Objectives: discuss the pathophysiology, presentation, diagnosis, and management of acetaminophen overdose.

Introduction: acetaminophen (APAP, Tylenol, paracetamol) was introduced in 1955. Since then it has become the most popular analgesic in the world, and the most common cause of ingested toxicologic poisoning in the US. It is also the most common cause of acute liver failure in the Western hemisphere (50% of all cases). The popular quip regarding APAP is “the drug is extremely safe… until it’s not”.

--Less than 4000mg every 24 hours in adults (80 mg/kg in children) is the maximum limit.

Metabolism and Pathophysiology - Testable stuff on exams!
Normal APAP levels: APAP is metabolized to sulfate and glucuronide conjugates → urinary excretion
Toxic levels of APAP: saturated safe pathways → shunting of APAP to accessory pathway → NAPQI (nasty little compound) made NAPQI causes oxidative injury to the liver which is irreversible and can quickly progress to liver failure.

Myth: chronic liver disease without alcoholism does NOT increase risk for APAP toxicity.

Stages of APAP Overdose
Stage I: < 24 hours. Nonspecific GI symptoms, possibly nausea/vomiting, lethargy, malaise. Some are asymptomatic. Laboratory studies are unremarkable.

Stage II: 24-72 hours. Evidence of hepatotoxicity. Elevated AST/ALT, bilirubin, PT/PTT. RUQ abdominal pain.

Stage III: 72-96 hours. Fulminant hepatic failure. Liver function tests peak during this time. All the signs and symptoms of acute liver failure with hepatic encephalopathy, jaundice, coagulopathy. AST/ALT will easily exceed >5-10,000, elevated PT/PTT and bilirubin, lactic acidosis, and renal failure.
(Please see our handout on “Hepatic Havoc: Acute liver failure” on our website for more details for management of patients with ALF).

Stage IV: >4 days. Either death occurs or complete resolution.

Diagnosis: serum acetaminophen level. Order on any patient with suspicion of overdose, either intentional or accidental. Other tests to grab: salicylates (often taken in combo), UDS, CBC, CMP. If the patient already exhibits signs of toxicity (Stage >1), order GGT, coagulation studies, lipase, ammonia.

The APAP level should be measured at 4 hours after time of ingestion, but often we are unsure of the exact time of ingestion. Therefore, if any suspicion for ingestion time being > 4 hours, immediately obtain APAP level upon arrival to ED and again at 4 hours following that.

The APAP level should be evaluated using the Rumack-Matthew Nomogram (see below) to determine need for NAC therapy. Note: the nomogram is not applicable to chronic APAP overdoses.

Obtaining a serum APAP level will result in the following scenarios:
1. The initial APAP level at 4 hours since time of ingestion is negative and patient is asymptomatic.
   a. Observe patient for extended period of time and remeasure at 4 hours again.
2. The initial APAP level at 4 hours since suspected time of ingestion is negative but patient has signs of hepatic toxicity.
   a. Begin NAC therapy and remeasure at 4 hours.
3. The APAP level drawn on arrival with unknown time of ingestion is negative.
   a. If patient has signs of hepatic toxicity, start NAC and re-draw level at 4 hours.
   b. If patient is asymptomatic, observe patient for extended period and repeat in 4 hours

Management
Activated Charcoal: Patients presenting <4 hours after a potentially toxic ingestion of APAP could benefit from this. As always, concern most be given for airway protection first.
-Charcoal has been studied in APAP overdose and has been effective in reducing serum APAP concentration and reduce liver injury.
**N-acetylcysteine (NAC)** is effective for preventing liver failure from APAP overdose. Studies have repeatedly shown its superior profile in reducing serious hepatotoxicity (<4%) and death are extremely rare (<1%) if NAC is given <8 hours from overdose. Mechanism? Unsure. Likely due to restoring glutathione stores. There are no placebo trials (try passing that through the IRB). However, there is no downside to giving NAC. Even if it is given in late presentations and/or patients with liver failure from unknown cause, NAC can reduce cerebral edema and improve hepatic function.

Adverse effects of NAC:
- Elevates the INR to <1.5 (interferes with analysis)
- Vomiting (~30%)
- Anaphylaxis (10-20% of patients).

If an allergic reaction occurs, treat it and continue the infusion. If anaphylaxis occurs (hypotension, airway concerns), the infusion should be stopped, and oral NAC given (usually safe). If oral route is deemed unsafe, call a toxicologist for further guidance because you are in some deep $#%^& to put it politely.

NAC can be given in pregnancy at the same dose.

**IV route > Oral route.** Both have been found to be basically equal but keep it simple and do IV. There is a lot of detail and ongoing research regarding the duration of the NAC protocol- do not worry about this. Start NAC at the proper dose and coordinate with pharmacy regarding later dosages. Therapy typically lasts for 20-72 hours.

**Disposition:** patients can be admitted to floor (Medical-Psychiatric unit) if hemodynamically normal, even with NAC infusion. If signs of hepatotoxicity, or risk of anaphylaxis from NAC, admit to ICU.

**Stopping NAC:** Only if all of the following are met- asymptomatic patient, APAP level nondetectable, serum transaminases have trended down or are normal.

**References:**