Foundations I:

Tox 1 Teaching Points

Opioid Overdose

- **Case Teaching Points**
  - The initial differential diagnosis for this young adult patient with AMS and reduced respirations should include head trauma, opioid overdose, other sedative overdose, alcohol intoxication and CO poisoning; a broader differential may also include infection, SAH and seizure.
  - The differential diagnosis for opioid toxidrome should include toxicological (e.g., benzodiazepine, barbiturate, ethanol, clonidine, and organophosphate toxicity) and metabolic (e.g., hypoglycemia) conditions.
    - Benzodiazepines and barbiturates enhance the inhibitory actions of the neurotransmitter GABA and thus cause CNS and respiratory depression, although barbiturates have a more potent effect on respiratory drive.
    - Assessment of the pupils is important since opioids cause miosis, whereas the pupils in a barbiturate overdose can be normal or even dilated if severely hypoxic.
    - Ethanol also potentiates GABA, increasing its release in the CNS, and can cause CNS depression and altered mental status. Co-ingestion of ethanol with other substances should be considered.
    - Clonidine overdose can mimic opioid toxicity, and include bradycardia and hypotension; this may respond to high doses of narcan (2mg doses up to 10mg total)
    - Organophosphates are irreversible acetylcholinesterase inhibitors that cause increased cholinergic activity. Although organophosphate poisoning can cause bradycardia and miosis, unlike in opioid overdose, these patients will have excessive secretions and appear diaphoretic.
    - The learner should also expand their differential to include other metabolic causes of altered status including hypoglycemia, which can be identified rapidly at the bedside with a point-of-care capillary blood glucose.

- **Epidemiology of the opioid epidemic**
  - From 2013-2019, there has been a significant rise (1040% increase) in death due to synthetic opioids such as fentanyl.
  - The opioid epidemic in North America and continued rise of opioid-related mortality is attributed not only to illicit use, but also misuse of prescription opioids.

- High-risk prescribing practices of some physicians have also contributed to a rise in mortality associated with therapeutic use.

- **Pathophysiology of opioid toxicity**
  - Respiratory depression – blunted response to hypercapnia at the medulla, loss of rhythmic breathing mechanisms, unstable breathing patterns; primary cause of death due to opioid overdose
  - CNS depression and sedation – stimulation of mu receptors within the CNS
  - Miosis – stimulation of the mu receptors in the Edinger-Westphal nuclei of CN3 causing the pupillary constrictors to contract
  - Reduced GI motility – stimulation of kappa receptors within the GI tract

- **How might opioid overdose present?**
  - Opioid overdose should be considered in ANY patient with CNS + respiratory depression; miosis is NOT always present.
  - Respiratory depression
    - Shallow, slow, and irregular breathing pattern
    - Hypercarbia
    - Hypoxia
    - Cyanosis
    - Aspiration pneumonia
  - CNS depression
    - Altered mental status
    - Reduced GCS
  - Miosis
  - Noncardiogenic pulmonary edema
    - Physical Exam: rales on auscultation
    - CXR: bilateral infiltrates without cardiomegaly
    - Tx: positive pressure ventilation or intubation
  - Hypothermia
  - Rhabdomyolysis
    - Acute kidney injury
  - Urticaria
    - Hives at the site of the injection site (in the case of IV heroin)

- **What are critical aspects of the management of opioid overdose in the ED?**
  - Airway and ventilatory support are the most important initial actions in the ED
    - The primary cause of mortality with opioid toxicity is respiratory failure.
    - Early airway and ventilatory support using adjuncts and bag-mask-ventilation are often necessary.
    - Early RSI and intubation to secure a definitive airway may also be needed, particularly if the patient does not respond adequately to naloxone.
  - Administer naloxone

        - Naloxone is a competitive opioid antagonist with an onset of < 1 minute
        - Routes of administration and dosing:
            - If no IV access, alternative routes include 2 mg IM, 1 mg per nostril intranasal (2 mg total) or 2 mg endotracheal
            - IV/IO
                - 0.1-0.4 mg IV if breathing spontaneously, 2 mg IV if apneic or cyanotic
                - Repeat dosing as needed q2-5 minutes until respiratory rate improves to at least 12 breaths per minute, ETCO2 is < 45mmHg, and SpO2 is > 95%.
                - Atypical opioids, including fentanyl and methadone may require doses as high as 10 mg
            - If a patient requires repeated doses of naloxone, an infusion may be required, starting at 2/3 the effective naloxone dose (required total over 1 hour).
            - If patients do not respond adequately to naloxone, intubation and mechanical ventilation may be required.
        - Naloxone's duration of action when given IV is 30-60 minutes; patients must be monitored for at least 1 hour after receiving naloxone for recurrent symptoms.
        - In chronic opioid users, administering naloxone may precipitate opioid withdrawal. In these patients, consider lower titrated doses.
            - Opioid withdrawal is rarely life-threatening, but suddenly precipitating withdrawal with a high dose of naloxone can pose risks to the patient and staff.
            - Symptoms of withdrawal include anxiety, sweating, rhinorrhea, vomiting, abdominal pain, headache, piloerection, diffuse myalgias, and yawning. Patients may also become agitated after naloxone administration.
            - If the patient is hemodynamically stable, it is important to start with low doses of naloxone and increase doses to desired effect.
            - Symptoms can be managed with clonidine, antiemetics, and antidiarrheals. Methadone and buprenorphine/naloxone (Suboxone®) may also be used to manage acute withdrawal.
    - Investigate and treat other life-threatening complications including:
        - Pulmonary edema
        - Rhabdomyolysis
        - Infectious endocarditis
        - Traumatic injuries
    - Investigate for co-ingestion
        - Ethanol
        - Acetaminophen
        - Salicylates

        - Note- urine drug screens have little clinical utility and often do not detect the wide variety of potential opioids
    - Disposition
        - The necessary period of monitoring for opioid ingestion is controversial, but generally should be at least 2-4 hours, or guided by the duration of action for the ingested opioid.
        - If the patient does not have further recurrence of symptoms, they may be discharged home with a referral for substance abuse counseling and a prescription for naloxone.
        - If the patient requires repeat doses of naloxone, a naloxone infusion or if long-acting opioid ingestion is suspected, admit to telemetry or step-down level of care.

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    - **References:**
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- Image References
  - ECG from “NYU Langone Health”: https://education.med.nyu.edu/ecg-database/app/search/results/18649
  - Chest X-ray from “Radiopaedia” courtesy of Assoc Prof Frank Gaillard: https://radiopaedia.org/cases/8090?lang=us

TCA Overdose

- **Case Teaching Points**
    - The differential for seizure in a young patient should include medication toxicity (TCA, isoniazid, tramadol, etc.), illicit substance use, hypoglycemia, intracranial bleed or mass, intracranial edema, infection (meningitis, encephalitis, intracranial abscess), metabolic derangements (hyponatremia), and eclampsia in female patients (pregnant or postpartum). A thorough history is imperative to narrowing down this broad differential diagnosis, in addition to a comprehensive physical exam.

- **What are Tricyclic Antidepressants (TCAs) and how do they work?**
    - TCAs are medications used to treat depression and less commonly obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), anxiety disorders, and panic and phobia disorders
    - It is important to note that TCAs have multiple pharmacologic properties that put patients at risk when toxicity occurs. Most importantly, when considering toxicity, these include:
        - Sodium channel blockade
        - Anticholinergic properties
        - Potassium channel blockade
        - Peripheral alpha blockade
        - Inhibition of serotonin reuptake
        - Inhibition of norepinephrine reuptake
        - Antagonism of postsynaptic muscarinic receptors
        - Antagonism of postsynaptic histamine receptors
    - TCAs have a narrow therapeutic window and have the highest reported ratio of deaths to exposures for all antidepressants.
        - Symptoms of overdose usually start 1-2 hours after ingestion.
        - About half of exposures involve coingestants as well, which often increase the severity of TCA overdose.
    - Common TCA medications include:
        - Amitriptyline
        - Imipramine
        - Nortriptyline
        - Clomipramine
        - Desipramine
        - Doxepin
        - Protriptyline
        - Trimipramine
        - Amoxapine, Maprotiline - have similar toxicity in overdose, but are structurally different from traditional TCAs

- **What are some signs/symptoms of TCA overdose?**

- The hallmarks of acute TCA overdose include
  - Anticholinergic symptoms
  - Decreased level of consciousness → seizures
  - Wide QRS
  - Cardiovascular collapse
- However, also considering the many pharmacologic properties of TCAs helps to define other signs and symptoms of toxicity as well:
  - Sodium channel blockade
    - Wide QRS
  - Anticholinergic properties
    - Decreased level of consciousness → seizures
    - Mydriasis, confusion, tachycardia, hyperthermia, hypertension, decreased secretions, dry skin, ileus, urinary retention, increased muscle tone, tremor
    - Think "Mad as a hatter, dry as a bone …"
  - Potassium channel blockade
    - IV or AV block, prolonged QTc
  - Peripheral alpha blockade
    - Hypotension
  - Inhibition of serotonin reuptake (i.e. similar to serotonin syndrome)
    - Sedation, mydriasis, hyperreflexia, myoclonus
  - Inhibition of norepinephrine reuptake
    - Agitation, mydriasis, tachycardia, early hypertension, diaphoresis
  - Antagonism of postsynaptic histamine receptors
    - Sedation
- ECG findings in TCA toxicity
  - Life in the Fast Lane provides a great review of the ECG in TCA toxicity
    - https://litfl.com/tricyclic-overdose-sodium-channel-blocker-toxicity/
  - Common ECG findings include:
    - Tachycardia
    - Wide QRS (>100 ms)
    - Terminal R wave in aVR (>3mm)
    - Deep, slurred S waves in I and aVL
    - QTc prolongation
    - Ventricular arrhythmias

- **How is TCA overdose treated?**
  - Sodium bicarbonate
    - Indication: wide QRS (> 100 ms)
    - Should be given in boluses 1-2 mEq/kg (2-3 amps) with repeat doses PRN until QRS narrowed
    - A continuous infusion may be made by adding 3 amps (150 mEq) to 850 mL of D5W, for a final concentration of 150 mEq/L.

        - Start the infusion at approximately 2 times the maintenance fluid rate (in general, 250 mL/hr in adults) and titrate as needed to maintain a QRS duration < 100 ms.
    - Serum alkalinization
        - To increase excretion
        - Goal serum pH 7.50-7.55
        - Must closely monitor serial labs (Q2 hr): serum pH, urine pH, serum electrolytes
            - Potassium repletion is commonly needed as bicarbonate will decrease serum potassium levels (remember, sodium bicarbonate is in the "hyperkalemia cocktail!")
            - Consider arterial line placement for frequent serum pH checks/electrolytes
    - Magnesium
        - Indication: wide QTc (>500 ms)
        - Give 2g IV
    - Seizures or severe agitation
        - Treat with benzodiazepines
        - Use typical seizure precautions
    - CNS Depression
        - May require intubation and mechanical ventilation
    - Decontamination
        - There is no proven outcome benefit with activated charcoal and in most patients, significant risk in giving activated charcoal (for instance, if altered mental status, sedation, seizures, risk of syncope or arrest from arrhythmia).
        - Rarely, activated charcoal is considered in concert with Poison Control due to the high mortality associated with acute overdoses.
        - To be a candidate for activated charcoal, the patient must present within 1 hour of ingestion with a narrow QRS and no seizures or mental status changes.
    - Hypotension
        - Fluid resuscitation is a mainstay of treatment
        - Vasopressors may be needed if the patient's hypotension is unresponsive to fluid resuscitation; phenylephrine or norepinephrine (α-agonist effects) may be considered.
    - Active cooling as needed for hyperthermia
    - Hemodialysis is ineffective (TCAs are highly protein bound).
    - Severe hemodynamic instability (in consultation with toxicology, ICU)
        - May consider IV lipid therapy
        - Lidocaine for refractory arrhythmia (avoid other anti-arrhythmics)
        - ECMO
    - Disposition
        - Any patient with a TCA overdose should be monitored for seizures and arrhythmias. The greatest risk of seizures and arrhythmias occurs within the first 6 to 8 hours of TCA ingestion.

        - Most will require ICU admission for frequent serial laboratory monitoring, hemodynamic monitoring, and neurologic monitoring given high incidence of seizures and mentation changes.

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            - Repeat ECG from Life in the Fast Lane: https://litfl.com/sinus-tachycardia-ecg-library/

Ethylene Glycol Ingestion

- **Case Teaching Points**
    - The differential diagnosis for altered mental status in a pediatric patient should include infection/sepsis, trauma (including non-accidental trauma), metabolic, and toxic ingestions. The patient is not febrile, so it is less likely to be infectious/sepsis, but the learner should still collect cultures and a chest x-ray to rule out sepsis. There is no history of trauma but the patient was in the backyard without supervision and then had a seizure so there is always potential of a head injury or perhaps non-accidental trauma. A broad workup for both metabolic and toxic pathologies should be instituted including BMP, LFTs and alcohol, acetaminophen and salicylate levels.

- **What are the toxic alcohols and where are they commonly found?**
    - Ethanol - commonly found in alcoholic beverages
    - Isopropanol - commonly found in rubbing alcohol and hand sanitizer
    - Methanol - commonly found in windshield cleaners, solvents and even some moonshine
    - Ethylene glycol - commonly found in antifreeze and hydraulic fluid

- **What are some clinical features of each?**
    - Ethanol
        - Clinical feature is clinical inebriation. Initially may see behavioral disinhibition, along with slurred speech, ataxia and decreased motor coordination. Severe toxicity may cause respiratory depression and coma.
    - Isopropanol
        - Clinical features include significant CNS depression and gastric irritation, which can range from nausea and vomiting to acute pancreatitis and upper GI bleeding. Can see hypotension and coma in severe toxicity.
    - Methanol
        - Clinical features include mild inebriation and eventually blurred or “snow field” vision, nausea and vomiting.
        - May not see clinical signs and symptoms until 12 to 24 hours after ingestion due to metabolism.
    - Ethylene glycol
        - Clinical features include inebriation, including ataxia and slurred speech, nausea and vomiting, then CNS depression, seizures, hypocalcemia and metabolic acidosis.
        - Initially within 30 min to 12 hours after ingestion can see CNS effects; then as metabolized can see tachycardia, tachypnea, hypocalcemia and eventually renal failure.

- **What is the mechanism of action of toxicity for methanol, ethylene glycol and isopropanol?**
    - Methanol

        - Methanol is metabolized by alcohol dehydrogenase to formaldehyde and then by aldehyde dehydrogenase to formic acid
        - Formic acid is the metabolite responsible for the toxicity and metabolic acidosis that occurs with poisoning
    - Ethylene glycol
        - Ethylene glycol is metabolized by alcohol dehydrogenase to glycoaldehyde and by aldehyde dehydrogenase to glycolic acid
        - Glycolic acid is the toxic metabolite and is responsible for the metabolic acidosis that occurs with poisoning
        - Glycolic acid can eventually be metabolized to oxalic acid (via conversion of glyoxylic acid) which can complex with calcium, leading to hypocalcemia and precipitation of calcium oxalate crystals
    - Isopropanol
        - Isopropanol is metabolized by alcohol dehydrogenase to acetone
        - Ketosis and an osmolar gap without acidosis should indicate an isopropanol toxicity
    - Ethanol competitively inhibits alcohol dehydrogenase, so coingestion with ethanol can be protective and slow down metabolism of the parent compound into its toxic metabolites

- **How do you work up a toxic alcohol ingestion?**
    - Check blood glucose to rule out hypoglycemia for altered mentation
    - Obtain acetaminophen and salicylate levels for common co-ingestions
    - Obtain an EKG to evaluate for prolonged QTC and QRS
    - Check a serum calcium, ethanol, osmolality
        - Calculate the plasma osmolality and subtract from measured osmolality to obtain osmolar gap
    - Obtain serum methanol, ethylene glycol and isopropanol levels
        - Testing for these may not be widely available and may be a send out depending on the hospital system
        - May not be able to rely on the results of this for initial treatment decisions
    - Order a urine sample
        - Can see formation of oxalate crystals in the urine in ethylene glycol poisoning but this is a late and nonspecific finding
        - Urine can fluoresce in ethylene glycol testing due to fluorescein added to most antifreeze solutions. This only appears transiently and lacks sensitivity as other substances can fluoresce.

- **How do you treat toxic alcohol poisoning?**
    - Call the poison center and involve a medical toxicologist.
    - Correct the acidosis
        - Administering IV bicarbonate to a patient with methanol poisoning helps limit the penetration of toxic acids

        - Reasonable to use IV bicarbonate if there is a severe metabolic acidosis (pH < 7.2) in ethylene glycol
    - Block metabolism
        - Fomepizole has a higher affinity for alcohol dehydrogenase
        - Initial loading dose of 15 mg/kg over 30 min, followed by 10 mg/kg IV q12h
        - Continue fomepizole until the toxic alcohol level is < 20 mg/dL and the metabolic acidosis is resolved
        - Ethanol can be used, but is difficult to titrate and has significant side effects such as CNS depression, GI irritation and hypoglycemia.
    - Cofactor administration
        - Administer folic/folinic acid (1 mg q4-6h) to patients with methanol poisoning as it helps shift metabolism to a nontoxic pathway
        - For ethylene glycol poisoning, treat with pyridoxine and thiamine
    - Hemodialysis
        - Best method to rapidly remove toxic acid metabolites and parent alcohols
        - Consider consulting nephrology if high anion gap metabolic acidosis or evidence of end-organ damage

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    - Chest XR from Radiopaedia.org, courtesy of Dr Ian Bickle, rID: 46487