump failure) refractory to maximal supportive care.
5. Only case reports are available to describe the use of atropine, which was associated with improvements in heart rate and blood pressure.[12]
6. A recent systematic review showed inconsistent response to pacemaker therapy.[12] Electrical and mechanical capture are not always successful, and hypotension may persist despite mechanical capture. Attempts to optimize pharmacotherapy may improve response to external or internal pacing.[23]
7. Observational studies in patients with critical poisoning due to atenolol or sotalol and kidney impairment reported clinical improvement after the use of hemodialysis.[24] Nadolol is also considered dialysable, but clinical data are lacking.[24]
8. The use of ILE is described in case reports and observational studies of patients with β-blocker poisoning.[25] Adverse effects are reported, including clogging of VA-ECMO filters, pancreatitis, and sudden cardiovascular collapse when ILE was administered to patients with oral β-blocker overdose.[26–28] A retrospective study did not find a benefit from ILE therapy.[29] Existing evidence-based recommendations advise against the routine use of ILE for β-blocker poisoning.[30]

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5. CALCIUM CHANNEL BLOCKERS

Introduction

Antagonists of the L-type calcium channel (commonly called CCBs) are divided into 2 pharmacological classes: dihydropyridines (eg, nifedipine, amlodipine) and nondihydropyridines (eg, diltiazem, verapamil). At therapeutic doses, nondihydropyridines have more pronounced effects on cardiac tissue, including the sinoatrial and atrioventricular nodes, resulting in negative chronotropy, whereas dihydropyridines cause peripheral vasodilation. These distinctions are often lost when therapeutic doses are exceeded, and patients present with severe shock from bradycardia, vasodilation, or loss of inotropy. Prolonged effects are common given that CCBs are frequently prescribed in sustained-release forms (diltiazem, verapamil, nifedipine) or have long half-lives (amlodipine). As a result, CCBs are a leading cause of poisoning mortality.[1] Commonly used treatment modalities include atropine, calcium, vasopressors, high-dose insulin therapy, nitric oxide inhibitors (eg, methylene blue), and ILE therapy. Extracorporeal life support such as VA-ECMO can be used in refractory cases. No randomized controlled clinical trials have evaluated the use of these therapies in the context of cardiac arrest or refractory shock. Therefore, recommendations are derived from lower-quality data in severely poisoned patients. Other nonadrenergic vasopressors such as vasopressin, angiotensin II, amrinone, milrinone, and hydroxocobalamin are not supported by sufficient evidence to support a recommendation.

Recommendations for the Management of Patients With Life-Threatening Calcium Channel Blocker Poisoning

COR	LOE	Recommendations
1	B-NR	1. We recommend administering vasopressors for hypotension from calcium channel blocker (CCB) poisoning.
1	B-NR	2. We recommend administering high-dose insulin for hypotension due to CCB poisoning.
2a	C-LD	3. It is reasonable to administer calcium for CCB poisoning.
2a	C-LD	4. It is reasonable to administer atropine for hemodynamically significant bradycardia from CCB poisoning.
2a	C-LD	5. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO for cardiogenic shock due to CCB poisoning that is refractory to pharmacological interventions.
2b	C-LD	6. It might be reasonable to attempt electrical pacing for CCB poisoning with refractory bradycardia.
2b	C-LD	7. The usefulness of a glucagon bolus and infusion for CCB poisoning is uncertain.
2b	C-LD	8. The usefulness of administering methylene blue for refractory vasodilatory shock due to CCB poisoning is uncertain.
3: No Benefit	C-LD	9. The routine use of intravenous lipid emulsion (ILE) therapy for CCB poisoning is not recommended.

Recommendation-Specific Supportive Text

1. Many patients with CCB-induced shock receive a vasopressor therapy.[1–3] One large retrospective case series demonstrated excellent survival rates with the primary use of vasopressors (most commonly norepinephrine at doses up to 100 µg/min in adults), with low rates of ischemic complications.[3] Three patients in this series had cardiac arrest before vasopressor therapy. There is no evidence to guide the choice of vasopressors.
2. High-dose insulin administration improves inotropy in patients with severe cardiogenic shock from CCB poisoning.[4–7] One large case series reported favorable outcomes with lower rates of vasoconstrictive complications than vasopressor-only therapy.[4] Survival is reported even after cardiac arrest.[4,8] Protocolized care reduces the risk of hypoglycemia.[7] Hypokalemia and volume overload are additional concerns.
3. The available literature on calcium monotherapy for severe CCB toxicity is limited. Improvements in heart rate, blood pressure, and conduction abnormalities are reported[9,10]; however, most patients require additional treatments.[3,4,9,11] In 1 case series, high doses of calcium gluconate (targeting ionized calcium concentrations up to twice normal) appeared to be more effective than lower doses.[9]
4. Atropine is commonly used as a first-line therapy for patients with bradycardia, including those with CCB poisoning.[2,4] Treatment failures are reported.[2,11]
5. The use of VA-ECMO for patients with refractory cardiogenic shock after CCB overdose is described in case series, with reported survival rates as high as 77%.[12–16] If available, VA-ECMO may be lifesaving for patients with persistent cardiogenic shock (pump failure) refractory to maximal supportive care.
6. Multiple case reports describe the use of electrical pacing for patients with bradydysrhythmias and hemodynamic instability after CCB poisoning. Results are mixed.[2,3,11,17,18] Electrical pacing may be reasonable for patients with hemodynamically significant bradydysrhythmias, but it is not always effective, particularly in patients with complete atrioventricular nodal blockade or vasodilatory shock.[2]
7. Glucagon is reported as an adjunctive therapy for severe CCB poisoning.[3,4,11] Reported response rates are variable; vomiting is common; and rapid tachyphylaxis may occur.[10,19,20]
8. Methylene blue, a nitric oxide synthase inhibitor, is described in case series and case reports as an effective adjunct to treat refractory vasodilatory shock after CCB overdose (involving primarily amlodipine).[21] However, responses are mixed, and the effects may be transient.
9. A large retrospective study did not find a benefit from ILE therapy in CCB poisoning.[22] Experimental and clinical data suggest that ILE increases absorption of lipophilic drugs from the gastrointestinal tract, potentially worsening poisoning from oral overdose.[8,23] As a result, evidence-based recommendations advise against the routine use of ILE for CCB poisoning.[24] Whether there is a role for ILE in patients who have failed other modalities and are in cardiac arrest or periarrest is uncertain.[24,25]

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6. COCAINE

Introduction

Cocaine toxicity is caused by sympathetic nervous system effects, CNS stimulation, and local anesthetic (LA) effects. Cocaine produces a sympathomimetic toxidrome marked by tachycardia, hypertension, hyperthermia, diaphoresis, increased psychomotor activity, and seizures.[1] Cocaine induces tachycardia (postsynaptic β-adrenergic receptor agonism) and hypertension (peripheral postsynaptic α-adrenergic receptor agonism) by catecholamine reuptake inhibition. In addition, reuptake blockade of norepinephrine, epinephrine, dopamine, and serotonin causes the CNS and neuropsychiatric symptoms of cocaine poisoning.[1,2]

The electrocardiographic changes and dysrhythmogenic properties of cocaine are a result of the effect of cocaine on cardiac sodium and potassium channels.[3] Sodium channel blockade leads to slowed conductance during phase 0 of the cardiac action potential. As a result, patients develop QRS prolongation and wide-complex tachycardia similar to what occurs with Vaughan-Williams Ia and Ic medications.[4,5] Cocaine may also cause QT interval prolongation through blockade of cardiac potassium channels.[1] Like other LAs, cocaine blocks neuronal sodium channels. Cocaine-induced dysrhythmias include sustained asystolic cardiac arrest and pulseless ventricular tachycardia.

Benzodiazepines remain the mainstay of initial management of blood pressure and psychomotor agitation for patients with acute cocaine poisoning. In addition, CCBs, α_1-adrenergic receptor antagonists, and nitrates can be used for severe cocaine-induced hypertension and chest pain.[2,6–8] These therapies are not germane to cardiac arrest.

Recommendations for the Management of Patients With Life-Threatening Cocaine Poisoning

COR	LOE	Recommendation
1	C-LD	1. We recommend rapid external cooling for life-threatening hyperthermia from cocaine poisoning.
2a	C-LD	2. It is reasonable to administer sodium bicarbonate for wide-complex tachycardia or cardiac arrest from cocaine poisoning.
2a	C-LD	3. It is reasonable to administer lidocaine for wide-complex tachycardia from cocaine poisoning.
2a	C-LD	4. It is reasonable to administer vasodilators (eg, nitrates, phentolamine, calcium channel blockers) for patients with cocaine-induced coronary vasospasm or hypertensive emergencies.

Recommendation-Specific Supportive Text

1. Hyperthermia can be rapidly life-threatening in cocaine poisoning.[9,10] Evaporative or immersive cooling modalities reduce temperature more rapidly than cooling blankets, the application of cold packs, or endovascular cooling devices.[9,11–17]
2. Retrospective observational studies[2,18] and case reports[19–22] describe the successful use of hypertonic solutions of sodium bicarbonate to treat wide-complex tachycardia from severe cocaine poisoning. A recent case report describes successful use of sodium bicarbonate in the resuscitation of a patient with asystolic cardiac arrest and subsequent wide-complex Brugada pattern.[20]
3. Well-conducted animal studies demonstrate the ability of lidocaine to reverse cocaine-induced QRS prolongation through competitive binding between lidocaine and cocaine at the sodium channel.[23,24] Lidocaine pretreatment prevents ataxia, seizures, and death after cocaine administration in mice.[25] Human evidence of efficacy is limited to case reports and small retrospective studies.[26,27] Lidocaine administration has demonstrated safety in patients with cocaine-induced myocardial infarction.[26] The use of lidocaine for cocaine-associated cardiac arrest is supported by case reports.[27,28]
4. Human clinical trials demonstrate improvements in coronary blood flow and myocardial oxygen delivery in patients with cocaine-induced coronary vasospasm after treatment with vasodilators (phentolamine, nitrates, verapamil).[6,29–32] These studies did not include patients with cardiac arrest or periarrest states. Patients with refractory ischemia from cocaine were successfully treated with phentolamine.[8,33] The safety of using β-blockers to treat life-threatening cardiovascular toxicity from cocaine is controversial, with studies showing both benefit and harm.[30,34–39]

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7. CYANIDE

Introduction

Cyanide is commonly used in jewelry cleaning, electroplating, metallurgy, and other industrial and laboratory processes. Cyanide is also liberated by the in vivo metabolism of naturally occurring cyanogens (eg, linamarin and amygdalin). In structure fires, cyanide gas is liberated by the incomplete combustion of nitrogen-containing products such as plastic, vinyl, wool, and silk. Rarely, cyanide is used in criminal poisoning or suicide attempts.

Cyanide inhibits cellular respiration in the mitochondria. Patients with cyanide poisoning can rapidly develop cardiovascular collapse, metabolic acidosis with elevated plasma lactate concentrations, depressed mental status, seizures, and death.[1] Confirmation of cyanide poisoning with laboratory measurement of cyanide concentrations is rarely available in clinical real time. Empirical treatment should be considered in laboratory workers, industrial workers, and people exposed to structure fires who present with cardiac arrest, altered mental status, elevated plasma lactate concentrations, severe metabolic acidosis, or hypotension. Concomitant poisoning with carbon monoxide and cyanide is common.

Hydroxocobalamin (vitamin B_{12a}) scavenges cyanide on an equimolar basis to form nontoxic cyanocobalamin. Alternatively, sodium nitrite oxidizes hemoglobin to methemoglobin, which then binds cyanide to form cyanmethemoglobin, although other mechanisms may be involved.[2,3]

Sodium thiosulfate acts as a substrate for cyanide metabolism, forming minimally toxic thiocyanate. This process is much slower than scavenging by hydroxocobalamin and sodium nitrite. Sodium thiosulfate may work synergistically with either hydroxocobalamin or sodium nitrite. However, hydroxocobalamin is approved for use alone (without sodium thiosulfate) by the US Food and Drug Administration and appears to be adequate for many overdoses.[4]

Typically, hydroxocobalamin is favored because of its rapid onset of action and simplicity of use. The principal adverse effects of hydroxocobalamin are transient hypertension, skin discoloration, rash, and interference with colorimetric laboratory assays.[5–8] Sodium nitrite administration can cause hypotension, and methemoglobin formation may worsen oxygen-carrying capacity in patients with concomitant carbon monoxide poisoning from smoke inhalation.[9]

Sodium thiosulfate, which has few adverse effects, works more slowly than the cyanide-scavenging therapies but may provide synergistic benefit, particularly when used after cyanide ingestion or when sodium nitrite is used. There are no human clinical trials comparing cyanide treatments with placebo, no human trials directly comparing cyanide treatment options alone or in combination, and no trials in human cardiac arrest.

Recommendations for the Management of Patients With Life-Threatening Cyanide Poisoning

COR	LOE	Recommendations
1	C-LD	1. We recommend that hydroxocobalamin be administered for cyanide poisoning.
1	C-LD	2. We recommend that sodium nitrite be administered for cyanide poisoning when hydroxocobalamin is unavailable.
2a	C-LD	3. In addition to administering hydroxocobalamin or sodium nitrite, it is reasonable to administer sodium thiosulfate for cyanide poisoning.
2a	C-EO	4. It is reasonable to administer 100% oxygen for cyanide poisoning.

Recommendation-Specific Supportive Text

1. Individuals who are exposed to structure fires likely represent the most common source of concern for cyanide poisoning.[1,5] Simultaneous poisoning with carbon monoxide and cyanide is common in individuals with smoke inhalation. Because hydroxocobalamin does not cause hypotension or exacerbate concerns about decreased oxygen-carrying capacity, hydroxocobalamin is the primary recommended treatment for patients with suspected cyanide poisoning.
2. Sodium nitrite effectively treats cyanide poisoning and is an appropriate alternative to hydroxocobalamin, particularly when carbon monoxide poisoning is not a concern.[10,11] To avoid excessive methemoglobin formation, the dosing of sodium nitrite in children and in patients with anemia must be precise; the prescribing information lists specifications.[12]
3. Sodium thiosulfate enhances cyanide elimination when given with hydroxocobalamin or sodium nitrite.[1,9] The mechanism of action of sodium thiosulfate is thought to be too slow to be considered monotherapy in life-threatening poisoning.
4. Animal studies suggest a benefit when cyanide-specific antidotes are combined with 100% oxygen.[13] No human studies have examined the use of 100% oxygen as cyanide therapy, but it is reasonable to use 100% oxygen as therapy even with a normal partial pressure of oxygen in the context of a cellular poison such as cyanide that impairs cellular respiration.

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8. DIGOXIN AND RELATED CARDIAC GLYCOSIDES

Introduction

Cardiac glycoside poisoning can be caused by medications such as digoxin and digitoxin, plants such as foxglove and oleander, and certain toad venoms ingested as ethnopharmaceuticals or hallucinogens. Despite decreasing prescription of digoxin and digitoxin in the past decades, poisoning remains frequent because of overdose, unintentional ingestion, drug-drug interactions, and drug accumulation due to reduced renal clearance. Patients with cardiac glycoside poisoning may develop gastrointestinal symptoms, confusion, hyperkalemia, and cardiac conduction abnormalities, including atrioventricular nodal block, ventricular tachycardia, ventricular fibrillation, and asystole. Although the cardiac glycosides include a range of structurally similar cardioactive steroids, most data involve digoxin poisoning.

Digoxin-specific immune antibody fragments (digoxin-fragment antigen binding [Fab]) bind to and inactivate digoxin and structurally similar cardiac glycosides. Different dosing regimens are advocated worldwide.[1–3] An observational study supports a likely survival advantage in patients who are in cardiac arrest.[4] The ideal empirical dose for cardiac arrest is unknown and likely differs for digoxin poisoning compared with other cardiac glycosides.

Acute digoxin poisoning commonly causes hyperkalemia,[1] and current ALS and pediatric ALS guidelines recommend administration of calcium for hyperkalemia.[5,6] Animal studies, ex vivo studies, and case reports raise concern that calcium administration might cause cardiac arrest due to myocardial tetany (stone heart) in this situation.[7–11] A retrospective cohort study including mostly patients with chronic digoxin poisoning and a porcine study suggest that calcium administration is neither harmful nor beneficial.[12,13] Although the risk of harm from calcium in patients with digoxin poisoning is not quantified, there is also no evidence of benefit given that the pathophysiology of hyperkalemia in digoxin poisoning is different from that of hyperkalemia from other causes.

Animal data raised concerns about defibrillation in digoxin-poisoned patients because of the risk of precipitating new life-threatening dysrhythmias.[14] Case reports in cardiac arrest[15–30] showed response in some cases, absence of response in others, but no new dysrhythmia. In the absence of data to the contrary, standard ALS and pediatric ALS guidelines for defibrillation should be followed, with the addition of digoxin-Fab therapy as detailed in the following table.

Recommendations for the Management of Patients With Life-Threatening Poisoning From Digoxin and Related Cardiac Glycosides

COR	LOE	Recommendations
1	B-NR	1. We recommend administration of digoxin-specific antibody fragments (digoxin-Fab) for digoxin or digitoxin poisoning.
2a	C-LD	2. It is reasonable to administer digoxin-Fab for poisoning due to *Bufo* toad venom and yellow oleander.
2b	C-LD	3. It may be reasonable to administer digoxin-Fab to treat poisoning from cardiac glycosides other than digoxin, digitoxin, *Bufo* toad venom, and yellow oleander.
2b	C-LD	4. It may be reasonable to administer atropine for bradydysrhythmias caused by digoxin and other cardiac glycoside poisoning.
2b	C-LD	5. It may be reasonable to attempt electrical pacing to treat bradydysrhythmias from digoxin and other cardiac glycoside poisoning.
2b	C-LD	6. It may be reasonable to administer lidocaine, phenytoin, or bretylium to treat ventricular dysrhythmias caused by digitalis and other cardiac glycoside poisoning until digoxin-Fab can be administered.
3: No Benefit	B-NR	7. We do not recommend the use of hemodialysis, hemofiltration, hemoperfusion, or plasmapheresis to treat digoxin poisoning.

Recommendation-Specific Supportive Text

1. Data from observational studies,[4,31–40] synthesized in a recent systematic review,[2] show resolution of life-threatening dysrhythmias after digoxin-Fab administration. Most studies report response rates of 50% to 90%, with dysrhythmia resolution in 30 to 45 minutes in most cases. Although there are no RCTs studying cardiac arrest from digoxin or digitoxin poisoning, excellent survival (30 of 56 patients, 54%) was reported in an observational study of digoxin-Fab–treated patients.[4] Treatment appears to be safe.[41]

2. An RCT among hemodynamically stable patients with yellow oleander (*Thevetia peruviana*, also known as *Cascabela thevetia*) poisoning showed promising response to digoxin-Fab,[42] as do many case reports and case series.[43] A Cochrane review did not identify any trials in patients with severe yellow oleander toxicity.[44] In vitro studies showed affinity between bufadienolides (cardiac glycosides found in *Bufo* toad venom) and digoxin-Fab,[45–48] murine studies showed protection,[49] and some published cases showed apparent response.[46,50,51]
3. Data supporting the use of digoxin-Fab to treat poisoning from cardiac glycosides other than digoxin, digitoxin, bufadienolides, and yellow oleander are limited to case reports.[43,52–58]
4. Published case reports describe the use of atropine to treat patients with bradycardia caused by cardiac glycoside toxicity, with variable effects.[57,59–62] No cohort studies or randomized clinical trials examining atropine for digitalis toxicity have been published.
5. Two observational studies from the same center, predating the introduction of digoxin-Fab,[63,64] reported a reduction in the mortality rate from 20% to 13% with transvenous pacing in digitalis-poisoned patients (mainly chronic poisoning) with bradydysrhythmias. Case reports and case series support a role for pacing as temporizing therapy.[15,17–20,26,29,30,58,65,66] However, iatrogenic complications from transvenous pacing are common[63] and were reported in 36% of patients in 1 series.[67] Some patients required a higher-than-normal current, and in some cases, pacing could not be successfully resumed after interruption. Case reports support a role for pacing in the scenario in which immunotherapy is delayed or while waiting for digoxin-Fab to take effect.
6. Many cases in the literature report the use of antidysrhythmic medications, including lidocaine, phenytoin, or bretylium, to treat ventricular dysrhythmias caused by digoxin poisoning, with various responses.[30,61,68,69] However, no high-quality cohort studies or randomized trials have evaluated their effect. Bretylium is not currently manufactured.
7. A recent systematic review found that digoxin is not well removed by extracorporeal treatments because of its large volume of distribution.[70]

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9. LOCAL ANESTHETICS

Introduction

LAs reversibly bind sodium channels to disrupt nerve transmission and block pain signals. Patients with LA poisoning present with a constellation of CNS and cardiovascular symptoms called "LA systemic toxicity" (LAST). CNS toxicity (77%–89% of patients with LAST) includes seizures (most common), agitation, syncope, dysarthria, perioral numbness, confusion, obtundation, and dizziness.[1,2] Although less common, cardiovascular toxicity (32%–55% of patients with LAST) can be life-threatening. In 1 case series, asystole occurred in 12% of cases, and ventricular fibrillation or ventricular tachycardia occurred in 13% of cases.[1]

LAs vary in toxicity depending on the potency associated with their lipophilic side chains. Bupivacaine is a more potent cardiotoxin than ropivacaine and lidocaine in a canine model through its greater affinity and binding durations to cardiac sodium channels.[3,4] Bupivacaine may also cause reentry dysrhythmias, suppress conduction pathways, and block calcium channels.[4] Optimal treatments for bupivacaine poisoning may differ from other LAs, and these differences are not well understood.[4,5]

Both hypoxia and acidemia worsen toxicity from bupivacaine in animal models.[5–7] Ventilation and treatment of acidemia are critical.[6,8] Many case reports of LAST occurred perioperatively, featured early advanced airway placement, and had return of spontaneous circulation through standard ALS measures without ILE.[1,2,9] Early adjunctive administration of ILE in addition to standard ALS resuscitation is efficacious in animal models, case reports, and observational studies.[5,9–11] Other pharmacological interventions (eg, hypertonic solutions of sodium bicarbonate) and mechanical support (eg, VA-ECMO) have been used for LAST, but the efficacy of these interventions remains unclear.

Evidence-based dosing recommendations for ILE are lacking. The majority of animal studies and human experience for the treatment of LAST use 20% ILE.[5] Attempts to reproduce this dose with propofol (which contains 10 mg/mL propofol in 10% ILE) would likely lead to profound hypotension.

LA poisoning can also produce methemoglobinemia; treatment recommendations are provided in Section 10.

Recommendations for the Management of Patients With Life-Threatening Local Anesthetic Poisoning

COR	LOE	Recommendations
1	C-LD	1. We recommend the administration of intravenous lipid emulsion for local anesthetic poisoning.
1	C-LD	2. We recommend the use of benzodiazepines to treat seizures associated with local anesthetic systemic toxicity.
2a	C-LD	3. It is reasonable to administer sodium bicarbonate for life-threatening wide-complex tachycardia associated with local anesthetic toxicity.
2a	C-EO	4. It is reasonable to administer atropine for life-threatening bradycardia associated with local anesthetic systemic toxicity.
2a	C-EO	5. It is reasonable to utilize extracorporeal life support techniques such as VA-ECMO in local anesthetic toxicity with refractory cardiogenic shock.

Recommendation-Specific Supportive Text

1. Early administration of 20% ILE in patients with LAST is supported by animal studies, case reports, registry studies, and 1 small RCT.[5,10,12] In conjunction with the prevention of hypoxia and acidemia, administration of ILE has led to successful resuscitation in these studies. However, most of the studies are uncontrolled. The single RCT (n=16) evaluated the pharmacology and tolerability of ropivacaine and levobupivacaine, dosed to produce mild neurotoxicity and administered concurrently with 20% ILE or placebo. Coadministration of ILE decreased the maximum plasma concentration of both ropivacaine and levobupivacaine, with no statistical difference in the dose of LA that produced neurological symptoms.[12] The study is severely limited by its small enrollment, use of proxy outcomes, and lack of clinical difference. Successful treatment of LAST with advanced airway management was reported in a case series before the introduction of ILE.[13]
2. Patients with LAST may progress rapidly from CNS toxicity to cardiotoxicity. Seizures associated with LAST may worsen hypoxia and acidemia. Administration of benzodiazepines to abort seizure-like activity may prevent LA-associated cardiotoxicity and is commonly reported as part of a therapeutic regimen.[2,10,14]
3. Sodium bicarbonate administration may overcome sodium channel blockade by LAs and correct acidemia. Evidence to support the use of hypertonic formulations of sodium bicarbonate is limited to case reports as part of a therapeutic regimen[10,14] and 1 porcine RCT demonstrating effective shortening of the QRS complex duration in bupivacaine toxicity.[15]
4. Bradycardia is the most common cardiovascular sign of LAST.[1] Atropine has been used successfully in case reports.[16,17]

5. Several case reports describe successful use of mechanical support such as cardiopulmonary bypass or VA-ECMO for patients with LAST and refractory cardiogenic shock.[18–22] Unfortunately, lack of widespread availability of VA-ECMO limits the use of these interventions.

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10. METHEMOGLOBINEMIA

Introduction

Acquired methemoglobinemia occurs after an exposure to an oxidant stressor that oxidizes iron in the hemoglobin molecule from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state. In the ferric state, hemoglobin no longer effectively binds and delivers oxygen to end organs. Common sources of oxidant stress that can cause methemoglobinemia include nitrates, nitrites, and many pharmaceuticals (eg, dapsone, benzocaine, phenazopyridine).[1–9] Patients with methemoglobinemia can appear cyanotic and dusky and complain of shortness of breath and fatigue. Frequently, a difference is observed between the oxygen saturation measured on pulse oximetry and the oxygen saturation calculated on an arterial blood gas. Although moderate methemoglobinemia is generally well tolerated, severe methemoglobinemia can lead to cardiovascular collapse and death.[6,7,9]

The most widely accepted treatment for methemoglobinemia is methylene blue, which acts as a cofactor to reduce methemoglobin to hemoglobin.[10] There are no randomized trials evaluating methylene blue for the treatment for methemoglobinemia, but observational data consistently demonstrate resolution or improvement after methylene blue administration. In addition to methylene blue, other treatment modalities that have been described include exchange transfusion, hyperbaric oxygen therapy, and ascorbic acid.

No studies have examined the treatment of methemoglobinemia in the context of cardiac arrest.

Recommendations for the Management of Patients With Life-Threatening Methemoglobinemia

COR	LOE	Recommendation
1	B-NR	1. We recommend administering methylene blue for methemoglobinemia.
2b	C-LD	2. Exchange transfusion may be reasonable as a treatment for methemoglobinemia that is not responsive to methylene blue.
2b	C-LD	3. Hyperbaric oxygen therapy may be reasonable as a treatment for methemoglobinemia that is not responsive to methylene blue.
3: No Benefit	B-R	4. N-acetylcysteine is not recommended as a treatment for methemoglobinemia.
3: No Benefit	C-LD	5. Ascorbic acid is not recommended as a treatment for methemoglobinemia.

Recommendation-Specific Supportive Text

1. Observational studies and published case reports consistently demonstrate that methylene blue effectively reverses methemoglobinemia.[1–5,11] Methylene blue may not improve methemoglobinemia or cause hemolysis in patients who have glucose-6-phosphate dehydrogenase deficiency, present in about 2% of the US population.[12–15] Glucose-6-phosphate dehydrogenase activity testing is rarely available in real time.
2. Exchange transfusion has been used successfully to treat methemoglobinemia and may be appropriate in patients for whom methylene blue is ineffective.[16–21]
3. Hyperbaric oxygen therapy has been used as monotherapy and in conjunction with other therapies. However, reduction of methemoglobinemia concentrations can be delayed up to several hours.[22–24] Its use may be impractical in the setting of cardiopulmonary collapse or cardiac arrest.
4. N-acetylcysteine did not reduce sodium nitrite–induced methemoglobinemia in a double-blind crossover human volunteer study.[25]
5. Ascorbic acid, or vitamin C, has been used to treat methemoglobinemia.[18,26,27] However, most published case reports demonstrate its use in conjunction with other treatment modalities. The effect is slow and often requires multiple doses over several hours to have any significant effect.[6,27–29] Ascorbic acid is not likely to be effective in resuscitation situations.

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11. OPIOIDS

Introduction

Since the publication of the last AHA guidelines for the treatment of opioid overdose in 2020,[1,2] the epidemic of

opioid poisoning continues to worsen in the United States and in many other nations worldwide. Data from the US National Center for Health Statistics report a staggering 75 673 deaths resulting from opioids in the 12-month period ending in April 2021, a nearly 35% increase from the year before.[3] Most deaths are unintentional. Effective primary prevention, emergency treatment, and secondary prevention strategies are urgently needed to address this rapidly escalating crisis.

In formulating these recommendations, the writing group reviewed the 2020 adult, pediatric, and resuscitation education science guidelines[1,2,4]; the AHA's 2021 scientific statement on opioid-associated out-of-hospital cardiac arrest[5]; and additional literature published since 2019. After careful review, the writing group reaffirms the "2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care," with additional supporting references and discussion.

As noted in the previous guidelines, isolated opioid toxicity is associated with CNS and respiratory depression that progresses to respiratory arrest followed by cardiac arrest. Most opioid-associated deaths involve the coingestion of multiple substances or medical and mental health comorbidities.[6–9] It can be difficult in the hospital setting, and may be impossible in the out-of-hospital setting, to accurately differentiate opioid-associated resuscitative emergencies from other causes of cardiac and respiratory arrest. Opioid-associated resuscitative emergencies are defined by the presence of cardiac arrest, respiratory arrest, or severe life-threatening instability (such as severe CNS or respiratory depression, hypotension, or cardiac dysrhythmia) that is suspected to be due to opioid toxicity.[5] In these situations, the mainstay of care remains early recognition and activation of the emergency response system (Figures 1 and 2). Opioid overdoses deteriorate to cardiopulmonary arrest because of loss of airway patency and lack of breathing; therefore, addressing the airway and ventilation in a periarrest patient is of the highest priority.

Naloxone, a μ-opioid receptor antagonist, can restore spontaneous respirations and protective airway reflexes in patients for whom these are impaired as a result of an opioid overdose. Harmful effects include precipitating opioid withdrawal; sudden-onset pulmonary edema can be severe, but it responds readily to positive pressure ventilation. Alternatives to naloxone include observation (in patients who are breathing normally regardless of CNS depression) and ventilatory support.

Educating patients with opioid use disorder[10,11] and their friends, families,[12] and close contacts[10] improves risk awareness, overdose recognition, willingness and ability to administer naloxone, and attitudes toward calling emergency medical services.[13,14] Given the tremendous scope of the problem, widespread community training in cardiopulmonary resuscitation (CPR) and naloxone administration is of growing importance.

Recommendations for the Acute Management of Opioid Overdose

COR	LOE	Recommendations
1	C-LD	1. For patients in respiratory arrest, rescue breathing or bag-mask ventilation should be maintained until spontaneous breathing returns, and standard BLS, ALS, and/or pediatric ALS measures should continue if return of spontaneous breathing does not occur.
1	C-EO	2. For patients known or suspected to be in cardiac arrest, in the absence of a proven benefit from the use of naloxone, standard resuscitative measures should take priority over naloxone administration, with a focus on high-quality CPR (compressions plus ventilation).
1	C-EO	3. Lay and trained responders should not delay activating emergency response systems while awaiting the patient's response to naloxone or other interventions.
2a	B-NR	4. For a patient with suspected opioid overdose who has a definite pulse but no normal breathing or only gasping (ie, a respiratory arrest), in addition to providing standard BLS and/or ALS care, it is reasonable for responders to administer naloxone.

Recommendation-Specific Supportive Text

1. Initial management should focus on support of the patient's airway and breathing. This begins with opening of the airway followed by delivery of rescue breaths, ideally with the use of a bag mask or barrier device.[1,15,16] Provision of BLS and ALS care should continue if return of spontaneous breathing does not occur.
2. There are no studies demonstrating improvement in patient outcomes from administration of naloxone during cardiac arrest. Provision of CPR should be the focus of initial care.[5] Naloxone can be administered along with standard care if it does not delay components of high-quality CPR.
3. Early activation of the emergency response system is critical for patients with suspected opioid overdose. Rescuers cannot be certain that the person's clinical condition is due to opioid-induced respiratory depression alone. This is particularly true in first aid and BLS settings, where determination of the presence of a pulse is unreliable,[17,18] but even trained first responders have difficulty rapidly determining pulselessness.[19] Naloxone is ineffective in other medical conditions, including overdose involving nonopioids and cardiac arrest from any cause. Patients who respond to naloxone administration may develop recurrent CNS or respiratory depression and require longer periods of observation before safe discharge.[20–23]
4. Twenty-four studies examined the use of naloxone in patients with CNS or respiratory depression from opioid poisoning. None compared naloxone administration with resuscitation/ventilatory support alone. Seven studies compared intramuscular and intranasal routes of naloxone

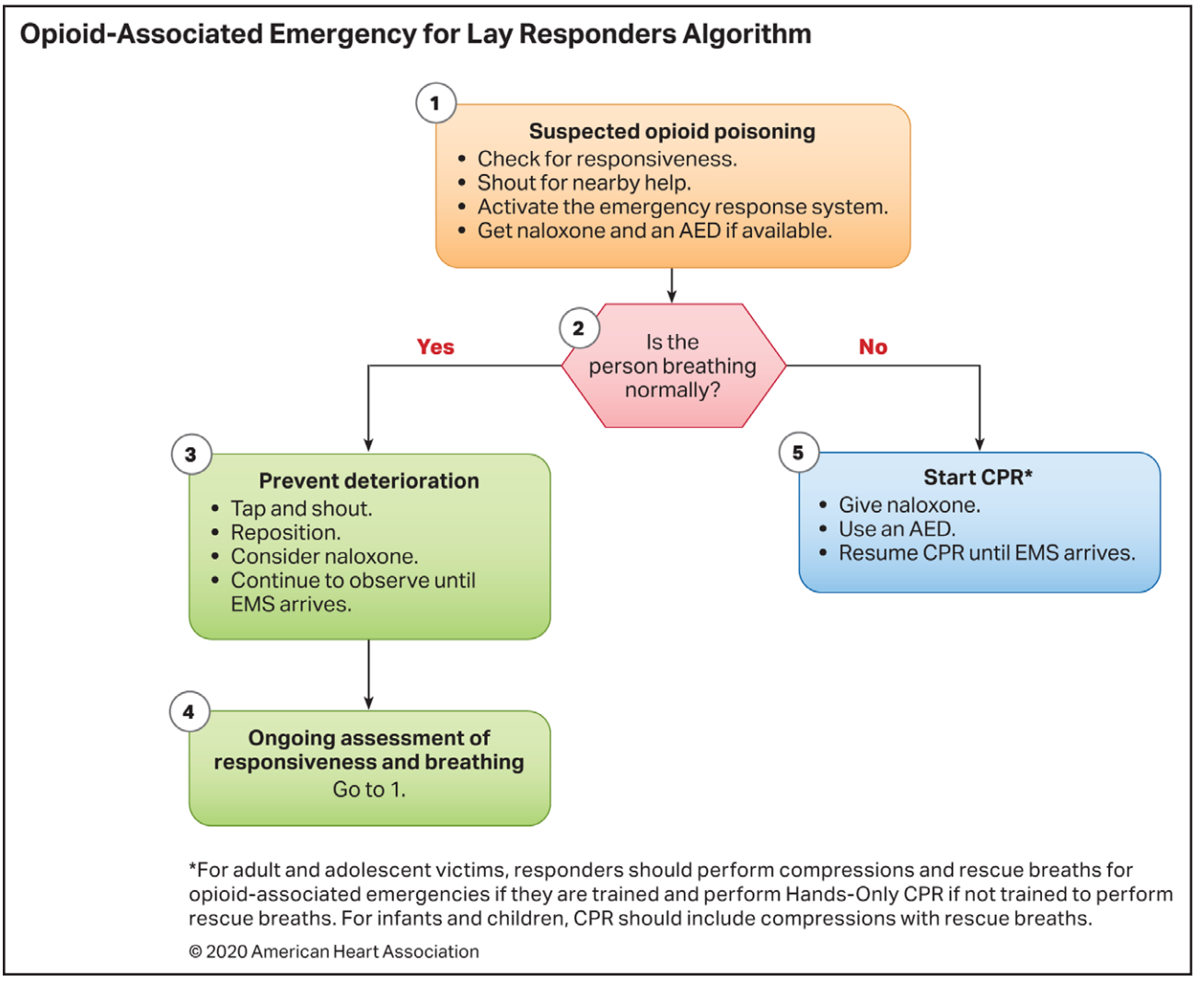

Figure 1. Opioid-Associated Emergency for Lay Responders Algorithm
AED indicates automated external defibrillator; CPR, cardiopulmonary resuscitation; and EMS, emergency medical services. Reprinted with permission from Panchal et al.[1] Copyright © 2020 American Heart Association, Inc.

administration (4 RCTs,[24–27] 3 non-RCTs[28–30]), and 18 other studies[31–48] assessed the safety, tolerability, or dosing of naloxone use for opioid poisoning in various settings, mostly out of hospital. These studies report that naloxone is safe and effective in treatment of opioid-induced respiratory depression and that major complications are rare and dose related.

Recommendations for the Management of Opioid Overdose Following Successful Response to Naloxone

COR	LOE	Recommendations
1	C-LD	1. After return of spontaneous breathing, patients should be observed in a healthcare setting until the risk of recurrent opioid toxicity is low and the patient's level of consciousness and vital signs have normalized.
2a	C-LD	2. If recurrent opioid toxicity develops, repeated small doses or an infusion of naloxone can be beneficial.

Recommendation-Specific Supportive Text

1. Patients with respiratory arrest who respond to naloxone administration may develop recurrent CNS or respiratory depression. Although abbreviated observation periods may be adequate for patients with fentanyl, morphine, or heroin overdose,[38,40,46,49–52] longer periods of observation may be required to safely discharge a patient with life-threatening overdose of a long-acting or sustained-release opioid.[20–22] Prehospital professionals who are faced with the challenge of a patient refusing transport after treatment for a life-threatening overdose are advised to follow local protocols and practices for determination of patient capacity to refuse care.
2. Because the duration of action of naloxone may be shorter than the respiratory depressive effect of the opioid, particularly that of long-acting formulations, repeat doses of naloxone or a naloxone infusion may be required.[20–22,46]

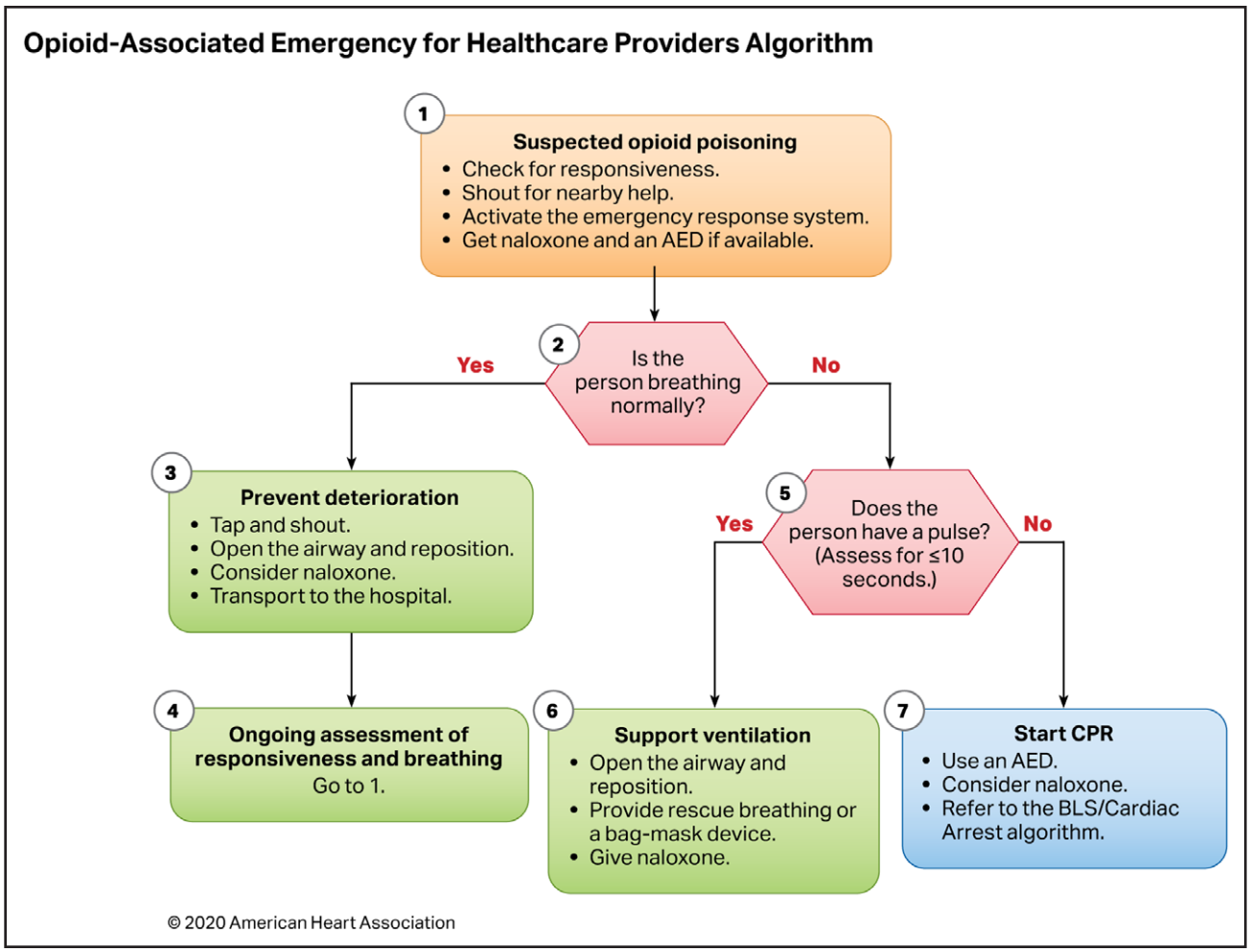

Figure 2. Opioid-Associated Emergency for Healthcare Providers Algorithm.
AED indicates automated external defibrillator; ALS, advanced life support; and BLS, basic life support. *For adult and adolescent victims, responders should perform compressions and rescue breaths for opioid-associated emergencies if they are trained and perform hands-only cardiopulmonary resuscitation (CPR) if not trained to perform rescue breaths. For infants and children, CPR should include compressions with rescue breaths. Reprinted with permission from Panchal et al.[1] Copyright © 2020 American Heart Association, Inc.

Recommendation for Opioid Overdose Training for Lay Rescuers		
COR	**LOE**	**Recommendation**
2a	B-R	1. It is reasonable for lay rescuers to receive training in responding to opioid overdose, including provision of naloxone.

Recommendation-Specific Supportive Text

1. Ten studies assessed the impact of opioid overdose training using a comparator group, with or without randomization, on the ability of individuals with opioid use disorder to recognize opioid-associated resuscitation emergencies and their willingness to administer naloxone.[10–12,53–59] One study[54] found that the rate of naloxone administration was higher in those who had received opioid training compared with those who did not (32% versus 0%), although another study found no difference in the provision of aid between trained and untrained responders.[53] Interventions that included skills practice (ie, naloxone administration) were more likely to lead to improved clinical performance compared with interventions without skills practice.[12,60–65]

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12. ORGANOPHOSPHATES AND CARBAMATES

Introduction

Organophosphates and carbamates, found in pesticides, nerve agents, and some medications, inhibit acetylcholinesterase, resulting in muscarinic and nicotinic toxicity. They produce parasympathetic excess (bradycardia, bronchospasm, bronchorrhea, miosis, hypersalivation, lacrimation, urination, diarrhea, vomiting, diaphoresis), nicotinic excess (tachycardia, mydriasis, fasciculations progressing to depolarizing neuromuscular blockade and paralysis), and CNS effects (altered mental status, central apnea, seizures).

Organophosphates eventually form a covalent bond with the acetylcholinesterase enzyme, causing permanent inactivation ("aging"). Carbamates spontaneously dissociate from acetylcholinesterase, which is then reactivated.

Early and effective treatment may prevent deterioration to respiratory and cardiac arrest. The cornerstones of treatment include decontamination, atropine, benzodiazepines, and oximes. Dermal decontamination through removal of contaminated clothing and copious irrigation with soap and water, performed by people wearing protective barriers, helps prevent further absorption and prevents contamination of caregivers and the care environment.[1] Atropine blocks parasympathetic overstimulation, mitigating bronchorrhea, bradycardia, bronchospasm, and CNS effects. Atropine does not block acetylcholine excess at the neuromuscular junction or nicotinic ganglia and therefore does not reverse paralysis. Benzodiazepines are

used to prevent and treat seizures. When administered early (before aging), oximes reactivate the acetylcholinesterase enzyme, reversing nicotinic effects to slowly improve respiratory and skeletal muscle strength, although this effect may be organophosphate specific.[2–6] Although the available data are not sufficient to support a recommendation for or against oxime use in carbamate poisoning, oximes should not be withheld in cases of cholinesterase poisoning when the class of poison is unknown.

No study to date has specifically evaluated therapy for organophosphate-induced or carbamate-induced cardiac arrest.

Recommendations for the Management of Patients With Life-Threatening Organophosphate or Carbamate Poisoning

COR	LOE	Recommendation
1	A	1. We recommend giving atropine immediately for severe poisoning, such as bronchospasm, bronchorrhea, seizures, or significant bradycardia, from organophosphate or carbamate poisoning.
1	B-NR	2. We recommend early endotracheal intubation for life-threatening organophosphate or carbamate poisoning.
1	C-LD	3. We recommend administration of benzodiazepines to treat seizures and agitation in the setting of organophosphate or carbamate poisoning.
1	C-LD	4. We recommend use of appropriate personal protective equipment when caring for patients with organophosphate or carbamate exposure.
1	C-EO	5. We recommend dermal decontamination for external organophosphate or carbamate exposure.
2a	A	6. The use of pralidoxime is reasonable for organophosphate poisoning.
3: No Benefit	C-LD	7. Use of neuromuscular blockers metabolized by cholinesterase (ie, succinylcholine and mivacurium) is not recommended for patients with organophosphate or carbamate poisoning.

Recommendation-Specific Supportive Text

1. For patients with life-threatening organophosphate or carbamate poisoning, including cardiac arrest, bradycardia, hypotension, bronchorrhea, or bronchospasm, early atropine administration improved survival in a clinical trial.[7] Much larger doses of atropine are often required for this indication than for typical bradycardia (Table 2). The initial dose is doubled every 5 minutes until full atropinization is achieved (clear chest on auscultation, heart rate >80/min, systolic blood pressure >80 mm Hg). Maintenance of atropinization can be achieved by an atropine infusion.[7]
2. Observational data suggest that patients with significant organophosphate poisoning have better outcomes with early endotracheal intubation.[8]
3. Benzodiazepines such as diazepam (first line) or midazolam have demonstrated efficacy in patients with organophosphate or carbamate-induced seizures and agitation, and they effectively manage organophosphate-induced status epilepticus and mitigate neuronal injury in animal models.[8–11]
4. Health care professionals not wearing appropriate personal protective equipment have developed symptoms consistent with organophosphate exposure after being in close contact with patients poisoned by organophosphates, including patients with respiratory and dermal exposures only.[12–15] Appropriate health care professional personal protective equipment depends on the circumstances of the organophosphate exposure and potency of the involved organophosphate.
5. Removal of contaminated garments and skin cleansing are highly effective at removing simulated organophosphate exposures.[1]
6. Early administration of oximes such as pralidoxime can be considered for significant organophosphate poisoning (especially for those with muscle fasciculations, weakness, or paralysis). Oximes are not universally effective; their effectiveness may be limited by rapid aging of some organophosphates (eg, tabun), their inability to cross the blood-brain barrier, structural differences among organophosphates, and rapid reinactivation of regenerated acetylcholinesterase in the presence of the poison.[6,16–19]
7. Neuromuscular blockade from medications metabolized by butyrylcholinesterase (aka pseudocholinesterase) such as succinylcholine and mivacurium can be prolonged by several hours in the context of organophosphate or carbamate poisoning.[20–22] Neuromuscular blockers not primarily metabolized by cholinesterases should be used if neuromuscular blockade is needed.

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13. SODIUM CHANNEL BLOCKERS

Introduction

Many poisons block cardiac sodium channels with properties similar to Vaughan-Williams class Ia or Ic antidysrhythmics. Sodium channel blocker poisoning causes QRS prolongation, hypotension, seizures, ventricular dysrhythmias, and cardiovascular collapse. Many sodium channel blockers have additional effects on other cardiac receptors and ion channels.[1] Although TCAs are the most commonly described and best-studied sodium channel blockers, many other poisons cause life-threatening sodium channel blockade in overdose (Table 3).

Table 3. Selected Sodium Channel Blockers

Carbamazepine
Chloroquine*
Cocaine†
Diphenhydramine
Flecainide
Hydroxychloroquine*
Lamotrigine
Lacosamide
Propafenone
Quinine
Quinidine
Thioridazine
Taxus spp. (yew)
Topiramate
TCAs‡
Venlafaxine
Zonisamide

TCA indicates tricyclic and tetracyclic antidepressant.

*Treatment of chloroquine and hydroxychloroquine toxicity is outside the scope of this focused update.

†Management of life-threatening cocaine toxicity is discussed in Section 6 of this focused update.

‡Common TCAs include amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine.

Treatment recommendations for poisoning by other sodium channel blockers are often extrapolated from TCA studies. Management of life-threatening poisoning from LAs, the pharmacological action of which is similar to that of class Ib antidysrhythmics, is discussed in Section 9 of this focused update. Treatment of cocaine poisoning, which has toxicity unique from that of other LAs, is discussed in Section 6. Management of chloroquine and hydroxychloroquine poisoning, which is unique but uncommon in North America, is outside the scope of these guidelines.

Characteristic electrocardiogram changes usually precede ventricular dysrhythmias in patients with sodium channel blocker poisoning. These include intraventricular conduction delay (QRS interval prolongation) and the development of a terminal rightward axis deviation, best appreciated in lead aVR (Figure 3).

No studies have compared treatments during cardiac arrest from sodium channel blocker poisoning. Human evidence is limited to retrospective observational studies and case reports, in which patients received multiple interventions. The vast majority of these involve TCA poisoning. The therapeutic intervention with the most evidence is sodium bicarbonate, typically given as bolus intravenous administration of hypertonic solutions (1000 mEq/L in adults, 500 mEq/L in children). Hypertonic sodium administration and induction of alkalemia are variably beneficial in case reports and animal

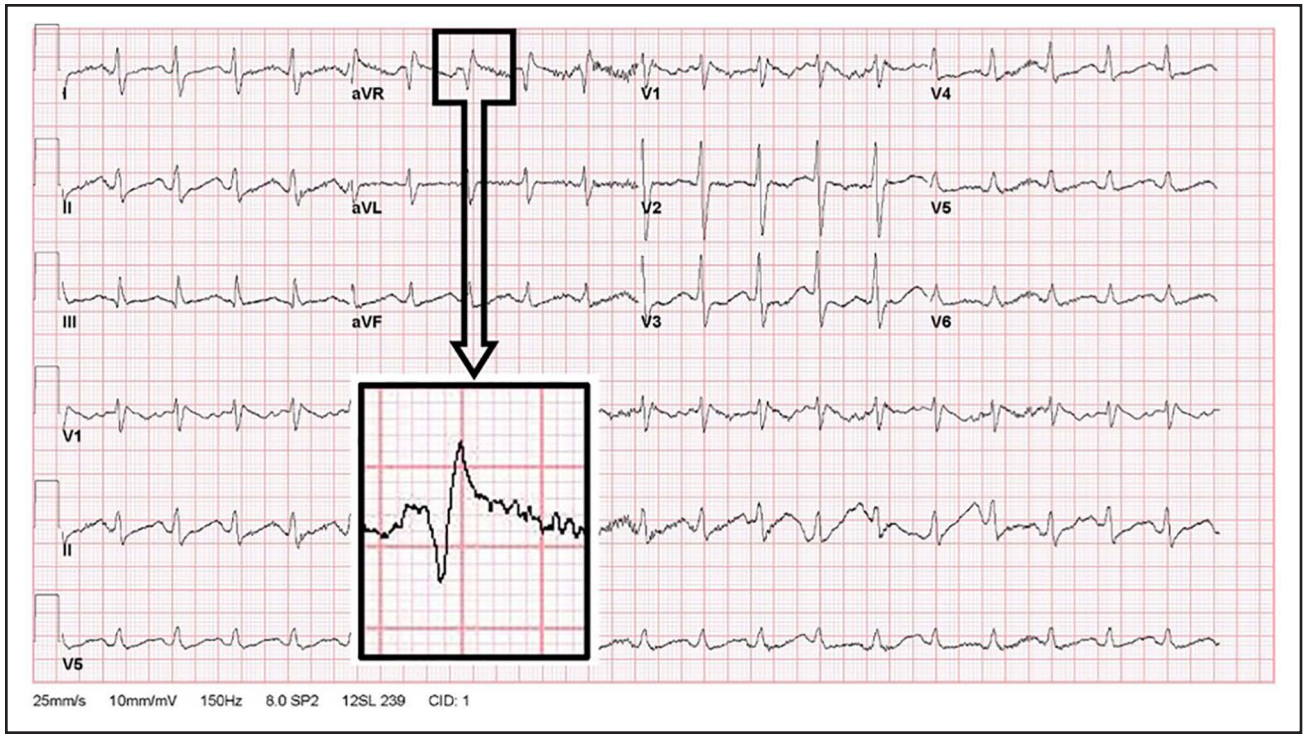

Figure 3. Typical electrocardiographic findings in a patient with sodium channel blocker poisoning.
Image courtesy of Robert S. Hoffman, MD, New York City Poison Control Center. Used with permission.

models.[2–4] Class Ib antidysrhythmics (eg, lidocaine or phenytoin) and ILE are proposed to treat cardiotoxicity by class Ia and Ic sodium channel blockers.[2–5] Other interventions, including sodium bicarbonate and benzodiazepines for seizures, magnesium for wide-complex tachycardia, and high-dose glucagon for hypotension, are not supported well enough to inform a recommendation.

Recommendations for the Treatment of Patients With Life-Threatening Sodium Channel Blocker Poisoning

COR	LOE	Recommendations
1	B-NR	1. We recommend using sodium bicarbonate to treat life-threatening cardiotoxicity from tricyclic and/or tetracyclic antidepressant poisoning.
2a	C-LD	2. It is reasonable to use sodium bicarbonate to treat life-threatening cardiotoxicity caused by poisoning from sodium channel blockers other than tricyclic or tetracyclic antidepressants.
2a	C-LD	3. It is reasonable to use extracorporeal life support, such as VA-ECMO, to treat refractory cardiogenic shock from sodium channel blocker poisoning.
2b	C-LD	4. It may be reasonable to use Vaughan-Williams class Ib antidysrhythmics (eg, lidocaine) to treat life-threatening cardiotoxicity from class Ia or Ic sodium channel blockers.
2b	C-LD	5. It may be reasonable to use intravenous lipid emulsion to treat life-threatening sodium channel blocker poisoning refractory to other treatment modalities.

Recommendation-Specific Supportive Text

1. and 2. Sodium loading and increasing the serum pH (correction of acidemia or inducing alkalemia) are each supported for the treatment of hypotension and dysrhythmia from TCA poisoning.[3,6–9] The combination has an additive effect. Administration of hypertonic solutions of sodium bicarbonate administration achieves both physiological goals, although its mechanism is not fully elucidated.[7,10] This practice is supported by case series in TCA poisoning[6,9] and case reports on poisoning by other sodium channel blockers,[7,11–14] although treatment failures are reported and the use of multiple interventions makes it difficult to attribute benefit to any one therapy. Sodium bicarbonate boluses are titrated to resolution of hypotension and QRS prolongation.[4,7,10] Whether it is superior to then start a continuous infusion or to monitor the patient and administer additional sodium bicarbonate boluses as needed is unsettled.[15] Experts recommend avoiding extremes of hypernatremia (serum sodium not to exceed 150–155 mEq/L) and alkalemia (serum pH not to exceed 7.50–7.55) to avoid iatrogenic harm.[3,7,8,16,17] If necessary, serum sodium can be increased separately by administration of hypertonic saline,[18] and pH can be controlled by adjusting minute ventilation in intubated patients.[19] Because hypertonic sodium bicarbonate therapy can cause hypokalemia,[20] patients should be monitored and treated for hypokalemia during alkalemia therapy.

3. Extracorporeal support, including VA-ECMO, has been used successfully in patients with refractory cardiogenic shock from sodium channel blocker poisoning.[21–25] Controlled observational studies and clinical trial data do not exist. Further discussion of the use of VA-ECMO in poisoning is provided in Section 15.
4. Lidocaine, a class Ib antidysrhythmic, competes with class Ia and Ic antidysrhythmics for binding at the sodium channel and dissociates from the receptor more rapidly than class Ia or Ic agents such as TCAs and therefore does not depress phase 0 depolarization.[2] The use of lidocaine to treat wide-complex tachycardia from TCA overdose is supported by animal studies and human case reports.[2] A similar role for phenytoin, another class Ib antidysrhythmic, is supported by human case reports,[2,26] although not consistently by animal studies.[27,28] Lidocaine and phenytoin are second-line therapies after sodium bicarbonate.
5. Most sodium channel blockers are highly lipophilic. Several case reports describe temporal improvement after ILE administration,[29–31] including successful treatment of TCA-induced cardiac arrest.[32–34] An RCT, published in abstract form only, found no benefit from ILE administration in the treatment of hypotension or electrocardiogram abnormalities from TCA poisoning.[35] Furthermore, ILE administration may increase drug absorption in oral overdose,[36] and animal studies are not supportive.[37] The Lipid Emulsion Workgroup recommends the use of ILE for life-threatening TCA toxicity "if other therapies fail/in last resort" or after failure of standard therapies but "not as first-line therapy."[38] The Lipid Emulsion Workgroup makes a neutral recommendation for cardiac arrest.

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14. SYMPATHOMIMETICS

Introduction

The hallmark of sympathomimetic poisoning is increased activity of the adrenergic nervous system. Amphetamines, cathinones, and some synthetic cannabinoid receptor agonists produce sympathomimetic poisoning. When treatment is required, clinicians are rarely able to determine which specific substance was used, and treatment must be based on presenting signs and symptoms and limited available history. Management of severe cocaine poisoning is discussed separately in Section 6. Complications of sympathomimetic poisoning result from excessive catecholamine release and an attendant increase in metabolic and psychomotor activity. Patients present on a spectrum of severity. Clinical manifestations include tachycardia, hypertension, agitation, seizures, hyperthermia, rhabdomyolysis, and acidosis.[1–4]

Sympathomimetic poisoning can cause sudden cardiac arrest, presenting as ventricular fibrillation, ventricular tachycardia, or pulseless electrical activity.[5–8] Vasospasm can cause myocardial infarction, even in patients with normal coronary arteries.[5,9–11] A stress (takotsubo) cardiomyopathy is also reported in sympathomimetic-poisoned patients; this condition can be fatal, but it resolves spontaneously in survivors.[10,12–15] Hyperthermia is a severe and rapidly life-threatening clinical manifestation.[2,3,6,16,17] Physical restraints may be temporarily necessary, but their prolonged use may exacerbate hyperthermia and agitation.

Although many clinical trials and observational studies have been published comparing various sedatives for patients with severe psychomotor agitation, none have focused on the prevention or treatment of cardiac arrest. Therefore, evidentiary support for management is primarily from nonhuman experiments, published cases, and expert opinion. Although there is no direct antidote to sympathomimetic poisoning, sedatives treat psychomotor agitation that results in delirium, rhabdomyolysis, and hyperthermia.[18–23] In some cases, large doses of sedatives are required.[4,24,25] External cooling directly treats hyperthermia, potentially reducing brain and other organ injury.[6]

Adequate sedation generally obviates the need for antihypertensive medications. Few studies specifically address the management of life-threatening cardiovascular toxicity from sympathomimetics other than cocaine that persists after sedation. Although α_1 receptor antagonists, α_2 receptor agonists, CCBs, nitrates, and mixed α-β blockers have all been used to treat hypertension and tachycardia, data to support a specific approach after provision of adequate sedation are lacking.

Management of Patients With Life-Threatening Sympathomimetic Poisoning

COR	LOE	Recommendations
1	B-NR	1. We recommend sedation for severe agitation from sympathomimetic poisoning.
1	C-LD	2. We recommend rapid external cooling for life-threatening hyperthermia from sympathomimetic poisoning.
2a	C-EO	3. Vasodilators, such as phentolamine and/or nitrates, are reasonable for coronary vasospasm from sympathomimetic poisoning.
2a	C-EO	4. Mechanical circulatory support, such as intra-aortic balloon pump or VA-ECMO, is reasonable for cardiogenic shock from sympathomimetic poisoning refractory to other treatment measures.
3: Harm	C-LD	5. Prolonged use of physical restraint without sedation is potentially harmful.

Recommendation-Specific Supportive Text

1. Sedatives (eg, benzodiazepines, antipsychotics, ketamine) have been used in nonhuman experiments and case reports to treat sympathomimetic poisoning.[26,27] Sedatives treat delirium and control psychomotor agitation that produces heat and rhabdomyolysis. Antipsychotics control agitation. Benzodiazepines control agitation, relax muscles, and treat seizures. Although several clinical trials compare specific therapies for severe psychomotor agitation, it is difficult to separate patients with sympathomimetic poisoning from other patients in these studies, and cardiac arrest was rare.[28–31]

2. Hyperthermia is rapidly life-threatening in sympathomimetic poisoning.[23] External and immersive cooling has been used to treat hyperthermia in patients with sympathomimetic poisoning.[6,32–34] Evaporative or immersive cooling modalities reduce temperature more rapidly than cooling blankets, the application of cold packs, or endovascular cooling devices.[35–39]
3. Vasodilators, including nitrates and α-adrenergic receptor antagonists, have been used to treat coronary vasospasm, reversing electrocardiographic and biochemical markers of ischemia in sympathomimetic-poisoned patients.[21,40,41]
4. Mechanical circulatory support, including VA-ECMO[14,42] and intra-aortic balloon pump,[10,43] has been used successfully to support cardiac output in patients in cardiogenic shock while stress cardiomyopathy resolves. Stress (takotsubo) cardiomyopathy can be fatal, but it often spontaneously resolves in days to weeks with circulatory support.
5. Although physical restraints may be necessary temporarily, their sustained use without effective sedation is associated with death in patients with severe agitation.[41,44–46] Restraints should be removed as soon as safely possible.

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15. EXTRACORPOREAL MEMBRANE OXYGENATION

Introduction

VA-ECMO is a resuscitative measure providing both cardiac and pulmonary support.[1] In the setting of poisoning, VA-ECMO treats refractory cardiogenic shock by providing mechanical circulatory support while the offending poison is eliminated. The use of VA-ECMO for poisoning is increasing.[2] There are no RCTs comparing the use of VA-ECMO with supportive care for the poisoned patient. An RCT comparing VA-ECMO with standard care for patients with refractory out-of-hospital cardiac arrest found improved survival with VA-ECMO.[3] However, this study excluded patients with drug overdose. Observational studies demonstrate that patients with cardiac arrest or refractory shock due to poisoning who are managed with VA-ECMO have lower mortality than other patients treated with VA-ECMO and lower mortality compared with poisoned patients treated with standard critical care and antidotal therapy alone.[4] The likely reason is that, in the absence of permanent end-organ damage, the natural course of drug overdose is recovery due to renal, hepatic, or extracorporeal removal of the poison.

The use of VA-ECMO in the poisoned patient is limited by availability, logistics of transport, patient comorbidities, and risks inherent to the procedure. Both the pathophysiology of the specific poisoning and the clinical features of the patient must be considered in the decision to initiate VA-ECMO. In particular, VA-ECMO does not generally correct distributive shock or reverse cellular injury. A multidisciplinary approach, including consultation from a poison center or medical toxicologist, is helpful to determine the appropriateness of VA-ECMO in specific cases.

The use of VA-ECMO in the context of cardiac arrest is also called extracorporeal CPR. Current AHA guidelines for ALS resuscitation state that "ECPR [extracorporeal CPR] may be considered for select cardiac arrest patients for whom the suspected cause of the cardiac arrest is potentially reversible during a limited period of mechanical circulatory support (COR 2a, LOE C-LD)."[5] The most recent pediatric ALS guidelines state, "ECPR [extracorporeal CPR] may be considered for pediatric patients with cardiac diagnoses who have IHCA [in-hospital cardiac arrest] in settings with existing ECMO [extracorporeal membrane oxygenation] protocols, expertise, and equipment (COR 2b, LOE C-LD)."[6]

Other forms of mechanical circulatory support, such as implanted left ventricular assist devices and percutaneous mechanical circulatory support devices (intra-aortic balloon pump and newer devices), have their own risks and benefits and may be considered for clinical scenarios similar to those described here.

Recommendations for the Use of VA-ECMO in Patients With Life-Threatening Poisoning

COR	LOE	Recommendations
2a	C-LD	1. It is reasonable to use VA-ECMO for persistent cardiogenic shock or cardiac arrest due to poisoning that is not responsive to maximal treatment measures.
2a	C-LD	2. It is reasonable to use VA-ECMO for persistent dysrhythmias due to poisoning when other treatment measures fail.
2b	C-EO	3. The effectiveness of VA-ECMO for poisoned patients with cardiovascular collapse from causes other than cardiogenic shock has not been established.

Recommendation-Specific Supportive Text

1. In a retrospective review of 64 patients treated with VA-ECMO for cardiac arrest or refractory shock regardless of cause, cardiotoxic poisoning was independently associated with survival.[7] In an observational study of 62 patients with cardiac arrest or severe shock after poisoning, VA-ECMO was associated with reduced mortality compared with standard care alone.[4] Another observational study of 22 patients reported survival of 7 of 10 patients with refractory shock and 3 of 12 patients with refractory cardiac arrest due to poisoning.[8] There are risks for significant complications, including limb ischemia, bleeding, stroke, and infection.[1,8,9]
2. For patients with persistent nonperfusing dysrhythmias, VA-ECMO provides forward blood flow to allow poison elimination. Case reports describe the use of VA-ECMO to support poisoned patients with persistent dysrhythmias.[10–15]
3. In a case series, patients with hematological and metabolic poisons had higher mortality on VA-ECMO compared with patients with other poisonings.[2] The efficacy of VA-ECMO is undefined in poisonings that cause refractory vasodilatory shock with preserved cardiac function, direct cellular toxicity, disruption of cellular oxygen use, or poisonings that are universally fatal despite temporary cardiac support.

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16. KNOWLEDGE GAPS AND PRIORITIES OF RESEARCH

Cardiac arrest and periarrest states due to poisoning are vastly underresearched. As part of the overall work for the development of these guidelines, the writing group reviewed a large amount of literature concerning the management of cardiac arrest due to poisoning. One expected challenge faced through this process was the lack of data in many areas of toxicology research. With the exception of opioid overdose, cardiac arrests due to poisoning are rare events and challenging to study. Reported cases are heterogeneous with regard to the poison(s) involved, dose, coingested substances, timing of presentation, and comorbidities of the patient. Case reports are highly susceptible to publication bias. Ethical concerns in randomizing critically ill patients, many of whom have attempted self-harm, are significant.[1] Although well-controlled animal studies can be useful, there is a great danger that the results are model dependent and therefore poorly applicable to the management of critical human poisoning. As a result, only a small minority of guideline recommendations (3%) were based on high-grade evidence (LOE A), and 77% were based on low-grade evidence (LOE C).

Some critical knowledge gaps identified by the writing group are summarized in Table 4.

Table 4. 2023 Resuscitation in Critical Poisoning: Key Knowledge Gaps

Benzodiazepines
For which patients does the benefit of flumazenil exceed the risk of seizure?
β-Blockers and CCBs
Does high-dose insulin therapy, administered in addition to or instead of standard vasopressors, reduce mortality or ischemic complications? What is the ideal vasopressor or inotropic strategy for refractory shock from β-blocker or CCB overdose? Does tailoring therapy to cardiogenic vs vasoplegic shock improve outcomes? Are nonadrenergic vasopressors effective? What are the benefits of glucagon for β-blocker poisoning? What are the benefits of glucagon for CCB poisoning? Is hemodialysis beneficial for atenolol, sotalol, or nadolol poisoning? What are the benefits of ILE for oral overdose of lipophilic β-blockers or CCBs? What are the benefits of gastrointestinal decontamination in patients with life-threatening β-blocker or CCB poisoning, particularly when extended-release formulations are involved?
Cocaine
What is the ideal management of cocaine-induced myocardial ischemia, hypertensive emergency, or dysrhythmia?
Cyanide
Does the addition of sodium thiosulfate to either hydroxocobalamin or sodium nitrite therapy improve outcomes in cyanide-poisoned patients?
Digoxin
What is the best empirical dose of digoxin-Fab for patients with cardiac arrest from digoxin poisoning? What is the appropriate dose of digoxin-Fab for patients with critical poisoning from cardiac glycosides other than digoxin?
LAs
What is the benefit of ILE when given in addition to standard resuscitation with vasopressors and sodium bicarbonate for patients with LA cardiotoxicity? What is the ideal dose of ILE for LA poisoning? Is the optimal treatment for poisoning from other LAs the same as for poisoning from bupivacaine?
Methemoglobinemia
What is the true risk of methylene blue therapy in patients with glucose-6-phosphate dehydrogenase deficiency? What is the benefit of methylene blue in patients in cardiac arrest due to methemoglobinemia?
Opioids
What is the ideal initial dose of naloxone in settings where fentanyl and fentanyl analog overdoses are common? What is the benefit of naloxone when given to patients in cardiac arrest? What is the minimum safe observation period for patients with opioid overdose treated with naloxone? What are the most effective forms of secondary prevention for patients with opioid use disorder who survive overdose?
OPs and carbamates
What personal protective equipment and decontamination protocols are necessary to protect health care workers caring for patients with OP and carbamate insecticide exposures (agents with lower potency than military nerve agents)? Which patients with OP poisoning benefit from oxime therapy? What is the most effective oxime for OP poisoning? What is the most appropriate dose of oximes? Do patients with poisoning from highly toxic carbamates (eg, aldicarb) benefit from oxime therapy?
Sodium channel blockers
What is the ideal treatment for poisoning from sodium channel blockers other than TCAs? What physiological or electrocardiographic targets are most appropriate for patients with sodium channel blocker to prevent deterioration to cardiac arrest?
Sympathomimetics
What factors predict which patients with severe sympathomimetic poisoning will suddenly decompensate to cardiac arrest? What is the ideal medication or combination of medications for sedation of patients with severe psychomotor agitation?
Role of VA-ECMO
Which patients with poisoning have improved outcomes from VA-ECMO compared with standard critical care plus antidotal therapy? In what situations can VA-EMCO benefit patients with distributive shock or cellular injury from poisoning? What is the optimal timing of VA-ECMO initiation? Are outcomes better when VA-ECMO is initiated in the periarrest period, or earlier in the course of illness?

β-blocker indicates β-adrenergic receptor antagonist; CCB, calcium channel blocker; Fab, fragment antigen binding; ILE, intravenous lipid emulsion; LA, local anesthetic; OP, organophosphate; TCA, tricyclic or tetracyclic antidepressants; and VA-ECMO, venoarterial extracorporeal membrane oxygenation.

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ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

Appendix 1. Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Appendix 2. Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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