

COMPLEX CASE: TOXICOLOGY - PEDIATRIC

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LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to

- Identify initial management in medical emergencies using available patient-specific information (e.g., age-related, risk factors, relevant acuity indices).
- Develop therapeutic and monitoring plans based on medication-related problems, patient- and disease-specific information, and laboratory data.
- Summarize strategies for procurement, preparation, and administration of time-sensitive therapies.
- Evaluate policies and processes for availability of essential drugs (e.g., drug shortages) and emergency preparedness.
- Modify treatment plan based upon patient's response to initial therapy.

I. Pertinent considerations in managing poisonings in healthcare.

- A. A patient may report a specific substance was ingested but may be mistaken or intentionally misleading on what the ingestion actually was. A detailed history and the patient's toxidrome (the clinical manifestations of a poisoning in overdose) may reveal an entirely different story. Examples include:
1. The patient reports amlodipine ingestion but has a wide QRS and husband has propranolol on their medication list
 2. Mom reports their son got into atorvastatin bottle but tablet identification shows there is zolpidem inside
 3. Patient says they have been taking aspirin around the clock for headache but their acetaminophen level is elevated and their salicylate is undetectable
- B. Additionally, once the toxin is identified, use of specific antidotes may be nuanced and relevant to only some drugs in a class or specific situations. For example:
1. Chelation of acute mercury poisoning but not chronic mercury poisoning
 2. Physostigmine for diphenhydramine overdose, but potentially not for mixed anticholinergic sympathomimetic overdose
 3. IV fat emulsion prior to cardiac arrest for amitriptyline but not for other Tricyclic Antidepressants (TCAs)
 4. Sodium bicarbonate for propranolol sodium channel blockade but not for other beta blockers
- C. After acute exposures, patients should have their risk of toxicity estimated, be monitored for the development of symptoms, and receive therapies off the clinical syndrome and likelihood of toxicity.
- D. **It is highly recommended that patient assessment, disposition, and treatment be determined in consultation with a toxicologist or poison center to ensure any unique aspects of a specific poisoning are appropriately addressed. Poison centers in the US can be contact at 1-800-222-1222 and are available for consultation 24/7.**

II. Basic therapeutic targets in poisoned patients after identification of substance and triaging of exposure severity¹

- A. Decontamination
1. Topical decontamination
 - a. Example: removing soiled clothing and washing exposed areas
 2. Gastric decontamination

- a. Example: activated charcoal if able to protect airway, toxin amenable to binding, and likely to still be in gastric tract.
 - 1) Consensus recommendation recommends completion within 1 hour. However, sustained release preparations, bezoars, and drugs with enterohepatic recirculation may benefit from later administration.²
 - 2) Adult dosing
 - a) 0.5-1g/kg OR 10 g per 1 g of substance ingested
 - b) Usual dose 25-100 g
 - 1) Pediatric dosing
 - a) 0.5-1g/kg
 - b. Example: Whole bowel irrigation for exposure where continued gastric contact time may increase risk of severe morbidity
 - 1) Recommended for sustained-release or enteric-coated drugs, particularly for those patients presenting later than 2 h after drug ingestion when activated charcoal is less effective.³
 - 2) Contraindicated in patients with bowel obstruction, perforation, or ileus, and in patients with hemodynamic instability or compromised unprotected airways.
 - 3) Dosing:
 - a) Children 9 months to 6 years: 500 mL/h
 - b) Children 6–12 years: 1000 mL/h
 - c) Adolescents and adults: 1500–2000 mL/h
 - d) Continue until effluent is clear or radio opaque ingestions are no longer present on radiograph
- B. Supportive care of Airway Breathing and Circulation (“ABCs”)
1. Maintenance of a patent airway and adequate breathing
 - a. Example: supplemental oxygen
 - b. Example: endotracheal intubation
 - c. Example: Venoarterial or Venovenous Extracorporeal Membrane Oxygenation (VA or VV ECMO)
 2. Resuscitation with Intravenous fluids, vasopressors, and inotropes to maintain circulating blood flow
- C. Reversal of toxicity
1. Example: use of antidotal therapies able to reverse or antagonize receptor effects (e.g., naloxone, flumazenil, physostigmine)

2. Example: use of pharmacologic agents to counteract agitation (e.g., benzodiazepines)
- D. Enhanced elimination*
1. Extracorporeal elimination
 2. Examples: intermittent hemodialysis, continuous renal replacement, plasmapheresis, gut dialysis with charcoal, cholestyramine for bile elimination Enzyme induction or supply
 - a. Example: use of phenobarbital to induce CYP3A4 enzymes responsible for metabolism, exogenous glucarpidase for methotrexate
 - b. *Enhanced elimination methods are highly toxin specific and dependent on physical properties of the drug such as lipophilicity or protein binding. Enhanced elimination techniques will not be discussed in this review.
 - 1) EXTRIP is a multidisciplinary work group that creates guidelines on extracorporeal elimination of poisons and drugs in overdose
 - a) Guidelines available here: <https://www.extrip-workgroup.org/>

Case 1

Ella Z, A 2-year-old female with no significant past medical history presents to the emergency department somnolence identified by mom.

The babysitter reported to mom that Ella was found with a bottle of medication, but she took it away before Ella got into any. Otherwise she reports Ella was acting normal all day, although she did have fewer wet diapers than normal.

Physical exam was notable for a minimally interactive child, mydriasis, flushed skin, and cracked lips. Normal tone and reflexes.

Vital signs: HR 175 bpm, BP 65/32 mm Hg RR 25/min T 100.2° F O₂ sat 99% on ambient air.

Electrocardiogram (ECG): PR 135, QRS 123 ms, QTc 457 ms and 3.2 mm R waves in the AVR lead.

Lab: A point of care blood glucose is 82 mg/dL

The provider suspects ingestion (not organic disease) and asks the Emergency Medicine (EM) pharmacist for help determining what could be in the home. Intravenous fluids are started.

- You interview the mother
 - “What kind of medications are available at home that Ella would have access to?”
- The mother responds
 - “There are a few over-the-counter medications, such as diphenhydramine and acetaminophen, at home.”
 - “Ella has a 6-year-old brother who takes something for ADHD and something for bed wetting but I can't remember the names of the medications.”
- The EM pharmacist searches the brother's medical record and determines that he takes guanfacine and desipramine.

Question #1

Which drug is the most likely cause of these symptoms?

- A. Diphenhydramine
- B. Desipramine
- C. Guanfacine
- D. Acetaminophen

Question #2

Which of the symptoms is most suggestive of potentially serious impending medical event?

- A. QRS greater than 120 ms
- B. R wave in AVR greater than 3 mm
- C. RR greater than 25
- D. QTc greater than 450 ms

III. Tricyclic Antidepressant (TCA) overdose ⁴**A. Epidemiology⁵**

- 1. U.S. poison centers 2020
 - a. 8,080 calls for TCA exposure
 - b. 36 Deaths
 - c. 25th most common poisoning fatality in 2020

B. Mechanism of toxicity⁴

- 1. Increase synaptic norepinephrine and serotonin
- 2. Alpha-1 and -2 antagonism
- 3. H1 antagonism
- 4. Anti-**muscarinic** acetylcholine antagonist (the muscarinic receptors are located on effector organs and stimulated by the parasympathetic nervous system with acetylcholine.)
 - a. Nicotinic receptors are pre-ganglionic and on the neuromuscular junctions and are not blocked by TCA
- 5. Sodium channel blockade

Question #3

You begin to assess which medications you would like to have rapidly available to treat Ella's overdose.

Which of the following effects should you anticipate needing to treat?

- A. Seizures, hypotension, arrhythmia
- B. Sedation, miosis, apnea
- C. Hypotension, bradycardia, hypoglycemia
- D. Hypotension, tachycardia, hyperglycemia

A. Clinical effects^{4,6,7}

1. Anticholinergic toxidrome (tachycardia, anhidrosis, mydriasis) with CNS and cardiovascular complications
2. Central nervous system
 - a. Anticholinergic delirium
 - b. Seizures
3. Cardiovascular
 - a. Hypotension from alpha-1 adrenergic blockade
 - b. Tachycardia from muscarinic blockade
 - c. QRS widening from sodium channel blockade (ventricular conduction delay)
 - d. R wave elevated in AVR
 - 1) AVR is positioned "behind" the heart and as the heart depolarizes downward (atria to ventricle) and with a leftward predominance (left ventricle is largest so generates most force). The net force of depolarization is moving away from AVR and it detects a negative R wave deflection under normal circumstances. Changes that occur during TCA overdose (as detailed below) can cause the R wave to become a positive deflection and be a marker of exposure.
 - 2) Mechanism
 - a) The left and right heart BEGIN depolarization via the bundle of His at the same time (creating a narrow QRS in a normal conducting heart)
 - b) The electrical path of the right ventricle is shorter than the left as it is anatomically smaller

- c) The sodium channels on the right ventricle must remain inactive longer while waiting for the left side to finish depolarizing, so that they can both start at the same time during the next cardiac depolarization
- d) TCAs are reverse use dependent (bind inactive sodium channel preferentially)
- e) Since the right side is inactive longer, it is more prone to TCA sodium channel blockade
- f) Extremely prolonged right-sided depolarization due to TCA binding preference causes the right ventricular to take longer than the left to depolarize.
- g) As the right ventricle beings to take LONGER than the left ventricle to depolarize, it shifts the net depolarizing force rightward, causing an upstroke in the R wave in AVR since force is now moving towards it

B. Prognostication

1. Useful indicators of poor outcome include signs of sodium channel blockade on ECG^{6,8,9}
 - a. QRS greater than 100 ms predicts seizure
 - b. Elevated R wave in AVR (the reciprocal lead) is more predictive of seizure than wide QRS

Question #4

Ella receives fluids but is persistently tachycardic and hypotensive. Which of the following is an appropriate initial treatment for Ella?

- A. Direct current cardioversion for hypotensive wide QRS tachycardia
- B. Dopamine, physostigmine, hydroxocobalamin
- C. Sodium bicarbonate, norepinephrine
- D. IV lipid emulsion, norepinephrine

C. Treatment^{4,10}

1. Decontamination
 - a. Activated charcoal
 - 1) Single-dose activated charcoal if drug likely still in gastric system, patient able to protect airway, or if intubated and has gastric access
 - b. Whole bowel irrigation
 - 1) Consider for those with large ingestions at risk for severe morbidity or those presenting more than 2 hours after ingestion when activated charcoal may be less effective

- c. Dosing available in the decontamination segment of section 2 (therapeutic targets in poisoned patients)
- 2. Supportive care
 - a. Maintenance of airway, breathing, and circulation as described in section 2 (basic therapeutic targets in poisoned patients)
 - b. Blood pressure maintenance
 - 1) Vasopressors
 - a) Many studies suggest norepinephrine is preferred to dopamine for management of TCA induced shock as the vasopressor effect of dopamine occurs via dopamine mediated release of norepinephrine, an effect that is inhibited by TCA's¹¹⁻¹⁴
 - 2) Serum alkalization¹⁵
 - a) Targeting a serum Ph of 7.45-7.55 with sodium bicarbonate or sodium acetate may reverse hypotension along with colloid therapy
 - b) Enhances protein binding of TCA to albumin, reverses negative effects of acidemia
- 3. Reverse toxicity
 - a. Agitation
 - 1) Benzodiazepines are recommended for seizures OR anticholinergic delirium
 - 2) Physostigmine for anticholinergic delirium
 - a) Stigma due to case reports of asystole ASSOCIATED with (and potentially caused by) physostigmine use in two peri-arrest TCA OD patients¹⁶
 - b) Since then, numerous data has emerged supporting its safety in anticholinergic delirium
 - i. A Systematic review of 2299 patients identified only one other case of asystole in a case of severe TCA overdose, although causation was not confirmed. Bradycardia and seizures occurred in less than 1% of patients¹⁷
 - ii. Use of physostigmine in anticholinergic delirium reduces the likelihood of ICU admission or need for intubation over other supportive measures and controls delirium better than non-antidotal therapy¹⁸⁻²⁰
 - iii. The increased safety and efficacy data in contrast to the case reports which document only association and not causation has caused some to advocate for increased use in low-risk anticholinergic toxicity²¹
 - c) Physostigmine may be reasonable in patients at low risk of seizure or cardiac events

- i. Clear anticholinergic symptoms
 - ii. No conduction delay
 - iii. No seizure causing or cardiovascular drug co-ingestion
 - iv. No coronary artery disease
 - v. No bradycardia
- d) Physostigmine dosing²²
 - i. Adult:
 - (a) IM, IV: 0.5 to 2 mg; Max infusion rate 1 mg/min adults
 - (b) may repeat every 10 to 30 minutes until response occur
 - ii. Pediatric:
 - (a) IM, IV: Initial: 0.02 mg/kg maximum 0.5 mg/dose AND 0.5 mg/min
 - (b) May repeat every 5 to 15 minutes until response occurs or 2 mg reached
 - iii. Administration
 - (a) Consider administering dose over 3-5 minutes
 - (b) Duration of effect ~1-2 hours
 - (c) Repeat doses or infusions may be needed
 - (d) Consider infusion of 0.02 mg/kg/hr (maximum 2 mg) if prolonged use needed²⁰
- b. Seizures²³
 - 1) Benzodiazepines are recommended for seizures (dosing recommendations are not different than recommendations for status epilepticus)
 - a) Other GABA-A directed therapies like propofol, benzodiazepine infusions, or phenobarbital may be used in severe cases
 - 2) The role of other anti-epileptics is not well established. Sodium channel blocking drugs like phenytoin should likely be avoided
- c. Wide QRS²⁴
 - 1) May appear to be ventricular tachycardia (VT) to a provider unfamiliar with toxicity, important to avoid overaggressive VT treatment and initiate hypertonic sodium first in the setting of poisoning (European Resuscitation Council 2000)
 - 2) Hypertonic sodium in the form of sodium bicarbonate will overcome slowed sodium current from sodium channel blockade and can narrow QRS

- 3) A common protocol is sodium bicarbonate 1-2 mEq/kg IV every 3-5 minutes until QRS narrows

d. Salvage therapies

- 1) Lidocaine or phenytoin may outcompete TCA's for the sodium channel and more rapidly unbind, reversing conduction disturbance. 10cor have been considered in arrhythmia refractory to increased sodium and adequate alkalization.²⁵
- 2) VA-ECMO
- 3) IV lipid emulsion may be considered in patients experiencing cardiac arrest or life threatening toxicity after failure of standard therapies²⁶
 - a) 20% fat emulsion: 1.5 mL/kg bolus over 2-3 minutes followed by 0.25 ml/kg/min (duration may vary from 3 to 60 minutes based on guideline followed)
 - i. American College of Medical Toxicology: Infuse at 0.25 ml/kg/min x 3 minutes, if initial response reduce dose to 0.025 ml/kg/min. Total infusion time based on clinical response. May increase to initial rate if clinical decompensation occurs²⁷
 - ii. American Heart Association: 0.25 ml/kg/min x 30-60 min²⁸
 - iii. American Society of Regional Anesthesia and Pain: 0.25ml/kg/min for 10 minutes, increase to 0.5 ml/kg/min if decompensation occurs²⁹
 - b) May repeat bolus x 2 if no effect or if patient condition is declining after initial bolus
 - c) Maximum suggested dose 10-12 ml/kg²⁷

D. Monitoring

1. ECG and telemetry to monitor cardiac manifestations
2. Serum electrolytes to maintain normal status and prevent arrhythmia
 - a. Potassium especially important if undergoing alkalization
3. Neurologic symptoms
4. Biomarkers of organ function to assess for sequelae of injury
 - a. If seizure occurs, Creatinine Kinase (CK) to monitor for rhabdomyolysis
 - b. Urinary output (some patient may need urethral catheterization if anticholinergic urinary retention present)
 - c. Arterial Ph while undergoing alkalization
5. Note diphenhydramine may create false positive for TCA on urine drug screen and have similar anticholinergic and sodium channel blocking effects³⁰

E. Summary

1. TCA overdose may be very severe, though the incidence is decreasing
2. Toxicity is derived from sodium channel blockade, antimuscarinic effects, and alpha blockade
3. Patients with wide QRS or elevated R wave in Avr are at higher risk of seizure or arrhythmia
4. Treatment is supportive and directed towards reversing specific manifestation of toxicity
 - a. Benzodiazepines for seizure or agitation
 - b. Physostigmine for anticholinergic delirium in select patients
 - c. Sodium bicarbonate for wide QRS
 - d. Alkalinization to aid redistribution into serum
 - e. Fluids, vasopressors, endotracheal intubation, and VA ECMO for supportive cares of ABC's

Case 2

David is a 6-month-old male with past medical history of 1-month premature birth, intrauterine growth retardation, fraternal twin presents to the emergency department with parents exhibiting extreme agitation and inconsolable crying. The child has had an upper respiratory infection for a few days, 6 hours prior the parents found the 5-year-old giving the child a medicine to "make David feel better".

They removed a white scored tablet from the child's mouth and whipped the mouth that was ~50% intact. The mom thinks it was one of her bupropion XL. She did not contact a poison center or seek health care as she believed the child did not get much.

Medications: none

Physical exam was notable for an inconsolable agitated child with mydriasis, diaphoresis, flushed skin. There is notable hyperreflexia and possible clonus or tremor of the ankles,

Vital signs: HR 175 BP 125/63 RR 25 T 99 F O2 sat 99% on ambient air.

An ECG reveals PR 140, QRS 97, QTc 420

A point of care blood glucose is 73 mg/dl

QUESTION #5

What toxicity is David likely to experience?

- A. Agitation, seizure, wide QRS tachycardia, refractory arrhythmia
- B. Initial nausea, vomiting, diarrhea and seizures followed by flaccid paralysis
- C. Pulmonary edema, diaphoresis, excess secretions requiring airway management
- D. Tachycardia, hypotension, anticholinergic delirium, and seizures

IV. Bupropion

A. Epidemiology⁵

1. US poison centers 2020
 - a. The single most fatal antidepressant in the US
 - b. 16,926 calls for bupropion exposure
 - c. 5,147 hospitalizations
 - d. 42 deaths involving bupropion (vs. 36 all TCA)
 - e. Accidental exposure in infants has caused fatalities. Many exposures are accidental pediatric exposures or intentional self-harm. Also used as a substance of abuse and may be insufflated or injected.³¹⁻³⁴

B. Mechanism of toxicity³⁵⁻³⁷

1. Norepinephrine and dopamine reuptake inhibitor
2. Structurally it is a cathinone
 - a. Similar to amphetamines and in the same class of drugs as the compounds commonly known as “bath salts” (i.e., mephedrone)
 - b. Frequently causes false positive for amphetamine on urine drug screen³⁸
3. May block gap junction in cardiac myocytes³⁹

C. Clinical effects^{34,40,41}

1. Sympathomimetic toxidrome
 - a. Tachycardia, diaphoresis, agitation, hypertension, arrhythmia, seizure
2. CNS
 - a. Agitation, hallucination, tremor
 - b. Somnolence and brain death mimic have also been reported⁴²
 - c. Seizures
 - 1) Tachycardia and the presence of agitation, tremor, or hallucination are significantly associated with seizures.
 - a) Absence of tachycardia has a negative predictive value of 92.9% for seizures³⁴
 - 2) Seizure onset may be very delayed and is dependent on product.
 - a) Immediate release: mean time 4 hours, reported as late as 8 hours⁴¹
 - b) Sustained release: 85% of seizure events in one case series occurred within 6 hours but may occur as late as 14 hours⁴⁰

- c) Extended release: XL product case series mean time to seizure 7.9 hours, maximum 24 hours, 25% occurred after 8 hours³⁴

3. Cardiovascular^{43,44}

- a. Hypertension
- b. Tachycardia
- c. Conduction abnormalities
 - 1) Wide QRS tachycardia
 - 2) Prolonged QTc interval
- d. Cardiogenic shock from cardiotoxic effects has been reported in numerous cases

D. Treatment

- 1. Decontamination (see section 2, therapeutic targets in toxicology, for dosing)
 - a. Activated charcoal if drug likely still in gastric system, patient able to protect airway, or if intubated and has gastric access.
 - b. Whole bowel irrigation is often utilized due to the potential for severe outcomes and continued absorption from SR or XL products⁴⁰
- 2. Supportive cares
 - a. Maintenance of airway, breathing, and circulation as described in section 2
- 3. Reverse toxicity
 - a. CNS
 - 1) Agitation, tremor, or other sympathomimetic toxicity
 - a) Benzodiazepines (i.e., IV lorazepam, midazolam, or diazepam) are recommended to reduce sympathetic outflow
 - b) Patient with sympathetic toxicity may require higher than normal dosing
 - c) Finding the right dose may require exploration of a patients “dose response curve” and is highly individualized
 - i. Titrate carefully to desired effect
 - ii. Maximum dose not established
 - iii. Concomitant withdrawal states such as alcohol withdrawal or other patient specific factors such as co ingestions may necessitate very large doses
 - d) Lorazepam suggested initial dosing⁴⁶
 - i. Adult

- (a) Lorazepam IV: 1-4 mg as needed (not to exceed 2 mg/min) until adequately symptom resolution
 - (b) Lorazepam IM: 2-4 mg
 - ii. Pediatric:
 - (a) Lorazepam IV: 0.04 mg/kg maximum dose 2 mg/min
 - (b) Lorazepam IM: 0.05 mg/kg maximum dose 4 mg
- 2) Seizures²³
 - a) Benzodiazepines are recommended for seizures (dosing recommendations are not different than recommendations for status epilepticus)
 - i. Other GABA-A directed therapies like propofol, benzodiazepine infusions, or phenobarbital may be used in severe cases
- 3) The role of other antiepileptic's are less well established
- b. Cardiovascular
 - 1) Cardiovascular shock
 - a) Consider early echocardiography to aid in determination of shock subtype as cardiogenic shock is often reported
 - b) Use of inotropes (dobutamine, dopamine, epinephrine) and vasopressors (norepinephrine, phenylephrine, vasopressin) as needed based on shock etiology
 - 2) Malignant hypertension causing end organ damage⁴⁷
 - a) Antihypertensives
 - i. Selection of agent is based off patient factors and considerations would be the same as selecting an agent in hypertensive emergency
 - ii. An IV agent is preferred and the ability to rapidly titrate to clinical effect may afford faster obtainment of blood pressure goal
 - b) For tachycardia and hypertension, consider an agent with beta-1 receptor blockade as well as alpha-1 receptor blockade or combine a beta-1 receptor blocker with an agent that has vasodilatory capacity
 - i. Examples
 - (a) Esmolol and nicardipine, nitroglycerin, nitroprusside
 - (b) Labetalol alone
 - c) For hypertension without tachycardia consider an agent with vasodilatory properties
 - i. Examples

(a) Nicardipine, nitroglycerine, or nitroprusside

3) Conduction abnormalities

a) Wide QRS or severe conduction delay²⁴

i. Sodium bicarbonate

(a) Often utilized but may be ineffective as most conduction delay may be mediated by gap junction blockade and not sodium channel blockade.⁴⁸

(b) Dosing: 1-2 meq/kg as a bolus

- May repeat until QRS interval narrows
- Note the goal is hypertonic sodium overwhelming potential sodium channel blockade, not alkalemia
- Avoid pH greater than 7.55
- Monitor for hypernatremia if repeated boluses given

4) Salvage therapy

i. Intralipid emulsion has been utilized in cases of refractory conduction delay or cardiac arrest as a last line agent.²⁶

(a) See dosing in TCA section

ii. VA- ECMO has been utilized for severe persistent arrhythmia or refractory cardiogenic shock⁴⁹

E. Monitoring

1. Vital signs and neurologic symptoms
2. ECG and telemetry to monitor cardiac manifestations
3. Arterial pH and lactate if in cardiovascular shock
 - a. Consider echocardiography to determine shock etiology
4. Biomarkers or organ function to assess for sequelae of injury
 - a. If seizure occurs, CK to monitor for rhabdomyolysis

F. Summary

1. Bupropion is a growing overdose of concern, the most lethal single antidepressant, and far more prevalent than TCA's
2. Toxicity is derived from sympathomimetic toxicity and potential cardiac toxicity from gap junction blockade
3. Patients with tachycardia, hallucination, agitation, or tremor are at higher risk of seizure
4. Seizures can be delayed due to SR and XL formulation

5. Treatment is supportive and directed towards reversing specific manifestation of toxicity
 - a. Benzodiazepines for seizure or agitation
 - b. Sodium bicarbonate for wide QRS (may be refractory)
 - c. Fluids, vasopressors, endotracheal intubation, and VA ECMO for supportive cares of ABC's

Case 3

James is a 14-year-old male who presents with behavioral changes per his mother. He is normally alert and oriented x 4 but today seems somnolent and oriented only to self. Two days ago, he was started on ziprasidone 40 mg orally daily and had his dose of sertraline increased to 100 mg orally daily. He has been receiving them daily.

Past medical history: Developmental delay, autism spectrum disorder, behavioral disorder, Anxiety

Medications (all taken orally): Clonidine 0.1 mcg TID, sertraline 100 mg daily, buspirone 15 mg TID, ziprasidone 40 mg daily, haloperidol 2.5 mg nightly as needed for sleep difficulty, Methylphenidate 10 mg daily

Physical exam was notable for a well-developed, well-nourished 14-year-old male. Pupils were normal, the patient was diaphoretic, had slight tremor of hands as well as cog wheel rigidity. There was notable hyperreflexia of all extremities and inducible ankle clonus.

Vitals signs: HR 122 bpm BP 147/75 mm Hg RR 21/min T 99° F O₂ sat 99% on ambient air
An ECG reveals PR interval 140 ms, QRS interval 71 ms, QTc interval 332 ms
A point of care blood glucose is 93 mg/dl

Question #6

Which of the following is the most likely etiology of James' condition?

- A. Serotonin syndrome due to autonomic dysfunction
- B. Neuroleptic malignant syndrome due to autonomic dysfunction
- C. Serotonin syndrome due to inducible clonus and hyperreflexia
- D. Neuroleptic malignant syndrome due to inducible clonus and hyperreflexia

V. Neuroleptic Malignant Syndrome (NMS) & Serotonin Syndrome (SS)

A. NMS

1. Definition/Mechanism⁵⁰

- a. Life-threatening reaction to relative dopamine deficiency due to antipsychotic dopaminergic blockade OR withdrawal of dopamine agonist

- b. Nigrostriatal Dopamine (DA)₂ Blockade- muscle rigidity, tremor, motor disorders
- c. Hypothalamic DA₂ blockade- Thermoregulatory set point alteration (hyperthermia)

B. Serotonin toxicity/syndrome

1. Definition/mechanism^{51,52}

- a. Life-threatening reaction to excess synaptic serotonin from serotonin-modulating drugs
- b. 5HT_{2A} receptor agonism believed to be highly involved in pathology
- c. High synaptic norepinephrine also correlated with adverse clinical outcome
- d. Most common with multiple mechanisms of increased 5HT
 - 1) i.e., Monoamine Oxidase Inhibitor (MAOI) + Selective Serotonin Reuptake Inhibitor (SSRI) higher risk than SSRI + SSRI

2. Clinical effects of NMS and SS^{50,51,53}

Table 1: Clinical effects of NMS and SS		
Symptoms	NMS	SS
Neurologic	Altered mental status, agitation, confusion	
Dysautonomia	Tachycardia, hyperthermia, flushing diarrhea	
<u>Motor</u>	Rigidity: <u>Lead pipe rigidity</u> Tremor <u>Bradykinesia</u>	Rigidity: <u>Cogwheel rigidity</u> Tremor <u>Ankle and eye clonus</u> <u>Hyperreflexia (lower extremity prominence)</u>
<u>Onset</u>	Days to weeks after starting medication	May have rapid onset
<u>Duration</u>	Can last weeks after stopping	Dissipates when medication clears body

3. Differentiation of NMS and SS (Perry 2012, Stork 2019, Velamoor 1994)

- a. History of serotonergic exposure vs dopamine blockade (or withdrawal of dopamine agonist)
- b. Presence of bradykinesia/lead pipe rigidity (NMS) vs hyperreflexia/clonus (SS)
- c. Onset/duration
 - 1) NMS: Days to weeks after starting medication, can last weeks after stopping
 - 2) SS: May have rapid onset, dissipates when medication clears body

C. NMS diagnostic criteria⁵⁴

1. An expert consensus scoring system has been developed to help identify NMS but *no minimum score has been determined to meet diagnostic criteria*
 - a. A score is assigned based off the relative value of symptom present (e.g. hyperthermia is more diagnostically than tachycardia)
 - b. No single criteria or group of criteria is diagnostic for NMS; however, an increasing score increases likelihood

Table 2: NMS Expert consensus diagnostic criteria	
Exposure to a DA antagonist or DA agonist withdrawal within 72 hours (20 points) AND a negative work-up for other causes (7 points) AND criteria in right column	Hyperthermia (18 points)
	Rigidity (17 points)
	tachycardia plus tachypnea (5 points)
	mental status alteration (13 points)
	creatine kinase elevation (10 points)
	sympathetic nervous system lability (10 points)

D. SS diagnostic criteria^{55,56}

1. Hunter Serotonin Toxicity Criteria:
 - a. Tool for diagnosing serotonin syndrome validated in large data set of patients diagnosed with serotonin syndrome at bedside by toxicologist
 - b. More sensitive and specific than prior criteria (i.e., Sternbach criteria)⁵⁵

Table 3: Hunter Criteria	
Cause for new increase in Serotonin -Recent addition of serotonergic agent -Increased dose (or overdose) -Drug interaction AND 1 of the following criteria in right column	Spontaneous clonus
	Inducible clonus + agitation OR diaphoresis
	Ocular clonus + agitation OR diaphoresis
	Ocular clonus OR Inducible clonus + hyperthermia OR hypertonia
	Tremor + hyperreflexia

E. Treatment^{50-52,56}

1. Withdrawal of offending serotonergic (SS) or DA antagonizing (NMS) agent
 - a. Potentially restart dopaminergic agonist if NMS related to DA agonist withdrawal
2. Supportive care
 - a. Maintenance of airway, breathing, and circulation as described in section 1
3. Thermoregulation
 - a. May be refractory to antipyretics, external and internal cooling measures may be needed
 - b. External Cooling
 - 1) Cold water poured or misted over skin and a fan directed at patient (evaporative cooling)
 - 2) Cooling blanket
 - 3) Packing axilla, groin, neck, and torso with ice or cold towels
 - 4) Body bag filled with ice
 - 5) Ice water bath
 - c. Internal cooling
 - 1) Cold fluids
 - 2) Foley catheter with cold water irrigation
 - 3) Intubation, paralysis, and sedation to reduce kinetic hyperthermia in severe cases
4. Agitation, motor dysfunction, dysautonomia
 - 1) Benzodiazepines are recommended to reduce sympathetic outflow
 - i. Benzodiazepine dosing is highly individualized and titrated to resolution of patient motor systems and dysautonomia.
 - ii. Suggested IV lorazepam dosing⁵⁷
 - (a) Adult: IV 0.5-2 mg every 6-8 hours
 - (b) Pediatrics: IV 0.05 mg/kg maximum of 2 mg every 6-8 hours
 - 2) See section on management of bupropion-related agitation; dosing frequency may be increased in setting of severe symptoms
5. Salvage therapy
 - a. The efficacy of these medications has been debated, additionally there is not consensus on indication, dose, and duration of use. It is recommended that use of

these agents as well as dosing regimens be selected in conjunction with a toxicologist, poison center, or provider experienced in utilizing these therapies

b. NMS

- 1) Bromocriptine: dopamine agonist; may reduce NMS symptom duration⁵⁸⁻⁶¹
 - a) Adverse effects and considerations: may cause nausea.
 - b) Suggested dosing^{60,62}
 - i. Adult/pediatric: 2.5-7.5 mg orally q 6 to 12 hr, increasing dose as tolerated for symptom control. Maximum dose 45 mg/day
- 2) Amantadine: dopamine agonist
 - a) Adverse effects and considerations: may cause nausea.
 - b) Suggested dosing⁶⁰
 - i. Adult dose: 200 to 400 mg orally in 2 or 3 divided doses
 - ii. Pediatric: Use not evaluated in pediatric NMS. Amantadine has been used safely in pediatrics more than 5 years old for other indications⁶³
- 3) Dantrolene: Sometimes used in hyperthermia and adult case series support reduction in temperature after use. However, use is controversial as hyperthermia is thought to be centrally mediated in NMS, not related to sarcoplasmic reticulum where dantrolene exerts its mechanism⁶¹
 - a) Adverse effects and considerations: transaminase elevations, monitor bio markers of liver injury
 - b) Suggested dosing:^{60,64}
 - i. Adult and pediatric: 1 to 2.5 mg/kg IV followed by 1 mg/kg IV every 6 hours, if rapid resolution of hyperthermia may change to oral dose of 100-200 mg daily and taper. Usual course of treatment 5-10 days or until symptoms resolved

c. SS

- 1) Cyproheptadine: Serotonin antagonist; PET scan demonstrates it blocks 85-95% of serotonin receptors Clinical efficacy based on case reports⁶⁵
- 2) Cyproheptadine is also an antihistamine with anticholinergic properties which may contribute to hyperthermia via decreased sweat production. It should be used cautiously in unclear toxidromes that may potentially be anticholinergic or NMS. The risk of worsened hyperthermia should be weighed against potential benefit.

3) Dose and indications are not well defined⁵⁶

a) Suggested dosing

i. Adult:⁵²

(a) 12 mg PO cyproheptadine and then 2 mg every two hours if symptoms continue

(b) Maintenance dosing: 8 mg of cyproheptadine every 6 hours

ii. Pediatric:⁵⁷

(a) Less than 2 years old: 0.0625 mg/kg q 6 h (0.25mg/kg/day)

(b) 2-6: years old 2 mg q 6 h

(c) 7-14 year: 4 mg q 6 h

F. Monitoring

1. Neurologic symptoms

2. Markers of autonomic function (e.g., heart rate, blood pressure, temperature)

3. Biomarkers or organ function to assess for sequelae of injury

a. CK to monitor for potential rhabdomyolysis related to motor dysfunctions

G. Summary

1. NMS and SS are similar syndromes of motor and autonomic dysfunction

2. They are differentiated based on history, onset, duration, and symptoms (bradykinesia with NMS vs hyperreflexia and clonus with SS), scoring tools exist to help with diagnosis

3. Treatment is primarily supportive; many patients will improve with withdrawal of offending agent and benzodiazepines to control agitation and motor dysfunction. In severe cases, treatment of hyperthermia is important, and disease specific salvage therapies may be utilized to reduce symptoms. Decisions on use of salvage therapies should likely be made in conjunction with a toxicologist or poison center.

Case 4

Shana is a 17-year-old female who is brought to the emergency department by paramedics after a suspected suicide attempt. She got into an argument with her father at 0900, made suicidal gestures, and locked herself in the bathroom. The father called 911 and Emergency Medical Services (EMS) removed the door approximately 90 minutes later. Paramedics found her in a state of emotional distress. She did not endorse an ingestion, but tablets were noted on the ground and a 90-count bottle of amlodipine 10 mg was found empty. She arrives to the emergency department AOX2 with depressed affect.

Medications: Lithium carbonate 300 mg PO TID, Sertraline 100 mg PO daily, Olanzapine 5 mg PO every evening

Physical exam: Pale, diaphoretic appearing female with decreased mental status, pedal edema. Pupils are equal and sluggishly reactive, reflexes are absent in lower extremities

On arrival they appeared to have normal vital signs (HR 94 bpm, BP 123/75 mm Hg) but her HR and BP have begun declining and she is becoming less responsive to questions

Vital signs: HR 127 bpm, BP 70/40 mm Hg, RR 21/min, T 99° F, O₂ sat 92% on 3 L/min by nasal cannula

ECG: PR interval 140 ms, QRS interval 91 ms, QTc interval 442 ms

Lab:

BMP: Na 140 meq/L Cl 99 meq/L, K 4.2 meq/L, HCO₃ 19 meq/L, BUN 25 mg/L, Creatinine 1.0 mg/L, Glucose 491 mg/dL

Troponin: undetectable

Lactate: 4.2 mmol/L

ABG pH: 7.3

Acetaminophen: <10 mg/dL

Salicylate: <0.4 mg

Lithium: 0.4 mg/dL

A point of care ultrasound demonstrates a heart with normal ejection fraction.

Shana is started on IV fluids, and you are consulted to assist in managing the patient.

Question #7

Which of the following laboratory assessments is pathognomonic and prognostic in Shana's overdose?

- A. Hyperglycemia
- B. Low pH
- C. Anion Gap
- D. Hyperkalemia

Question #8**Which therapy should you recommend initiating in Shana?**

- A. High dose insulin
- B. Calcium gluconate and norepinephrine
- C. Dopamine
- D. Activated charcoal and whole bowel irrigation

VI. Beta Blocker and Calcium Channel Blocker (CCB) overdose**A. Epidemiology⁵****1. U.S. poison centers 2020****a. Beta blockers**

- 1) 27,836 exposures
- 2) 7th most common fatality reported to U.S. poison centers
- 3) 104 Deaths

b. Calcium channel blocker

- 1) 15,987 exposures
- 2) 6th most common fatality reported to U.S. poison centers
- 3) 152 Deaths

B. Mechanism of toxicity**1. Beta Blocker^{66,67}**

- a. Blockade of cardiac beta-adrenergic receptor prevents g-coupled protein receptor activation and reduces cyclic adenosine monophosphate, decreasing calcium stores needed for automaticity and contractility
- b. Some beta blockers have additional pharmacologic effects
 - 1) Propranolol: Sodium channel blockade, high CNS penetration (lipophilic)
 - 2) Sotalol: Potassium channel blockade
 - 3) Carvedilol, labetalol: alpha 1 adrenergic blockade

2. CCB^{68,69}

- a. Non-dihydropyridine (non-DHP)- e.g., verapamil, diltiazem
 - 1) Block L-type (cardiac) and T-type (vascular) calcium channels
 - a) Reduce depolarizing calcium current of automatic pacemaker cells leading to reduced chronotropy

- b) Block calcium myocyte and vascular calcium channels responsible for calcium dependent calcium release from the sarcoplasmic reticulum. Downstream effect of reduced actin-myosin cross bridge formation and contraction
 - b. Dihydropyridine (DHP)
 - 1) Block T-type vascular calcium channels preventing contraction actin myosin cross bridge formation and vascular contraction
 - 2) In large overdose, can also block cardiac calcium channels, appearing similar to NDH
 - c. Class effect (DHP + non-DHP)
 - 1) Prevention of pancreatic beta cell insulin release in overdose⁷⁰
 - a) Glucose entry into beta cell causes depolarization leading to opening of voltage gated calcium channels
 - b) Calcium enters and binds to SNARE protein on insulin vesicle, allowing for membrane fusion and exocytosis
 - c) Calcium channel blockade prevents calcium entry after depolarization and prevents insulin vesicle exocytosis, thus preventing insulin release
- 3. Clinical effects
 - a. Beta-blockers⁶⁷
 - 1) Class effects
 - a) Bradycardia
 - b) Cardiogenic shock
 - c) Hypoglycemia (may inhibit glycogenolysis which is sympathetically mediated, preventing mobilization of glucose stores)
 - 2) Nonselective alpha/beta blockers (carvedilol/labetalol)
 - a) Vasodilatory hypotension from alpha 1 blockade
 - 3) Sodium channel blockers (propranolol)
 - a) Wide QRS
 - b) Seizure
 - 4) Potassium channel blocker (sotalol)
 - a) Prolonged QTc interval
 - b. Calcium channel blockers⁶⁸
 - 1) Dihydropyridines (DHP, e.g. amlodipine, felodipine)

- a) Tachycardia (reflex tachycardia from vasodilation) OR bradycardia (large overdose)
- b) Cardiogenic and/or vasodilatory shock
- 2) Non Dihydropyridines (non-DHP, e.g. diltiazem, verapamil)
 - a) Bradycardia
 - b) Cardiogenic and/or vasodilatory shock
- 3) Class effect
 - a) Hyperglycemia⁷¹
 - i. Prognostic sign in severe CCB poisoning
 - ii. Mean initial blood glucose in non-DHP overdose that needed invasive interventions (vasopressors or pacemaker) or died = 188 mg/dL vs. 122 mg/dL in those who needed no intervention. Peak glucose and rise in glucose were also all significantly higher in those that required invasive intervention

Consensus recommendation for treatment of adult calcium channel blocker overdose	
First line therapy	
Recommended <ul style="list-style-type: none"> • IV fluids if needed • IV calcium (1D) • Norepinephrine and/or epinephrine in the presence of shock (even if myocardial function has not yet been assessed), with preferential use of norepinephrine in the presence of vasodilatory shock (1D). • HIE with other first line treatment(s) if evidence of myocardial dysfunction is present (1D), 	Suggested (lower quality recommendation) <ul style="list-style-type: none"> • HIE as a monotherapy in the presence of myocardial dysfunction (2D), • HIE in the absence of documented myocardial dysfunction if used in combination with IV fluids, calcium, and vasopressors (2D), • Dobutamine or epinephrine in the presence of cardiogenic shock (2D), • Atropine in the presence of symptomatic bradycardia or conduction disturbances (2D). Suggest against <ul style="list-style-type: none"> • Dopamine in the presence of shock (2D), • Vasopressin as a single vasoactive agent in the presence of documented cardiogenic shock (2D).
Refractory to First Line agents	
<ul style="list-style-type: none"> • Incremental doses of HIE (up to 10 U/kg/hr) if evidence of myocardial dysfunction is present (2D), • Pacemaker in the presence of unstable bradycardia or high-grade AV block, without significant alteration in cardiac inotropism (2D) • IV lipid-emulsion therapy (2D) 	

Continued Refractory Shock or Peri Arrest (Step 3)	
Recommended <ul style="list-style-type: none"> Incremental doses of HIE (up to 10 U/kg/hr) if evidence of myocardial dysfunction is present if not administered previously (1D), Lipid-emulsion therapy if not administered previously (1D) 	Suggested (lower quality recommendation) <ul style="list-style-type: none"> Incremental doses HIE (up to 10 U/kg/hr) even in the absence of myocardial dysfunction if not administered previously (2D), VA-ECMO in presence of cardiogenic shock in centers where the treatment is available (2D), Pacemaker in the presence of unstable bradycardia or high-grade AV block, without significant alteration in cardiac inotropy if not tried previously (2D).
Cardiac arrest	
Recommended <ul style="list-style-type: none"> Standard ACLS IV calcium, even if previously administered (1D) Lipid-emulsion therapy if not administered previously (1D). 	Suggested (lower quality recommendation) <ul style="list-style-type: none"> Lipid-emulsion therapy, even if previously administered (2D), VA-ECMO in centers where the treatment is available (2D).

C. Treatment^{66,68,72,73}

a. Decontamination

- 1) Activated charcoal if drug likely still in gastric system, patient able to protect airway, or if intubated and has gastric access
- 2) Whole bowel irrigation may be utilized due to the potential for severe outcomes and continued absorption from extended-release products. Generally initiated prior to the onset of symptoms. If bradycardia or hypotension are present, gut perfusion may be compromised⁶⁶

b. Supportive care

- 1) Maintenance of airway, breathing, and circulation as described in section 2

Question #9

Which of the following is a proposed mechanism of high-dose insulin therapy for cardiotoxicity in CCB or BB OD?

- Reduced glucose requirement for myocardial cells
- Increased vasoconstriction
- Decreased systemic vascular resistance
- Decreased intracellular calcium

c. Maintenance of hemodynamics (BB & CCB)^{66,68,72,73}

- 1) It is important to recognize BB and CCB overdoses can present as diverse shock subtypes
- 2) Many adjunctive therapies exist to aid in cardiovascular drug overdose but basic ACLS measures still apply
- 3) Administration of atropine for bradycardia, fluids for hypovolemia, and vasopressors or inotropes can be started to quickly restore circulation.
- 4) It is important to recognize BB and CCB overdoses can present as diverse shock subtypes. Selection of vasopressors and inotropic agents is dependent on the perceived shock subtype
 - a) Vasoplegic shock (characterized primarily by low afterload with normal cardiac output): DHP overdose, pure alpha-blocker overdose
 - b) Cardiogenic: Beta-1 selective beta blocker overdose, non-DHP overdose, large non-DHP overdose
 - c) Cardiogenic shock with low afterload (i.e. “warm wet”): Nonselective Beta and alpha-blocker overdose, non-DHP overdose, DHP overdose.
 - d) Bedside cardiac ultrasound may be beneficial in assessing ejection fraction and determining shock etiology
 - i. Normal cardiac output: initiate afterload increasing therapy such as norepinephrine, vasopressin, or phenylephrine
 - ii. Low ejection fraction or bradycardia: Inotropic agent such as dobutamine or epinephrine.
 - (a) Dobutamine may need to be coupled with afterload increasing therapy such as norepinephrine if afterload is also low
 - (b) Dopamine may be ineffective and expert consensus guidelines recommend against use of this agent as a 1st line therapy⁷²
 - e) Some patients can be managed entirely with standard vasopressor and inotropic therapies without the need for adjunctive therapies. and if vasopressors are ineffective, they do appear to worsen outcomes.
 - i. Skoog⁷⁴ 2017: 91% survival rate with vasopressor management, though only 31% completely effective.
 - ii. Levine⁷⁵ 2013: 45/48 non-DHP CCB overdose patients managed without high dose insulin
- 5) High dose Insulin Euglycemia (HIE)⁷²
 - a) Normal dose: Regular insulin 1 unit/kg IV bolus followed by infusion of 1 unit/kg/hr along with 0.5-1 g/kg/hr dextrose to maintain euglycemia. Dose may be increased every 20-30 minutes. A suggested maximum threshold is 10 u/kg/hr, although no maximum has been established

- b) Mechanism: Enhances intracellular calcium release (via insulin mediated calcium release from the sarcoplasmic reticulum to enable glut-4 receptor endocytosis) allowing for increased inotropy and chronotropy. Also enhances cardiac glucose utilization⁷⁶
- c) Clinical effect: Animal studies support it exerts effect as an inodilator, increasing cardiac output and reducing afterload.⁷⁷
- d) Recommend in the setting of myocardial dysfunction due to increase in cardiac output, however some case reports demonstrate blood pressure increase even with normal cardiac output so may be considered in states of normal cardiac output⁷²
- e) May be initiated with or without vasopressors
 - i. Logistically more challenging to initiate and longer time to effect, therefore, vasopressors are often used first
 - ii. Vasopressor (norepinephrine) in combination with HIE show better survival than either agent alone in animal models⁸¹
- f) Monitoring
 - i. Hemodynamics: MAP Goal at least 65 mmHg, avoidance of excessive tachycardia (i.e., HR greater than 150 bpm)
 - (a) If available, the following assessment of cardiovascular parameters may aid in tailoring resuscitation:
 - **Preload**: Central Venous Pressure (CVP) or Pulmonary Catheter Wedge Pressure (PCWP)
 - **Cardiac output**(CO)
 - **Afterload**: Systemic Vascular Resistance (SVR, dynes)
 - ii. Hypoglycemia, hypokalemia, hypomagnesemia
 - (a) Ensure protocol is in place for close monitoring of glucose and electrolytes while receiving therapy
 - (b) Blood glucose targets are not different than other critically ill patients (i.e., less than 180 mg/dL)
 - (c) Rates of hypoglycemia, hypokalemia and hypomagnesemia are higher in studies that did not have an institutional protocol for HIE monitoring^{79,80}
 - iii. Fluid status
 - (a) CCB OD receives median 7.8 L of fluid in first day, with dextrose and insulin comprising ~30% of all fluid⁸¹

- (b) Concentrate all fluids as much as possible to reduce fluid volume
 - A1600 u/mL insulin product can be made by adding 8 ml of 100 u/ml insulin to 100 ml NS and is stable for 7 days⁸²
 - Maximally concentrate vasopressors, antibiotics, and dextrose as much as possible
- 6) Calcium supplementation for CCB overdose^{72,83}
 - a) Generally considered a readily available, potentially low risk intervention. Traditionally used in CCB OD but has also been used in BB OD⁷³
 - b) Mechanism: increase calcium current via enhanced calcium diffusion gradient
 - c) Clinical effect: case series support increased blood pressure and resolution of some conduction delays with administration^{84,85}
 - d) Optimal dose unknown:
 - e) Expert consensus suggested dosing:⁷²
 - i. Central line: 10% calcium chloride 10–20 mL (1–2 g) every 10–20 minutes, OR continuous infusion at 0.2–0.4 mL/kg/hr (0.02–0.04 g/kg/hr)
 - ii. Peripheral line: 10% Calcium gluconate, 30–60 mL (3–6 g) every 10–20 minutes, OR continuous infusion at 0.6–1.2 mL/kg/hr (0.06–0.12 g/kg/hr)
- 7) No known maximum dose, however death has been reported after massive calcium administration in CCB overdose^{86,87}
- d. Glucagon^{66,73,88}
 - 1) A 2nd line therapy in BB OD, also has limited data for use in CCB OD⁷²
 - 2) Mechanism: Increases cellular cyclic adenosine monophosphate (Camp) via non-adrenergic pathway, downstream increase in intracellular calcium leading to inotropy and chronotropy
 - 3) Clinical effects: Increase in HR, minimal effect on MAP in animal studies
 - 4) Adverse effect/s: Tachyphylaxis, nausea/vomiting is common, monitor for and treat with anti-emetics as needed
 - 5) Dosing:⁸⁸
 - a) Adult:
 - i. IV 5-10 mg bolus followed by 1-10 mg/hr infusion
 - b) Pediatric 12 years old or younger
 - i. IV 0.05 mg/kg bolus follow by 0.05-0.1 mg/kg/hr

- 6) May rapidly deplete hospital supply
 - 7) Due to potential for adverse effects, limited and potentially transient benefit, as well as logistic issues with supply (high doses needed), glucagon is not an ideal agent
- e. Salvage therapies
- 1) Phosphodiesterase (PDE) inhibitors: milrinone⁶⁶
 - a) May increase Camp and be reasonable if persistent myocardial dysfunction in inotrope refractory shock, however, carries potential to worsen vasodilation (via PDE mediated vascular cyclic guanosine monophosphate increase)
 - 2) Lipid emulsion therapy
 - a) In CCB overdose, may be considered if arrhythmia or myocardial dysfunction is refractory to vasopressors and HIE or consider giving if in cardiac arrest⁷²
 - b) Expert consensus guidelines²⁶
 - i. Non-lipophilic beta blockers: do not use IV lipid emulsion unless in cardiac arrest
 - ii. Lipophilic beta blockers: Neutral recommendation for use of IV lipid emulsion with lipophilic beta blockers (defined as Log P octanol/water >0) in the setting of cardiac arrest OR severe disease
 - c) Use has been reported in propranolol, bisoprolol, carvedilol, nebivolol and atenolol⁶⁶
 - d) For dosing refer to IV lipid emulsion under section 3 (TCAs)
 - 3) Methylene blue
 - a) Free radical oxygen scavengers that scavenge nitric oxide, reducing vasodilation and increasing systemic vascular resistance
 - b) Reports of use in refractory amlodipine overdose⁶⁶
 - c) Adverse effects: potent oxidizer, can cause hemolysis in G6PD deficient patients, also has monoamine oxidase activity and has been reported to cause serotonin syndrome
 - 4) Hydroxocobalamin⁸⁹
 - a) Similar to methylene blue in action and has been evaluated in vasoplegic shock from cardiac surgery. Data for use in vasodilatory drug overdose not available
 - b) Adverse effects: red discoloration of body fluids, interferes with labs and may activate blood leak alarm on dialysis machine⁹⁰

5) Mechanical support devices ^{66,72,73}

- a) Implantable pacemakers are recommended in CCB OD patients who are refractory to pharmacologic therapies for bradycardia
- b) VA ECMO is recommended in CCB OD in the setting of severe treatment refractory cardiogenic shock or in cardiac arrest. Early consultation with ECMO capable facility recommended. ECMO has been successfully used in many cases of BB OD as well.
- c) Left ventricular assist device and intra-aortic balloon pumps have also been reported

Shana is initiated on norepinephrine and calcium but is having continued unstable blood pressures. A central line is placed to facilitate resuscitation and HIE is ordered. The concentrated insulin bag is coming from central pharmacy. In the meantime, several vasoactive medications are started at bedside.

Current medications:

Calcium gluconate 10% 0.6 mL/kg/hr

Norepinephrine 0.3 mcg/kg/min

Phenylephrine 4 mcg/kg/min

Vasopressin 0.04 u/min

Dobutamine 5 mcg/min

Regular insulin 1 unit/kg bolus and 1 unit/kg/hr infusion (ordered, not started)

Dextrose 20% 0.5 g/kg/hr (ordered, not started)

Vitals

HR: 110 bpm, BP 83/61 mm Hg, RR 24/min, PO2 94% on 4 L/min by nasal cannula

Question #10

What monitoring should be done for HIE?

- A. Sodium, bicarbonate, lactic acid
- B. Potassium, glucose, fluid status
- C. CK, calcium, phosphate
- D. Troponin, pro-brain natriuretic peptide, electrocardiogram

A. BB and CCB OD Summary

- 1. BB and CCB OD can have diverse phenotypes of shock
 - a. Vasodilatory (DHP)
 - b. Cardiogenic (non-DHP, DHP, BB)
 - c. Cardiogenic/vasodilatory (non-DHP, DHP, Beta/alpha blocker)
 - d. Hyperglycemia may be present with CCB OD and is associated with worse outcomes

2. Initial assessment of cardiac output and determining exposure history is valuable in determining shock phenotype
3. Initial treatment with standard therapies such as fluids, atropine, vasopressors and inotropes are reasonable and often more quickly available than adjunctive therapies such as HIE or glucagon
4. Adjunctive therapies such as HIE for myocardial dysfunction may provide a significant benefit and have a synergetic effect with afterload increasing vasopressors
 - a. HIE may cause hypokalemia, hypoglycemia, and fluid overload
 - b. Institutional standardized monitoring protocols may reduce likelihood of adverse effects
 - c. Concentrate drug therapies to avoid fluid overload
5. Calcium is rapidly available and may aid in increasing MAP and diminishing conduction delays
 - a. Poses little harm but avoid excessive dosing as iatrogenic hypercalcemic death has been reported
6. Intralipid emulsion is recommended in certain BB overdoses as well as in CCB OD refractory to vasopressors or HIE
7. Glucagon may increase heart rate
 - a. Also causes nausea and vomiting, high doses are needed and tachyphylaxis may occur
8. VA-ECMO in the setting of cardiovascular drug overdose refractory to standard therapies may be of value
9. Other salvage therapies include methylene blue, milrinone, intra-aortic balloon pumps, and ventricular assist devices
10. Consultation with a toxicologist or poison center to aid in shock phenotype identification and antidote utilization is recommended. Poison centers can be reached at 1-800-222-1222.

VII. Alpha-2 agonists

A. Epidemiology⁵

1. Alpha-2 agonists (e.g., guanfacine, guanbenz, clonidine) are common accidental pediatric exposure, frequently from ingestion of a sibling's attention deficit hyperactivity disorder medication
 - a. U.S. poison centers: 10,636 calls for pediatric clonidine exposure, 0 deaths reported.

B. Mechanism of toxicity⁹¹

1. Stimulation of presynaptic alpha-2 receptor and imidazoline receptors

- a. Presynaptic symaptholysis, pupillary constriction (oxymetazoline is an imidazoline eye drop used for eye redness)
- 2. In a large overdose, may also stimulate alpha-1 adrenergic receptors, causing early hypertension
- C. Clinical effects^{91,92}
 - 1. Primarily CNS and cardiovascular
 - a. Sometimes referred to as an opioid mimic due to toxidrome of sedation, decreased responsiveness, and miosis
 - 2. CNS: can mimic an opioid toxidrome
 - a. Drowsiness
 - b. Miosis
 - c. Hypoventilation
 - d. Hypothermia
 - 3. Cardiovascular
 - a. Bradycardia
 - b. Hypotension
 - c. Early presentation may be hypertension due to non-selective alpha-1 agonism in overdose
- D. Treatment⁹¹
 - 1. Decontamination
 - a. Activated charcoal if drug likely still in gastric system, patient able to protect airway, or if intubated and has gastric access
 - b. Whole bowel irrigation has been sometimes utilized for cases of whole clonidine patch ingestion
 - 2. Supportive cares
 - a. Maintenance of airway, breathing, and circulation
 - b. Hemodynamic compromise may first be addressed with fluids. Atropine is useful if symptomatic bradycardia. Hemodynamic compromise is usually responsive to vasopressors and inotropes, refractory shock is rare
 - 3. Reverse toxicity
 - a. Naloxone⁹³
 - 1) May reverse neurologic and some cardiac manifestation of alpha-2 agonist overdose. May increase mental status enough to avoid intubation.

- 2) Mechanism: Likely reverse the action of endogenous β -endorphin which is released in response to α -2 receptor agonism
- 3) Clinical effect: increased blood pressure, heart rate, respiratory rate, and arousal level
- 4) Dose
 - a) Extremely high doses may be needed comparatively to opioid overdose to adequately rouse patients in both adults and children.
 - b) Seger⁹³ 2018: study of 51 clonidine overdoses age 6 month-16 year
 - i. 78% (40/51) responded to naloxone with a median dose of 5.5 mg (range 3.5-10 mg)
 - (a) 65% (13/20) of patients who received a 10 mg naloxone bolus awoke
 - (b) 70% (22/31) of patients who received a 3.5-6 mg naloxone bolus awoke
 - ii. No adverse effects observed from naloxone
 - c) Some may respond at lower doses, however some may not respond even after 10 mg dose achieved
 - d) Suggested dosing
 - i. Pediatric younger than 5 years⁹³
 - (a) There is no consensus on initial naloxone dose for α -2 agonist reversal in pediatric patients
 - (b) The opioid reversal dose of naloxone 0.1 mg/kg q 1-3 recommended by the American Academy of Pediatrics was chosen with the “lowest possible effective dose” in mind to prevent withdrawal in newborns, this is not extrapolatable to α -2 agonist overdose⁹⁴
 - (c) In a study of pediatric clonidine overdose 11 children younger than 3 years of age received 10 mg IV naloxone boluses with no adverse effect⁹³
 - (d) Doses of 0.4 mg/kg appear to be safe and may be an appropriate starting dose, higher doses may also be tolerated
 - If no immediate effect seen repeat dose every 1-3 minutes to reach a high cumulative dose, maximum of 10 mg
 - ii. Adult
 - (a) Naloxone IV bolus: 2-10 mg q 2-3 minutes. Maximum dose 10 mg
 - iii. Naloxone continuous infusion: (0.67-1 x effective dose)/hr

Case 5

Andrew is a 3-year-old male who presents to the emergency department with parents after waking them in the night with inconsolable agitation, crying, and ear pain. He arrived talking and acting age appropriate but rapidly developed severe pain, excessive salivation, diaphoresis, and opsoclonus.

Physical exam: Inconsolable, agitated, and diaphoretic toddler. Head exams reveals a single raised lesion with surrounding edema near the pinna of the right ear and notable opsoclonus. There is wheezing present in the lungs.

Vital signs: HR 132 bpm, BP 135/75 mm Hg, RR 40/min, PO₂ 98% on room air.

Question #11

What is the most likely cause of this presentation?

- A. Organophosphate insecticide exposure
- B. Coral snake envenomation
- C. Cotton mouth viper envenomation
- D. *Centruroides* bark scorpion

VIII. Environmental Toxicology

A. North American envenomations

- 1. There are a number of venomous animals in the United States and North America
- 2. Common names of some venomous animals in North America: Gila monsters, woolly bear caterpillar, wasps, ants, rattlesnakes, cottonmouth viper, copperhead snake, black widow spiders, bark scorpions, brown recluse spider

B. Envenomations for which there are readily available antidotes

- 1. *Centruroides* Scorpions (Bark scorpions)
- 2. *Crotalinae* ("pit vipers", rattlesnake, cottonmouth, copperhead)
- 3. *Micrurus fulvius* (Coral snakes)
- 4. *Latrodectus* sp (widow spiders)

C. Scorpions⁹⁵⁻⁹⁷

- 1. Epidemiology
 - a. *Centruroides exillacauda*, also called the bark scorpion, is the most toxicologically relevant scorpion in the US
 - b. Geographically, it is located the southwestern United States (e.g., Arizona, New Mexico)
 - c. 11,393 scorpion envenomations reported to U.S. poison centers in 2020, no deaths⁵

- d. Fatality is extremely rare; if it does occur, it is generally in the very young (younger than 6 years of age)⁹⁸
 - e. Stings usually occur on extremity when human accidentally places foot or hand into area where scorpion was residing
2. Toxicity: *Centruroides* venom is complex and contains numerous active compounds. Neurotoxicity is the primary manifestation. Sodium channel opening neurotoxins cause repeated depolarization of both sympathetic and parasympathetic nervous system.
3. Clinical effect: Peak effects generally within 5 hours of envenomation
 - a. Grade 1: Local pain and paresthesia at site
 - b. Grade 2: Pain and paresthesia at site and proximal to it.
 - c. Grade 3: Grade 2 and cranial nerve deficits (oral secretions, blurry vision, nystagmus), severe pain causing motor hyperactivity, opisthotonos, or autonomic dysfunction such as vomiting, bronchoconstriction, diaphoresis, tachycardia and hypertension
 - d. Grade 4: Grade 2 with cranial nerve deficits AND autonomic dysfunction. May progress to severe disease (rhabdomyolysis, hyperthermia, and organ damage)
4. Treatment
 - a. Grades 1 and 2 are treated with cleaning of wound, tetanus prophylaxis, analgesics, and anxiolytics.
 - b. Grades 3 and 4
 - 1) Antivenom may be indicated
 - a) May aid in maintaining patent airway if serious autonomic dysfunction is present
 - b) In randomized trial of *Centruroides*-envenomated children, antivenom reduced symptoms at 4 hours compared to placebo and reduced need for benzodiazepines⁹⁹
 - c) Consultation with a toxicologist or poison center (1-800-222-1222) familiar with antivenom use is recommended
 - 2) Antivenom: *Centruroides* scorpion-specific F(ab')₂ equine antivenom¹⁰⁰
 - a) Neutralizes scorpion venom
 - b) Dose (adult and pediatric): 3 vials, may administer additional vial every 30-60 minutes until control achieved
 - c) Monitor for hypersensitivity
 - 3) Benzodiazepines may help motor hyperactivity and autonomic dysfunction.
 - a) Caution with excess dosing if antivenom planned as sedation may occur when symptoms resolve

- 4) Opioid analgesics
 - 5) Management of airway and oral secretions
 - 6) Laboratory assessment for secondary injury from motor hyperactivity (e.g., rhabdomyolysis)
5. *Crotalinae*^{101,102}
- a. *Crotalinae* are a subfamily of *Viperidae* (vipers) with heat sensing “pits” (thus pit vipers)
 - 1) Copperhead (*Agkistrodon piscivorus*)
 - a) Location: Southeastern U.S.
 - b) U.S. poison centers 2020: 2590 exposures⁵
 - 2) Cottonmouths (water moccasin) (*Agkistrodon contortrix*)
 - a) Location: Midwest, southeast and northeast US
 - b) US poison centers 2020: 269 exposures⁵
 - 3) Rattlesnakes (Genus *Crotalus*)
 - a) Location: Found throughout US
 - b) US poison centers: 1255 exposures⁵
 - 4) Pigmy rattlesnake and massasauga (genus *Sistrurus*)
 - a) Location: Pigmy rattlesnake, Mexico
 - b) Location: Massasauga, Northeast, Midwest
 - c) US poison centers 2020: not reported
 - 5) Deaths are rare and occur most often after rattlesnake envenomation. Death often involves anaphylaxis, a patient with significant comorbid conditions, or those who do not seek medical care^{102,103}
 - b. Envenomation predominantly occurs in males during intentional interaction (e.g., hunting, aggravating, handling) as opposed to accidental environmental exposure. Alcohol ingestion and inappropriate protective equipment often play a role¹⁰⁴
 - 1) Not all bites are venomous – up to 25% may be dry bites¹⁰¹
 - c. Toxicity:
 - 1) *Crotalinae* venom contains numerous compounds, including enzymes aimed at local tissue damage that also induce coagulopathy. Small amounts of neurologic and cardiotoxins may all be present. For example, Mojave rattlesnakes have significant neurotoxin.

- d. Clinical effects:
 - 1) Generally characterized by tissue necrosis, coagulopathy, and rarely myokymia (muscle “rippling”). A severity grading system helps identify treatment need:
 - 2) None: no clinical effect after 8-12 hours usually represents a dry bite
 - 3) Minimal: Minor, non-progressing local swelling and discomfort without systemic effects or hematologic abnormalities (generally should be assessed at least 8 hours after bite)
 - 4) Moderate: Progression of swelling beyond area of bite with or without local tissue destruction, hematologic abnormalities, or non-life-threatening systemic effects
 - 5) Severe: Marked progressive swelling, pain with or without local tissue destruction. Systemic effects such as diarrhea, weakness, shock, or angioedema, and/or pronounced thrombocytopenia or coagulopathy
 - 6) Late, persistent coagulopathy may develop in patients and rebound after antivenom administration¹⁰⁵
6. *Crotalinae* Treatment^{101,102}
 - a. Application of tourniquet to prevent lymphatic spread of venom is not recommended as it may enhance local tissue destruction
 - b. Ensure airway breathing and circulation are appropriately supported
 - c. Hypotension related to anaphylaxis may require epinephrine
 - d. Tetanus prophylaxis and wound cleaning
 - e. Monitor bite for progression (demarcate leading line or measure circumference).
 - f. Assess for coagulopathy at least 8 hours after envenomation
 - 1) Complete blood count (hemoglobin, hematocrit, platelet)
 - 2) PT/INR
 - 3) Fibrinogen
 - 4) D-dimer
 - g. Antivenom is recommended for moderate to severe envenomation. As it does not reverse tissue damage, early administration is preferred.
 - 1) May halt progression of swelling and reverse coagulopathy¹⁰⁶
 - 2) May reduce likelihood of pain¹⁰⁷
 - 3) Consultation with a toxicologist or poison center (1-800-222-1222) familiar with antivenom use is recommended
 - h. Two antivenom agents are available,

- 1) Ovine derived crotalid polyvalent immune Fab¹⁰⁸
 - a) May have more activity against Mojave rattlesnake neurotoxin than other antivenom (derived in part from Mojave rattlesnake)
 - b) Dosing (adult and pediatric)
 - i. Load: 8-12 vials (alternatively some opt for 6 vials and will repeat dose at 1 hour if control not achieved)¹⁰⁷ and then 4-6 vials q 1 hour until swelling no longer progresses, and coagulopathy has resolved (i.e. control achieved)
 - ii. Maintenance: 2 vials every 6 hours for 3 additional doses (of note, maintenance is not always continued, some choose to observe for symptom progression and withhold doses unless toxicity redevelops).¹⁰²
- 2) Equine derived *bothrops asper* and *crotalus simus* Fab2 fragments¹⁰⁹
 - a) May have a longer half-life due to being a larger antibody fragment (Fab2 > Fab). Longer half-life may result in less delayed coagulopathy than ovine antivenom¹⁰⁶
 - b) Dosing (adult and pediatric)
 - i. Load: Administer 10 vials. Can administer an additional 10 vials every hour as until systemic symptoms are resolved and coagulation parameters have normalized or are trending toward normal.
 - ii. Maintenance: it is recommended the patient be monitored for 18 hours for progression of swelling or recurrent coagulopathy. If symptoms recrudescence, an additional 4 vials may be administered.
- 3) Both antivenoms should be given over a total of 1 hour (starting slow and increasing rate after patient demonstrates tolerance). Monitor for signs of anaphylaxis^{102,110}
 - a) If immune mediated infusion reaction occurs (e.g., urticaria, rash, tightness of the chest, wheezing, hypotension), discontinue and provide treatment for anaphylaxis
 - b) Need for additional antivenom must be weighed against risk of type I hypersensitivity, pyrogenic reaction, or serum sickness reaction
- i. Coagulopathy management
 - 1) The primary treatment for coagulopathy is antivenom.
 - a) Due to circulating venom, coagulopathy may be difficult to correct with blood products (plasma, cryoprecipitate, platelets, etc.)
 - b) Presence of persistent coagulopathy implies the continued presence of venom

- 2) Platelets may exhibit a transient recovery followed by rebound thrombocytopenia¹⁰⁵
- 3) In the absence of bleeding, continued monitoring for persistent thrombocytopenia resolution (up to 2-3 weeks in some species like the timber rattlesnake) is often elected over repeated antivenom.

D. *Micrurus*^{101,102}

1. Snakes in the family *Elapidae* are neurotoxic snakes (coral snakes, mambas, cobra, krait)
 - a. *Elapidae* native to North America include the Eastern coral snake (*Micrurus fulvius*), found in the Southeastern US, and the Texas coral snake (*Micrurus fulvius tenere*)
 - b. Other coral snakes exist (Sonoran coral snake) in the Southwest but envenomations have not produced significant symptoms
 - c. U.S. poison centers reported 76 coral snake envenomations in 2020⁵
 - d. Envenomation occurs with fixed hollow fangs. The snake must “chew” and remain in contact with victim to deliver venom as opposed to crotalid envenomations that are rapid “bites”.
 - 1) Eastern coral snake venom appears more potent than the Texas coral snake and often causes more severe toxicity
 - e. Death generally occurs from respiratory paralysis. With the advent of advanced supportive cares, deaths are extremely rare. Only one death has been reported in approximately the last 50 years in an individual who did not seek care¹¹¹
2. Toxicity: Coral snake venom contain “alpha neurotoxin,” which competitively displaces acetylcholine at the neuromuscular junction.
3. Clinical effects:
 - a. Minimal local injury with potential delayed neurotoxicity (a “toxic time bomb”)
 - 1) Bite wounds may not be present due to lack of tissue damaging toxins
 - 2) Slowly developing neurotoxicity (onset reported as late as 13 hours): paresthesia, slurred speech, ptosis, diplopia, dysphagia, weakness, paralysis
 - 3) Weakness may take weeks to months to resolve, and some require respiratory support for as long as one week¹¹²
4. Treatment
 - a. Ensure airway breathing and circulation are appropriately supported
 - 1) Paralysis can rapidly progress and may not be reversible with antivenom; early intubation may be needed if difficulty swallowing, speaking, or handling secretions
 - b. Tetanus prophylaxis and wound cleaning
 - c. Observation for the development of neurologic symptoms (generally for 24 hours)

- d. Antivenom is indicated at ANY sign of neurologic symptoms
 - 1) It may reduce symptoms or shorten ventilation time, however, paralysis/weakness can still progress after¹¹²
 - 2) Some experts recommend a prophylactic strategy as the antivenom often does not reverse paralysis, but this must be weighed against the high rates of antivenom reaction rates. Outcomes did not appear different in limited data assessing prophylactic vs symptom triggered approach¹¹³
 - 3) Consultation with a toxicologist or poison center (1-800-222-1222) familiar with antivenom use is recommended
- e. North American Coral Snake Antivenom: Equine derived Fab2¹¹⁴
 - 1) Dosing (adult and pediatric): 30 to 50 mL (3 to 5 vials) by slow injection (dependent on severity of signs/symptoms; some patients may need more than 10 vials). Inject the first 1 to 2 mL of antivenin over 3 to 5 minutes with careful observation for the development of a hypersensitivity reaction
 - 2) Skin testing may be warranted prior to administration
 - 3) Have treatment for hypersensitivity reactions readily available
- f. Neostigmine coupled with an anticholinergic (e.g., atropine) to prevent bradycardia has been recommended as a temporizing measure when antivenom is not immediately available¹¹⁵

E. *Latrodectus*⁹⁵

- 1. Many different *Latrodectus* species exist and are distributed throughout the entire continental U.S.
 - a. Two species responsible for many envenomations are *Latrodectus mactans* (Black widow) and *Latrodectus Hesperus* (western widow)
 - b. *Latrodectus mactans*, also known as the black widow spider or Southern widow, is primarily located in the Southeast United States, but has been found as far North as Ohio
 - 1) While there are many different “widows”, the red hourglass abdominal marking often associated with the “black widow” is found exclusively on *Latrodectus mactans*. Other species have different markings
 - c. The Western widow *L. Hesperus* is found in the Western US
 - d. US Poison centers received 1,002 calls regarding exposures to black widow spiders in 2020⁵
 - e. Envenomation usually occurs on an extremity when a human accidentally places a foot or hand into an area where widow is residing¹¹⁵
 - f. Deaths are exceedingly rare from North American widow species

2. Toxicity: Contains “alpha latrotoxin” as well as other biologic agents which bind to presynaptic receptors and cause widespread release of neurotransmitters (norepinephrine, dopamine, GABA, glutamate, acetylcholine). This leads to autonomic dysfunction, muscle spasms, and pain that starts locally and can progress to systemic symptoms.
3. Clinical effects: Latrodectism^{116,117}
 - a. Pain: local envenomation site pain that may spread proximally to the trunk, some bites are asymptomatic and develop pain 30-120 minutes later. May progress to severe abdominal pain and has been misdiagnosed as acute appendicitis causing unnecessary surgery. Generally resolves within 24-48 hours
 - b. Autonomic dysfunction: tachycardia, hypertension, priapism, excess secretions, paresthesias, agitation, and nystagmus have all been reported
 - c. Other effects: facial twitching, sardonic grin. More severe effect such as compartment syndrome, rhabdomyolysis, pulmonary edema, and cardiac arrest have been rarely reported
4. Envenomation grading¹¹⁸
 - a. Mild: Pain and muscle twitching near site of envenomation
 - b. Moderate envenomation: Pain or spasms involving bitten extremity or trunk, accompanied by diaphoresis
 - c. Severe envenomation: Severe envenomation causes pain that is severe and difficult to control or accompanied by systemic findings such as tachycardia and hypertension, nausea and vomiting, or headache
5. Treatment
 - a. Ensure airway breathing and circulation are appropriately supported
 - b. Tetanus prophylaxis and wound cleaning
 - c. Analgesics as well as benzodiazepines may be useful for pain control and reduction in muscle spasms
 - d. Calcium was once utilized to reduce pain but has not been proven effective and its theoretical mechanism of action is unknown¹¹⁶
 - e. Antivenom may be considered in moderate or severe envenomation
 - 1) Antivenom may facilitate discharge by rapid reduction in symptoms (approximately 30 minutes) and shortening duration of symptoms from 22 hours in untreated patients to only 9 hours in treated patients¹¹⁶
 - 2) Death from black widow envenomations are rare; fatalities have also been reported from widow antivenom, making its use controversial¹¹⁹
 - 3) Some suggest antivenom use only in severe morbidity, end organ damage such as priapism or compartment syndrome, pain unable to manage with intravenous analgesics⁹⁵

- 4) Consultation with a toxicologist or poison center (1-800-222-1222) familiar with antivenom use is recommended
- f. Black widow spider (*Latrodectus mactans*) antivenom: Equine serum IgG available from Merck and shipped directly by manufacturer¹²⁰
 - 1) IM, IV: One vial (2.5 ML); a second dose may be needed in some cases; more than 1 to 2 vials are rarely required
 - 2) Skin testing may be warranted prior to administration
 - 3) Have treatment for hypersensitivity reactions readily available

Case 5

Andrew has received intravenous opioids and benzodiazepines and still has persistent pain, salivation, and vital derangement. The poison center was contacted, and the decision was made to administer centruroides antivenom due to the severe symptoms. He is administered 3 vials of centruroides antivenom starting at 25 ml/hr. He appears to tolerate without issue and the infusion is increased to 50 ml/hr. A few moments later he becomes tachycardic to HR 160 bpm, his oxygen saturation drops to 83%, and he appears more diaphoretic.

Question #12

What is an appropriate course of action?

- A. Venom redistribution after antivenom binding has caused recrudescence, increase rate to 75 ml/hr
- B. Continue infusion, administer epinephrine, diphenhydramine, and methylprednisolone
- C. Stop infusion, administer epinephrine, diphenhydramine, and methylprednisolone
- D. Stop infusion, pretreat with methylprednisolone 1000 mg, intubate to protect airway and resume infusion at lower rate

D. Exotic envenomation

1. Many envenomations in the U.S. occur via nonnative animals
 - a. Exotic pet keeping
 - b. Snake venom milking labs
 - c. Zoo or aquarium
2. Poison centers are crucial in the case of exotic animal envenomation¹²¹
 - a. Poison centers can determine if antivenom exists for species
 - 1) Poison centers have access to the antivenom index (<https://www.aza.org/antivenom-index?locale=en>) and can locate and contact zoos or facilities housing antivenom
 - 2) Can coordinate delivery of antivenom to healthcare facility

3. Use of non-FDA approved biologics
 - a. Use of non-FDA approved antivenoms (i.e., commercially available in country where envenomation occurs, but not in U.S.) is considered use of an experimental drug by the FDA and completion of a Biologic Based Investigational New Drug (BB-IND) form is required by any facility administering non-FDA approved antivenom
 - b. FDA steps for BB-IND for antivenom are found here <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-applications-inds-cber-regulated-products/information-use-antivenoms>
 - c. FDA BB-IND application steps to be submitted in triplicate to Director, Center for Biologics Evaluation and Research (CBER)
 - 1) An investigational new drug form (form FDA 1571) must be submitted
 - 2) A statement naming a local physician who will supervise antivenom storage and administration must be made and submitted alongside a new investigator form (FDA 1572)
 - 3) Name, address of manufacturer, species for which antivenom being used for, lot number, and package insert if available
 - 4) Manufacturer statement that antivenom has passed safety and sterility tests
 - 5) Statement that product is imported solely for emergency use and that a case report of use will be submitted to CBER
 - 6) (*note this only needs to be completed once, after which an annual report can be sent to maintain approval)
 - d. The American College of Medical Toxicology recommends IRB approval for all non-FDA approved antivenom use and having an emergency IRB approval process in place PRIOR to needing antivenom
4. Facilities housing venomous animals are recommend by American College of Medical Toxicology (ACMT) guidelines to have a formal written plan for envenomation including:¹²²
 - a. Collaboration with poison control centers, toxicologists, and predesignated medical facilities
 - b. Stocking of any commercially available antivenom for the venomous animal (on site or at a designated healthcare facility)
 - c. Completed FDA procedures for use (see above)
5. Emergency departments should be aware of venom milking labs and venomous animals in surrounding zoos and aquariums
6. Proactive planning should be done to designate a treatment facility and expedite appropriate BB-IND and IRB approval for use if necessary

E. Summary

1. Envenomation in which antidote might be considered include
 - a. *Centruroides* Scorpions (Bark scorpions)
 - b. *Crotalinae* ("pit vipers", rattlesnake, cottonmouth, copperhead)
 - c. *Micrurus fulvius* (Coral snakes)
 - d. *Latrodectus* sp (widow spiders)
 - e. Exotic animal envenomation
2. Treatment for all envenomations included providing analgesics, tetanus prophylaxis, wound care, and assessing clinical signs based off expected toxicity from venom
3. Venom toxicity is often graded to determine if antivenom is appropriate
 - a. The same amount of venom is delivered to pediatrics as to adults thus the doses of antivenom are the same in pediatrics as in adults
 - b. Monitor for signs and symptoms of hypersensitivity
4. Consultation with a poison center (1-800-222-1222) is crucial in the event of an envenomation to aid in antivenom sourcing, appropriate use, dosing, and monitoring

F. Frostbite^{123,124}

- G. Clinically diagnosed cold exposure injury caused when tissue freezes due to prolonged exposure to cold temperatures
1. Areas with low perfusion are highest risk, such as hands, digits, feet, face (including nose and cheeks), and ears.

H. Mechanism

1. Tissue damage is multifactorial
 - a. Early cell death due to cold temperatures
 - b. Intracellular and extracellular ice crystals formation interfering with electrolyte function
 - c. Microvascular blood flow impedance
 - d. Reperfusion injury occurs during thawing. (Injured tissue becomes reperfused and spreads inflammatory cytokines to adjacent tissue, with original tissue further damaged via complex mechanisms¹²⁵)

I. Clinical effects:

1. Cold, numb, and reduced fine motor movement of the affected area
2. Tissue may appear white, gray, or yellow. Necrosis may be present as well as bullae after thawing in deeper tissue injury

- J. Grading of injury should be performed after rewarming to guide treatment and imaging (done after 1 hour warm bath at 38 c in validation study)
 1. Grade 1: Absence of cyanotic lesion
 2. Grade 2: Initial cyanotic lesion on distal phalanx (1% need bone amputation)
 3. Grade 3: Initial cyanotic lesion on intermediary and proximal phalanx (Intermediary- 31% needed bone amputation, proximal 67% bone amputation))
 4. Grade 4: Initial lesion on carpal/tarsal (100% needed bone amputation)
- K. Imaging- numerous imaging techniques are possible^{126,127}
 1. Technicium 99m scintigraphy (bone scan) has been studied as a prognostication tool in a variety of studies
 - a. Technicium 99 bone scan immediately after thawing may help identify candidates for thrombolysis
 - b. Imaging 48 hours after injury (commonly technicium 99 bone scan) may help identify candidate for amputation
- L. Treatment^{123,124,128}
 1. Rewarming
 - a. Warm whirlpool or stagnant water immersion
 2. Analgesics for rewarming pain and secondary injury pain
 3. Tetanus prophylaxis
 4. Thrombolytic therapy may be reasonable if the patient presents within 24 hours of injury and imaging demonstrates appropriate perfusion deficits^{123,124,127}
 - a. The American Burn Association recommends alteplase for patients with Grade 3 or 4 frostbite injury and demonstrated loss of perfusion at or proximal to the middle phalanx immediately after rewarming¹²⁴
 - b. Alteplase should be avoided in those with contraindication¹²⁹
 - 1) Contraindications are not well defined in the frostbite population, risk of bleeding versus potential benefit should be evaluated.
 - 2) Contraindications utilized in prior studies include, but are not limited to:
 - a) Superficial frost bite
 - b) Impaired mental status
 - c) More than 48 hours of cold exposure
 - d) Severe hypertension
 - e) Recent trauma, stroke, or hemorrhage

- f) Bleeding disorder
 - g) Pregnancy
- c. Intravenous as well as intraarterial alteplase have been evaluated in frost bite patients^{130,131}
 - 1) Data is limited and IV versus IA have not been compared but intra-arterial is more commonly reported¹²⁸
- 5. No superior dose has been established and infusions intervals range from 6-72 hours
 - a. **IV:**
 - 1) Alteplase: 0.15 mg/kg bolus over 15 minutes, followed by a continuous IV infusion of 0.15 mg/kg/hour for up to 6 hours (maximum total dose: 100 mg)^{132,133}
 - b. **Intra-arterial via femoral or brachial artery:**
 - 1) Alteplase: 0.5 to 1.0 mg/h with heparin 500 u/h until reperfusion restored via angiogram or MAX 48 hours¹³⁴
 - 2) Alteplase: 1.0 mg/h with heparin and papaverine until reperfusion restored via angiogram or MAX 72 hours¹³¹
 - 3) Alteplase: 0.5 mg/h to each effected digit with heparin 12 u/kg/hr systemic for MAXIMUM 72 hours¹³⁵
 - 4) Tenecteplase: 0.25-0.5 mg/h with heparin and papaverine until reperfusion restored via angiogram or MAX 72 hours¹³¹
- 6. Thrombolytic therapy is often followed by systemic anticoagulation for one to four weeks and antithrombotic therapy with aspirin may be continued after^{132,133,135}
- 7. Intravenous iloprost has also been assessed and shown positive outcome of digital salvage however may not be available at all institutions. Use should generally be within 48 hours¹²⁷
- M. High altitude sickness¹³⁶
 - 1. Clinical diagnosis of adverse reaction to reduced levels of oxygen in air at high elevation (usually greater than 2500 m). Generally occurs 6-12 hours from ascent.
 - 2. Mechanism: Atmospheric pressure is reduced, which reduces oxygen diffusion gradient into blood due to lower partial pressures causing tissue hypoxia when ascension is done too rapidly for the body to adapt. This can lead to maladaptive changes in vasculature and sympathetic tone¹³⁷
 - 3. Clinical effects^{136,137}
 - a. Acute Mountain Sickness (AMS): Headache, dizziness, malaise, anorexia
 - b. High Altitude Cerebral Edema (HACE): Presents as altered mental status with encephalopathy/ataxia. Cerebral edema results related to extravascular fluids shifts.

- c. High Altitude Pulmonary Edema (HAPE): non-cardiogenic pulmonary edema due to pulmonary vascular changes developing after rapid ascent
- 4. Treatment¹³⁸
 - a. Stop ascent until acclimated
 - 1) Descent may be needed if symptoms progress despite supportive care and acclimation time
 - b. Supplemental oxygen is an effective treatment
 - c. Dexamethasone may aid in reduction of symptoms (headache, nausea, dizziness, and derangements of spirometry values) during acute episode¹³⁹
 - d. Supportive care with analgesics and antiemetics
 - e. Acetazolamide may be started to aid in acclimatation if not already taking prophylactically¹⁴⁰
 - 1) Increases ventilation via acidotic stimulation of central chemoreceptors
 - f. High altitude cerebral edema
 - 1) Descent as soon as possible
 - 2) Supplemental oxygen and dexamethasone
 - a) Dexamethasone 8 mg IM, IV, or PO, followed by 4 mg IM, IV, or PO q 6 h to temporize while awaiting descent¹³⁹
 - g. HAPE
 - 1) Descent as soon as possible
 - 2) Supplemental oxygen
 - 3) Numerous pharmacologic therapies have been described including nifedipine, phosphodiesterase inhibitors, and glucocorticoids but extraction is recommended first line¹⁴¹⁻¹⁴³

You are the EM pharmacist on a hot July day in 2019 when three different providers consult you...

- Jayna: 16-year-old female who represents to the ED two days after her initial visit. She was originally seen for 2 weeks of nausea, recent vomiting, shortness of breath, and hemoptysis
 - A chest X-ray 2 days ago showed a retrocardiac opacity
 - She was discharged home on azithromycin and amoxicillin
 - Today she is having worsened shortness of breath and a new oxygen requirement of 6 L/min
 - Her chest x-ray shows multiple bilateral ground glass opacities
 - The provider would like help broadening antibiotic therapy
- Kyle: Is a 15-year-old with worsening cough and fever x 2 days
 - He has no past medical history and lives at home with his mother, father, and sister
 - No one else in the home has developed symptoms and he has had no other recent contact with sick persons.

- He has shortness of breath that is worsening despite oxygen therapy, his work of breathing is getting progressively greater, and he is requiring 10 L/min by oxygen mask
- An infectious diseases work up is begun. A chest x-ray shows bilateral ground glass opacities
- You are consulted to assist with intubation and help select antibiotics
 - You briefly interview the patient prior to intubation about home medications and he says
 - “The only drugs I need are right here” and holds his electronic vaping device
- Kimmy Is a 14-year-old with cough, fever, diarrhea, and increasing shortness of breath x 7 days
 - She is noted to be desaturating to 89% on room air and is placed on oxygen by nasal cannula
 - An infectious diseases work up is begun
 - She has no past medical history or sick persons in her household
 - You are reviewing her chart to ensure appropriate antibiotic selection

You identified 3 young individuals with infectious syndromes, pulmonary complaints, and new oxygen requirements and alerted the providers who care for them about this phenomenon

- You interview Kimmy about her social history
 - She reported occasional alcohol use, rare marijuana use, and the use of friends' marijuana vape pens at parties
- You also note a urine drug screen for Jayna has tested positive for marijuana
 - An exposure history for Jayna reveals that she also uses marijuana vape pens

The providers report the situation with the three patients to the local health department
 You contact the poison center to report your concerns that the respiratory illnesses in these patients might be attributed to the use of contaminated vaping devices and determine whether any other similar cases have been reported

- The poison center shares your reports with the local health department and informs you that two similar cases have been reported in the last 36 hours

The health department pushes a news bulletin describing a potential syndrome that providers should be aware of, how to document it, and who to report it to

- A massive outbreak of respiratory infections traced to contaminated vaping devices is identified and plans for tracking reports are made thanks to the combined surveillance efforts of astute providers and pharmacists

Question #13

Which of the following is an important action for clinical pharmacists to take during a disaster or mass casualty?

- A. Avoid educating colleagues and public about the potential health effects of the event to prevent conflicting messaging from public health organizations such as the Federal Emergency Management Agency (FEMA) or Centers for Disease Control (CDC)
- B. Advise institutions and public health officials on antidotal availability, stocking recommendations, and create treatment guidelines for use

- C. Avoid sharing information with other institutions and public health organizations to facilitate a single source of information flow from the public health organization overseeing management of the disaster
- D. Become a direct reporter to your local public health organization for all potential cases seen at your facility

IX. Pharmacist role in disaster management

- A. Pharmacists are integral in disaster management and mass poisoning
 - 1. Practice as bedside clinicians to solicit information (e.g., exposure history) directly from patients
 - 2. Well positioned to coordinate information documentation and transmission
 - 3. Training as educators of healthcare workers
 - 4. Strategic role in identifying syndromes because of responsibility for large patient population
 - 5. Antidote experts
 - 6. Responsible for sourcing, stocking, and dispensing antidotes
 - 7. Able to create guidelines for antidotal use that address shortages
- B. Examples of pharmacists in mass disasters
 - 1. E-cigarette and Vaping device Associated Lung Injury (EVALI)
 - a. Assessment of novel toxins possibly responsible for mass outbreak of pulmonary disease in EVALI^{144,145}
 - b. History taking and reporting of products used to health departments and poison centers
 - c. Sharing of data and patient outcomes with public health organizations and frontline workers
 - d. Developing treatment guidelines in ongoing outbreak
 - 2. Outbreak of long-acting anticoagulant contaminated rodenticide contaminated synthetic marijuana¹⁴⁶
 - a. Assisted in policy making drug and guideline development for vitamin K dosing
 - b. Collaborated with other agencies to manage large public health outbreaks
 - c. Provided bedside care for poisoned patients
 - d. Took medication histories and reported products used to health departments and poison centers

3. COVID-19 Worldwide pandemic
 - a. Mass vaccination¹⁴⁷
 - b. Sourced and ensured availability of vaccine
 - c. Spreading evidence-based health information to combat treatment hesitancy due to misinformation¹⁴⁸
4. H1N1 Influenza pandemic
 - a. Distribution of antivirals from mass distribution sites¹⁴⁹
- C. Potential roles of emergency medicine pharmacists in mass disasters¹⁵⁰
 1. Key member of bed side mass casualty response team
 2. Participation on institutional disaster response planning committee
 3. Maintenance of adequate antidote stock for potential poisoning emergencies within department (See Toxicology module 1 for list of antidotes)
 4. Maintenance of CDC national antidote stockpiles
 5. Participation in mass dispensing of antidotes after a mass casualty
 6. Creation of treatment guidelines for novel drug therapies or antidotes not frequently used
 7. History taking and toxidromal identification
 8. Coordination of information sharing amongst other facilities and public health departments
 9. Education of health care team and patients on novel drug therapies or new outbreaks
- D. There are many roles for pharmacists to prepare for and respond to potential disasters
- E. Additional resources
 1. Pharmacy disaster response resources
 - a. <https://www.ashp.org/pharmacy-practice/resource-centers/emergency-preparedness>
 2. Training for hazardous materials disasters
 - a. <https://www.ahls.org/site/>
 3. Federal Emergency Management Agency (FEMA)
 - a. <https://www.fema.gov/emergency-managers/national-preparedness>
 4. Centers for Disease Control (CDC) and Prevention
 - a. <https://emergency.cdc.gov/>
 5. Radiation emergencies
 - a. <https://orise.orau.gov/reacts/index.html>

Answers to Self-Assessment Questions

QUESTION #1 (Presentation and workbook)

- A. The child has signs and symptoms of anticholinergic toxicity (sedation, decreased urination, dry mucous membranes, tachycardia) and sodium channel blockade (wide QRS, dry mucous membranes), which is consistent with diphenhydramine; however, the presence of hypotension suggests TCA, which also has alpha adrenergic blockade
- B. ***This is consistent with TCA, sodium channel blockade (Wide QRS), anticholinergic toxicity (sedation, decreased urination, dry mucous membranes, tachycardia), and hypotension (alpha blockade)**
- C. Guanfacine is an alpha 2 agonist which would cause sedation, bradycardia, and mydriasis
- D. Early acetaminophen overdose is characterized by nausea and vomiting and is inconsistent with this presentation

(BCEMP Outline 1.8.K; 1.1.T; 1.3.T; 1.4.T; 1.5.T)

QUESTION #2 (Presentation and workbook)

- A. QRS does not perform as well as AVR (see answer B)
- B. ***Three studies have demonstrated elevated R wave in Avr is more predictive of seizure and arrhythmia than QRS.**^{6,8,9}
- C. RR has not been assessed as prognosticator in TCA overdose
- D. QTc has not been assessed as prognosticator in TCA overdose

(BCEMP Outline 1.8.K; 1.1.T)

QUESTION #3 (Presentation and workbook)

- 1. ***Seizures (sodium channel blockade, excess norepinephrine, GABA antagonism), hypotension (alpha blockade), tachycardia (anticholinergic) and wide QRS/arrhythmia (sodium channel blockade)**
- 2. This is more consistent with alpha 2 agonists or opioids
- 3. This is more consistent with beta blocker overdose
- 4. This is more consistent with calcium channel blocker overdose

(BCEMP Outline 1.13.K; 1.8.T; 1.1.T; 1.11T)

QUESTION #4 (Presentation and workbook)

- A. The wide QRS is not from ventricular tachycardia and is likely from sodium channel blockade. A trial of hypertonic sodium would be reasonable given the likely reversible cause (European Resuscitation Council 2000)
- B. ***The patient is hypotensive and tachycardic, so treatment of hypotension is reasonable but dopamine is less effective than norepinephrine in managing TCA induced shock.**¹¹⁻¹⁴

- C. She has signs of sodium channel blockade that should be reversed with hypertonic sodium. Serum alkalization is likely. Fluids have been started, norepinephrine is a good 1st line vasopressor if hypotension is refractory to fluid.
- D. Intralipid is recommended only in cardiac arrest, prioritization of conduction abnormality correction with hypertonic sodium is warranted

(BCEMP Outline 1.8.K; 1.1.T; 1.11T; 1.7.K; 1.13.T)

QUESTION #5 (Workbook only, Question is not in presentation)

- A. ***Bupropion toxicity demonstrates a sympathomimetic toxidrome (agitation, diaphoresis, tachycardia, hypertension). Hallmark of toxicity also includes delayed onset seizures and severe arrhythmia (wide QRS tachycardia) that may be refractory to hypertonic sodium (gap junction mediated and not sodium channel mediated).**
- B. This is a nicotinic acetylcholine agonist (i.e. nicotine, poison hemlock) toxidrome
- C. This is a cholinergic toxidrome
- D. This is a TCA toxidrome

(BCEMP Outline 1.8.K, 1.1.T; 1.3.T; 1.4.T; 1.5.T)

QUESTION #6 (Presentation Question #5)

- A. See rationale in answer C
- B. See rationale in answer C
- C. ***Serotonin syndrome and neuroleptic malignant syndrome have significant overlap (autonomic dysfunction, tremor, cogwheel rigidity (SS) vs lead pipe (NMS). A key differentiator is the presence of hyperreflexia and clonus in serotonin syndrome as opposed to bradykinesia in NMS. This case reaches Hunter criteria for serotonin syndrome, recent increase in serotonergic dose + tremor and hyperreflexia**
- D. See rationale in answer C

(BCEMP Outline 1.7.K; 1.1T; 1.3.T; 1.4.T; 1.5.T)

QUESTION #7 (Presentation Question #6)

- A. See answer D rationale
- B. See answer D rationale
- C. See answer D rationale
- D. ***Calcium channel blocker overdose blocks calcium channels on pancreatic beta cells inhibiting insulin secretion, this leads to hyperglycemia. Hyperglycemia in CCB OD is independently associated with worse outcomes.⁷¹ The other factors may be deranged in severe shock (i.e., low pH, anion gap acidosis from hyperlactatemia, hyperkalemia from low pH) but are not specific to the mechanism of CCBs.**

(BCEMP Outline 1.7.K; 1.8.K; 1.1.T; 1.3.T; 1.4.T; 1.5.T)

QUESTION #8 (Presentation Question # 7)

- A. High dose insulin euglycemia acts as an inodilator similar to dobutamine.⁷⁷ It is recommended in the setting of myocardial dysfunction and in cases without myocardial dysfunction refractory to standard therapy to raise blood pressure.⁷² This patient appears to have retained cardiac function, and likely is in a vasodilatory shock. Initiating afterload increasing therapies may be warranted prior to starting HIE.
- B. ***Calcium gluconate has been shown to increase blood pressure and overcome conduction blocks in calcium overdose. It is a relatively benign initial therapy with a potential benefit that can be utilized. The patients shock phenotype is consistent with a vasodilatory shock with retained cardiac function, afterload increasing therapy such as norepinephrine to vasoconstrict would be warranted.**
- C. Dopamine may be ineffective and expert consensus guidelines recommend against use of this agent as a 1st line therapy⁷²
- D. The ingestion was greater than 1 hour ago. Expert consensus guidelines for CCB OD follow the expert consensus guidelines for activated charcoal (ingestion within 1 hour),⁷² though state that some substance may benefit beyond 1 hour. The patients unprotected airway and decreased mental status makes this contraindicated. Whole bowel irrigation is recommended for ingestion beyond 2 hours with potential severe morbidity however hemodynamic instability is a relative contraindication³

(BCEMP Outline 1.7K; 1.8k; 1.8.T; 1.1.T; 1.11T; 1.7.K; 1.13.T)

QUESTION#9 (Presentation Question #8)

All of the following are proposed mechanisms of high-dose insulin therapy for cardiotoxicity, except:

- A. HIE Increases glucose utilization via insulin mediated glucose intake (Contreras-Ferrat 2010)
- B. Animal studies demonstrate a decrease in afterload
- C. ***Animal studies demonstrate a decrease in afterload and increase in cardiac output⁷⁷**
- D. There is increased intracellular calcium via insulin mediated calcium release from the sarcoplasmic reticulum to increase glut 4 endocytosis⁷⁶

(BCEMP Outline 1.8.T; 1.1.T; 1.11T; 1.7.K; 1.13.T)

QUESTION#10 (Presentation Question #9)

- A. Sodium, bicarbonate, and lactic acid should be monitored but are not directly affected by HIE
- B. ***Potassium, glucose, fluid status are important as insulin causes hypokalemia, hypoglycemia, and patients are at high risk of fluid overload especially if not using concentrated insulin products**
- C. CK does not need routine monitoring specially for insulin
- D. Troponin, pro-brain natriuretic peptide, and electrocardiograms do not need routine monitoring specially for insulin

(BCEMP Outline 1.8.K; 1.1.T; 1.4.T; 1.8T; 1.10.T; 1.11.T)

QUESTION#11 (Workbook only, Question is not in presentation)

- A. Acute onset pain and opsochonus are not consistent with organophosphate exposure
- B. This envenomation is not consistent with coral snake envenomation (Animal latching on to bite or chew followed by slowly developing neurotoxicity, paresthesia, slurred speech, ptosis, diplopia, dysphagia, weakness, paralysis)
- C. This envenomation is not consistent with crotaline envenomation (tissue destruction and coagulopathy)
- D. ***Centruroides (bark scorpions) are in the southwestern United States. Symptoms generally present as pain, autonomic dysfunction (tachycardia, hypersalivation), and cranial nerve deficits (nystagmus, blurred vision).**

(BCEMP Outline 1.8.K; 1.1.T; 1.3.T; 1.4.T; 1.5.T)

QUESTION# 12 (Workbook only, Question is not in presentation)

- A. While envenomation symptoms can recur after initial control, redistribution of venom during therapy does not. These signs are consistent with anaphylaxis
- B. The infusion should be stopped and immediate antihypersensitivity supportive care should be initiated to maintain airway and circulation
- C. ***The infusion should be stopped and immediate antihypersensitivity supportive care should be initiated to maintain airway and circulation**
- D. Nonimmune related infusion reactions occur with some antivenoms (crotaline) and rechallenging at slower rates in order to treat coagulopathy is sometimes tried. In *centruroides* envenomation the goal of the antivenom is to reduce pain and intensive care stay. The risks of rechallenging are not warranted.

(BCEMP Outline 1.8.K; 1.13.K; 1.1.T; 1.3.T; 1.4.T; 1.10.T)

QUESTION# 13 (presentation Question # 10)

- A. Providing education on antidotal use, drug safety, and potential adverse outcomes of antidotes to healthcare workers and information about health risks of an event to the public are key roles for pharmacists. It is important to review national organization recommendations remain up to date on guidance.
- B. ***Creating of antidote stocking recommendation from consensus guidelines as well as advising on how to use antidotes is a key role of pharmacist during a disaster event.**
- C. Collaborating with other institutions and public health organizations is crucial to rapid dissemination of information regarding resource utilization, treatment, and management.
- D. As pharmacists are not involved in the care of every patient who enters the emergency department, this may be better suited for a physician or nurse since each patient is guaranteed to encounter one of these roles.

(BCEMP Outline 2.6.K; 2.7K)

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