Foundations I:

Tox II Teaching Points

Acetaminophen Overdose

- **Case Teaching Points**
  - The differential for vomiting and LFT elevation should include cholecystitis, cholangitis, hepatitis (viral, chemical), hepatic abscess, and hepatic congestion. A careful and thorough history can help focus the differential diagnosis. Acetaminophen and salicylate are commonly used and easily accessible over-the-counter medications. Overdoses of these medications can lead to significant consequences. If identified early, there are effective treatments.

- **What is acetaminophen and how is it metabolized?**
  - Acetaminophen (APAP) is sold as a single formulation, or combined with other analgesics, opioids, sedatives, decongestants, expectorants, and antihistamines. It is available in oral, rectal, and intravenous formulations.
    - Be on the look out for symptoms of co-ingestions for combined formulations.
  - When ingested, APAP is absorbed from the small intestine in 30 to 45 minutes.
  - During normal ingestion, less than 5% of APAP is excreted unchanged in the urine. About 90% is conjugated in the liver: 40-70% is conjugated with glucuronide and 20-45% is conjugated with sulfate. Once conjugated, APAP becomes inactive and is eliminated through the urine. The remaining small fraction (5-15%) is oxidized by cytochrome P450 and forms a very toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI).
  - Hepatic glutathione quickly binds to and reduces NAPQI and eliminates it into the urine.

- **How does acetaminophen cause hepatotoxicity?**
  - When APAP is ingested in overdose, hepatic conjugation with glucuronide and sulfate becomes saturated. A larger proportion of APAP goes through the cytochrome P450 system and more NAPQI is produced.
  - When the amount of NAPQI exceeds the supply of hepatic glutathione, NAPQI binds to hepatocytes and causes cell death.

- **What are the four stages of acetaminophen toxicity?**
  - Stage 1
    - First 24 hours after ingestion
    - Generally SILENT, typically asymptomatic or may have nonspecific GI symptoms such as anorexia, nausea, vomiting
    - LFT values may be normal or show mild elevation

    - Stage 2
        - Day 2 to 3 post-ingestion
        - Abdominal pain with RUQ tenderness develops
        - Labs show transaminitis (AST more sensitive)
    - Stage 3
        - Day 3 to 4 post-ingestion
        - Liver failure develops
        - May develop encephalopathy, kidney injury, and/or jaundice
        - Labs may show hepatic failure, metabolic acidosis, coagulopathy, kidney injury, and/or pancreatitis
    - Stage 4
        - Day 5 or later
        - May recover or develop multiorgan failure and/or death

- **How do you predict hepatic toxicity?**
    - A single oral dose of 7.5 g in an adult or 150 mg/kg in a child are the lowest amount of APAP to cause acute toxicity.
    - The serum APAP level (Rumack-Matthew nomogram) is used to determine the risk of APAP hepatotoxicity after a single acute ingestion. This can NOT be used for staggered acute or chronic toxicity.
    - Ideally, measure acetaminophen level at 4 hours post ingestion (if known ingestion time), or as soon as possible. Do NOT use levels at < 4 hours to determine need for treatment.
    - Rumack-Matthew nomogram is used only when:
        - Single acute ingestion
        - Time of ingestion is known
        - > 4 hours and < 24 hours since the time of ingestion

- **How is acetaminophen toxicity treated?**
    - GI decontamination
        - Administration of activated charcoal (1 g/kg) may be considered if a patient presents within an hour of ingestion.
    - N-Acetylcysteine (NAC)
        - NAC is a glutathione precursor. It increases the supply of glutathione, which detoxifies NAPQI.
        - If given within 8 hours after the APAP ingestion, NAC is 100% effective to prevent hepatotoxicity. Delayed administration beyond 8 hours increases the risk of hepatotoxicity.
        - Give NAC if the patient falls above the treatment threshold on the Rumack-Matthew nomogram.
        - Oral and IV forms are available; if compliance with PO is questionable, give IV.
            - Oral loading dose: 140 mg/kg
            - IV loading dose: 150 mg/kg

- Maintenance dosing: 300 mg/kg over 20 hours
- NAC is safe in pregnancy and dosing is unchanged
- Higher doses may be necessary for “massive ingestion” (> 30 g)

○ If the time of ingestion is unknown or > 24 hours:
  ■ Check APAP level and liver transaminases
  ■ Start NAC when:
    - Transaminases are elevated
    - Serum APAP is more than 10 µg/ml

- **What are the criteria of liver transplant in acetaminophen-induced liver failure?**
  ○ King’s College Criteria (KCC) is the most commonly used predictor of the mortality in APAP induced liver failure.
  ○ According to the KCC, the survival rate is 25 to 40% without transplant if
    ■ Any of the following despite fluid resuscitation:
      - Arterial pH < 7.3
      - Lactate > 3.0 mmol/L
      - Refractory hypotension

    OR
    ■ All of the following:
      - Creatinine > 3.3 mg/dL
      - PT > 100 sec or INR > 6.5
      - Grade III of IV encephalopathy (altered mental status)

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    ■ Wightman R, Nelson L. Chapter 190: Acetaminophen. In: Judith E. Tintinalli, O. John Ma, et al, editors. Tintinalli's Emergency Medicine: A Comprehensive Study Guide (9th ed). New York: McGraw-Hill; 2020.
    ■ Hendrickson R, McKeown N. Chapter 33: Acetaminophen. In: L Nelson, M Howland, et al, editors. Goldfrank’s Toxicologic Emergencies (11th ed). New York McGraw-Hill Medical; 2019.
    ■ Rumack-Matthew Nomogram from Wikipedia File:Rumack Matthew nomogram with treatment (study) line.pdf by Merlin Crystal under CC BY SA-3.0
    ■ Mullins M, Nordt S. Acetaminophen Toxicity and Poisoning. In: Swadron S, Nordt S, Mattu A, and Johnson W, eds. CorePendium. 5th ed. Burbank, CA: CorePendium, LLC. https://www.emrap.org/corependium/chapter/recIyIdV76pEgSeY4/Acetaminophen-Toxicity-and-Poisoning. Updated August 26, 2024. Accessed March 4, 2025.

Organophosphate Overdose

- **Case Teaching Points**
    - The differential diagnosis for a young unresponsive patient with unstable vitals should include traumatic or spontaneous intracranial hemorrhage, sepsis, metabolic derangement, and both recreational and non recreational toxic exposures.
    - **Decontamination** is an important part of management. Clothing should be treated as hazardous waste. The patient's skin should be cleaned with soap and water. Healthcare workers should take care to avoid contamination by using personal protective equipment including masks, gloves, and gowns.
    - Treatment requires **aggressive airway monitoring and intubation as necessary**, although atropine given in adequate doses may prevent the need for intubation. If a patient is intubated with suspicion for organophosphate exposure, succinylcholine should be avoided (degraded by acetylcholinesterase) as it may result in prolonged paralysis.
    - **Atropine** (competitive inhibitor at *muscarinic* cholinergic receptors) is the mainstay of treatment and very high doses are often required. The initial dose should generally be 2 mg IV push, repeated every 5 min as needed. The endpoint of therapy is dried pulmonary secretions and adequate oxygenation. In patients with acute respiratory distress/failure, consider doubling the dose of atropine with each round of administration for more rapid effect.

- **What are organophosphates?**
    - Chemical compounds (insecticides, nerve gases) that inhibit acetylcholinesterase, leading to accumulation of acetylcholine and overstimulation of muscarinic and nicotinic receptors.
    - Organophosphates are the most common chemical exposure related reason for an ED visit.
    - Examples include: diazinon, acephate, malathion, parathion, and chlorpyrifos.

- **What are the muscarinic effects of cholinesterase inhibition?**
    - Use the mnemonic "SLUDGE/DUMBELLS"
        - **S**alivation, **L**acrimation, **U**rinary incontinence, **D**efecation, **G**I pain, **E**mesis
        - **D**efecation, **U**rination, **M**iosis, **B**radycardia, **B**ronchorrhea, **B**ronchospasm, **E**mesis, **L**acrimation, **S**alivation
        - Remember the "Killer Bs:" bradycardia, bronchorrhea, and bronchospasm

- **What are the nicotinic and CNS effects of cholinesterase inhibition?**
    - Nicotinic
        - Muscle fasciculations, cramps, weakness
        - Mydriasis, pallor
        - Tachycardia, hypertension
    - CNS

        - Anxiety, restlessness, emotional lability
        - Tremor, headache, dizziness
        - Confusion, delirium, hallucinations
        - Seizures, coma

- **What is the progression of organophosphate poisoning?**
    - Acute
        - Symptom onset typically within the first 8 hours after exposure
        - Usually CNS, muscarinic, nicotinic and somatic motor symptoms seen
    - Intermediate syndrome
        - Typically 1 to 5 days after exposure, with resolution in 7 days
        - Symptoms include paralysis of neck flexor muscles, muscles innervated by cranial nerves, proximal limb muscles and respiratory muscles
        - No signs of cholinergic excess
    - Organophosphate-induced delayed neuropathy
        - Cognitive dysfunction, impaired memory, mood changes, autonomic dysfunction, peripheral neuropathy, extrapyramidal signs
        - More likely related to inhalation as opposed to cutaneous exposure
    - Chronic toxicity
        - Usually agricultural workers
        - Symptoms include symmetrical sensorimotor axonopathy such as leg cramps, weakness and paralysis, can mimic Guillain-Barre

- **What is the role of atropine and 2-PAM in the treatment of organophosphate poisoning? Are there additional treatment options?**
    - Atropine (competitive inhibitor at *muscarinic* cholinergic receptors) dosing begins at 2 mg IV and can be given every 5 minutes. It may even be doubled on each subsequent dosing. The titration endpoint for atropine is drying of pulmonary secretions. Very high doses of atropine may be required (even as high as double-digit doses and > 100 mg total).
    - If atropine is limited or patients develop anticholinergic delirium, glycopyrrolate (peripheral antimuscarinic) or diphenhydramine may be used to improve some symptoms as a last resort. Atropine toxicity may present as dilated pupils and HR > 120.
    - 2-PAM (pralidoxime) reactivates acetylcholinesterase (treats both muscarinic and nicotinic symptoms) and historically was used to reverse fasciculations and neuromuscular blockade. For adult patients, start with a bolus dose 30 mg/kg IV over 30 min, followed by continuous infusion of 8 mg/kg/hour for 24-48 hours.
    - Use benzodiazepines (diazepam 5-10 mg IV) to prevent seizures and reduce fasciculations.
    - Give IVF for euvolemia, then epinephrine prn for MAP > 65 mm Hg.
    - Patients with symptomatic organophosphate toxicity should be admitted to the ICU.

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    - Shaun Greene. Chapter 201: Pesticides. In: Judith E. Tintinalli, O. John Ma, et al, editors. Tintinalli's Emergency Medicine: A Comprehensive Study Guide (9th ed). New York: McGraw-Hill; 2020.
    - Katherine Welker, Trevonne M. Thompson. Chapter 157: Pesticides. In: Ron Walls, Robert Hockberger, Marianne Gausche-Hill et al, editors. Rosen's Emergency Medicine: Concepts and Clinical Practice (9th ed). Philadelphia: Elsevier, Inc; 2018.
    - Katz K. Organophosphate Toxicity Clinical Presentation. 2020 [cited 2021, August 30] In: Medscape eMedicine [Internet]. Available from: Organophosphate Toxicity Clinical Presentation: History, Physical (medscape.com)
    - Cook M, Frey A. Pesticides and Cholinergic Toxicity and Poisoning. In: Swadron S, Nordt S, Mattu A, and Johnson W, eds. CorePendium. 5th ed. Burbank, CA: CorePendium, LLC. https://www.emrap.org/corependium/chapter/recdvP3Xjhrp9vbC8/Pesticides-and-Cholinergic-Toxicity-and-Poisoning. Updated September 14, 2020. Accessed March 24, 2025.
    - UpToDate: Bird S. Organophosphate and carbamate poisoning. In: UpToDate, Mallory GB et al (Ed), UpToDate, Waltham, MA. (Accessed on March 5th, 2024.)

Calcium Channel Blocker Overdose

- **Case Teaching Points**
    - The differential for bradycardia and hypotension after suspected medication ingestion should include CCB, BB, Digoxin, and Clonidine (“The Brady Bunch”). Additionally, one must keep other co-ingestants as well as CNS etiologies on the differential, including opioid and CNS depressant overdose, etoh intoxication, toxic alcohol intoxication, cholinergic poisoning, and aspirin or acetaminophen intoxication. Non-toxicologic causes of bradycardia must also be considered, including hyperkalemia, hypothermia, cardiac ischemia, conduction issues, CNS bleed, and neurogenic shock.

- **What is the pathophysiology of a calcium channel blocker overdose?**
    - Calcium-Channel Blocker Types
        - Dihydropyridines (DHPs) - nifedipine, amlodipine, nimodipine, nicardipine
            - Peripheral-acting L-type Ca-Channel blockers
        - Non-DHPs - diltiazem, verapamil
            - Central-acting L-type Ca-Channel blockers
    - Antagonism of L-Type Calcium Channels By Site
        - Myocardial - decreases myocardial contraction and inhibits conduction of SA and AV nodes -> bradycardia and hypotension
        - Vascular Smooth Muscle - vasodilation -> hypotension
        - Pancreatic Beta Cells - inhibits insulin release -> hyperglycemia, myocardial dysfunction (less efficient energy utilization of the myocardium -free fatty acids instead of glucose)
    - Beta-Blockers
        - Decrease myocardial intracellular cAMP -> bradycardia, hypotension
        - Decreases gluconeogenesis and glycogenolysis -> hypoglycemia

- **How should a patient be evaluated for CCB overdose?**
    - Suspect in any patients with hypotension but NO compensatory tachycardia
    - ECG may reveal sinus rhythm, bradycardia, junctional rhythm, or atrioventricular block; select BBs (propranolol, acebutolol, and sotalol) may result in QRS or QT prolongation
    - Diagnosis is made clinically
        - Drug assays are sometimes available, but often not necessary
        - Tox panel to assess for co-ingestants
    - Glucose
        - Hypoglycemia or Euglycemia - Beta Blockers
        - Hyperglycemia - CCB

- **What is the role of GI decontamination in CCB overdose?**
    - As there is no antidote for these medications, consider if the ingestion occurred < 1-2 hours (may extend window depending on drug ingested and amount)

        - May consider intubation and gastric lavage but all decontamination measures are not clear cut, therefore they should not delay other more evidence-based aspects of treatment
        - Activated charcoal- 1 g/kg up to 50 g (only give if airway is protected)
        - Whole-Bowel Irrigation for extended-release ingestions or large ingestions
        - Even asymptomatic patients with a suspected overdose should undergo GI decontamination and be monitored for stability based on the preparation of the medication: immediate-release (6 hr), standard release (6–12 hr) and extended-release/sustained release/long-acting (24 hr)

- **What is the management of CCB overdose?**
    - Primary
        - Isotonic IVFs for volume expansion: 10-30 cc/kg
            - CCB has associated risk of pulmonary edema - POCUS or CXR can help with fluid administration decision
        - Atropine
            - 0.5–1 mg IV, may repeat q2–3 minutes to a max of 3mg
            - Expect treatment failure in severe CCB or BB overdoses.
        - Calcium - direct competitor of calcium channels
            - Calcium chloride 1–2 grams IV (13.4 mEq Ca^{2+}/g) or calcium gluconate 3–6 grams IV (4.65 mEq Ca^{2+}/g)
        - Glucagon - bypass ß-receptor to stimulate cardiac activity via adenylate cyclase
            - Since CCBs act downstream to glucagon's bindings site, will likely not have an effect, but still recommended.
            - 5–10 mg IV (followed by 5–10 mg/hr infusion if bolus dose produces adequate response)
            - Anticipate nausea/vomiting
        - HIET - Hyper-insulin Euglycemia Therapy
            - High dose regular insulin acts as a direct inotrope, increases intracellular calcium release, and increases myocardial glucose uptake
            - 1 UNIT/kg regular insulin IV, followed by 0.5–1 UNIT/kg/hr infusion
            - Couple with 0.5 g/kg glucose bolus followed by D10 or D25 at 1.5 maintenance (titrated to maintain blood glucose > 250 mg/dL)
            - Monitor glucose and lytes/K q 15-30 min while actively titrating insulin infusion, replete as needed (may monitor hourly once stabilized)
        - Vasopressors/Inotropes
            - Epinephrine is first-line (i.e. cardiogenic shock), norepinephrine may be considered as an alternative
            - Epi: bolus of 20-50 mcg epinephrine followed by gtt at 2-10 mcg/min
            - Norepi: start at 2 mcg/min and titrate up
    - Secondary
        - Pacing - likely ineffective and theoretical risk of myocardial irritation with TVP

        - Intralipids - 1.5 mL/kg IV bolus; may repeat bolus for persistent CV collapse. Then, begin 30–60 minute infusion at 0.25–0.5mL/kg (keep cumulative dose to <10–12 mL/kg)
        - Consider ECMO, if available

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        - Beck-Esmay, Jenny MD, Lugassy, Daniel MD. Hyperinsulinemia Euglycemia Therapy (HIET) for Beta Blocker and Calcium Channel Blocker Toxicity. 2015 Sept 9 [cited 2021 June 4] In: Core EM [Internet]. Available from: https://coreem.net/core/hiet/
        - Levine, Michael. Beta and Calcium Channel Blockers. In: Mattu A and Swadron S, ed. CorePendium. Burbank, CA: CorePendium, LLC. https://www.emrap.org/corependium/chapter/recVOjoN9xWAKy9Aa/Beta-and-Calcium-Channel-Blockers#h.5ajrs6cflzfp. Updated May 19, 2021. Accessed June 5, 2021.
        - Masom, Clifford P., and Christian Tomaszewski. Chapter 195:Calcium Channel Blockers. In: Judith E. Tintinalli, O. John Ma, et al, editors. Tintinalli's Emergency Medicine: A Comprehensive Study Guide (9th ed). New York: McGraw-Hill; 2020.
        - Morgenstern, J. Management of calcium channel blocker overdose in the emergency department. 2015 Aug 3 [cited 2021 June 4] In: First10EM [Internet]. Available from: https://first10em.com/calcium-channel-overdose/
        - Image References
            - ECG courtesy of NYU School of Medicine Emergency Care Electrocardiogram (ECG) Database; ECG - 24058
            - CXR from: Normal Post-Intubation CXR from “JETem” https://jetem.org/ettcxr
