ACETAMINOPHEN TOXICITY:

TOXICITY:	• Metabolized by CYP2E1 to toxic intermediate (NAPQI)
LIVER TOXICITY	• AST/ALT can see ↑ within 24-30 hours • INR rises later, but indicates ↓ liver function • Death from severe liver failure can be delayed, prolonged ○ Most common cause of acute liver failure in NA, UK

PATIENTS AT RISK FOR APAP TOXICITY:

- All ages – acute and chronic
- Multiple OTC med users
- Chronic pain med users
- Codeine abusers
- Chronic alcoholics
- Malnourished
  - Eating disorders
- Concurrent CYP inducers

RISK ASSESSMENT:

ACUTE	**DOSE**	**ADULT**	> 7.5 - 10 g
		CHILD	> 200 mg/kg
	LABS	• AST, ALT, INR, SCr, anion gap, *clinical status*	
	TXT?	• Acetaminophen level > txt level on nomogram ○ 4 hour level earliest you can plot	
CHRONIC	**DOSE**	**ADULT**	> 10 g or 200 mg/kg over single 24-hr period > 6 g/day or > 150 mg/kg/day for > 2 days If risk factors: 4 g/day or > 100 mg/kg/day
		CHILD	> 200 mg/kg over single 24-hr period > 150 mg/kg/day for 48 hours > 100 mg/kg/day for 72 hours or longer
	LABS	• AST, ALT, INR, acetaminophen, SCr, *clinical signs*	
	TXT	• If ALT or AST x [APAP] > 10,000 may be more at risk for possible toxicity	

APPROACH TO TREATMENT:

- Activated charcoal if recent and acute
  - Massive ingestions – may need more than 1 dose
- N-acetylcysteine (NAC): indications
  - Acetaminophen level > treatment line, if acute
  - S/S of hepatic injury regardless of level
  - Early acidosis, coma following massive overdose (even prior to level)
- NAC effective in both early and late presentation
  - Prevents primary and secondary liver damage
- Liver transplant
  - Arterial pH < 7.3 on admission after initial fluid resuscitation **OR**
  - A combination of:
    - Severe, sustained coagulopathy (INR > 6.5) **AND**
    - Serum creatinine > 300 in patients with advanced encephalopathy (greater than grade III)

NAC DURATION OF TREATMENT:

- At end of 21 hour infusion, NAC can be discontinued if:
  - Serum acetaminophen level is undetectable **AND**
  - AST is normal and has not risen from baseline **AND**
  - INR is less than 1.5 **AND**
  - Serum creatinine is normal or at patient's baseline **AND**
  - Patient is clinically well
- If these criteria are not met, then NAC should be continued at 6.25 mg/kg/hr (150 mg/kg/24 h) and labs should be done every 12-24 hours, **until:**
  - Serum acetaminophen level is undetectable **AND**
  - Serum AST is normal or has significantly improved (ex// two consecutive declining levels and AST < 1000 IU/L) **AND**
  - INR is less than 1.5 **AND**
  - Serum creatinine is normal or at patient's baseline **AND**
  - Patient is clinically well

MASSIVE INGESTION:

- Early onset lactic acidosis 2° to inhibition of mitochondrial respiration
  - **Precedes** liver injury, not secondary to liver necrosis (as with late onset lactic acidosis)
- Also: inherited or acquired 5-oxoproline deficiency can result in acidosis without elevated lactate

SALICYLATES:

- NOTE: oil of Wintergreen (methyl salicylate)
  - Used as flavoring in cooking (100%), ingredient in topical rubs (10-30%) and in herbal liniments (white/red flower oil – 67%)
  - 1 mL of 98-100% v/v oil → 1400 mg ASA

TOXIC DOSE:

ACUTE	• Mild toxicity: 150 – 200 mg/kg • Severe: 300 – 500 mg/kg
CHRONIC	• > 100 mg/kg/day for > 2 days

CLINICAL EFFECTS AND TOXIC MECHANISM:

- Direct GI effects → N/V → **volume depletion**
- Interference with cochlear cells → **tinnitus**
- Direct stimulation of resp. centre → ↑ RR → **resp. alkalosis**
- Uncoupling of oxidative phosphorylation in mitochondria →
  - **Metabolic acidosis**
  - Low brain glucose → **confusion, agitation, seizures**
  - Heat production → **fever**
- Increased capillary permeability → **cerebral & pulmonary edema**
- Alteration of platelet function → **↑ INR**
- **Death**

ASA ASSESSMENT:

- Exposure history (time, chronicity, dose, product, formulation)
- Clinical effects
- Serial serum salicylate levels in conjunction with ABGs & AG
  - Cannot rely on only one level
  - Cannot use a nomogram

APPROACH TO TREATMENT:

- GI decontamination
- **GASP**
  - **Glucose** (D50 for mental status changes)
  - **Alkali** (bicarbonate infusion to enhance urinary excretion, goal urine pH 7.5 – 8)
  - **Saline** (rehydrate, often several litres)
  - **Potassium** (difficult to alkalnize urine if hypokalemic)
- Hemodialysis
  - Serum salicylate > 6-7 mmol/L, regardless of status **OR**
  - **ANY** of the following, regardless of level:
    - Acidemia, hypotension unresponsive to fluid/bicarbonate/supportive care
    - Sick pt– coma, seizures, hyperthermia, renal failure
    - Deteriorating clinical condition despite support

MONITORING & ENDPOINT:

- Serum salicylate levels every 2 hours
  - ENDPOINT: serum salicylate < 1.5 mmol/L (x 2 levels)
- Lytes, gases, urine pH
  - Serum pH 7.45 – 7.55 (do not exceed 7.55)
    - ENDPOINT: pH ≥ 7.45 with normal PCO2
  - Serum potassium 3.5 – 4.5
  - Urine pH 7.5 – 8, urine output 2-3 mL/kg
- CNS normal

PITFALLS TO MANAGEMENT:

- Unrecognized salicylate presence
- Relying on single ASA level
- Inadequate fluid replacement (not enough, wrong type)
- Not correcting hypokalemia
- Not giving glucose for altered mental status
- Hypoventilation caused by sedation/co-ingesants
- Failure to hyperventilate post-intubation
- Delayed dialysis
- Premature discharge

NSAIDs:

- Acute overdose commonly only results in mild GI and CNS symptoms
- Toxicity is dose-related
- Massive ingestions can result in:
  - Coma
  - Hypotension
  - Metabolic acidosis
  - Acute renal failure
- Death from NASID overdose alone is rare

MECHANISM OF TOXICITY:

- Decrease prostaglandin synthesis by inhibition of COX-1, COX-2 →
  - GI effects (also due to direct irritation)
  - Renal toxicity
- Metabolic acidosis may be from:
  - Weak acid metabolites
  - Hypotension
  - Hypoxia
- Mechanism of neurologic toxicity?

TOXIC DOSE:

IBUPROFEN	**CHILD**	• < 200 mg/kg in children → mild GI symptoms • More sensitive to CNS effects than adults • Severe toxicity with > 400 mg/kg
	ADULT	• Most cases of life-threatening toxicity > 20 g
NAPROXEN	**ADULT**	• 10-25 g → only GI symptoms • Limited data

TREATMENT:

- Symptomatic and supportive
  - IV fluids if hypotensive
  - Intubation as needed
  - Acidosis usually responds to fluids
- Labs should include: lytes, renal function, ASA and acetaminophen
- Asymptomatic patients should be observe for 4-6 hours
- Symptomatic patients should be observed until all sx resolve

PEARLS FOR OTC ANALGESICS:

- Common substances in poisonings and overdoses in all ages
- Consider patient may refer to all analgesics by their favorite one
  - Ex// call everything Tylenol when it is Advil
- Always check salicylate, acetaminophen levels even if the patients insist it was ibuprofen
- All of these agents are on the differential anion gap acidosis
  - MUDPILESCAT

PEARLS FOR ACETAMINOPHEN:

- Common overdose – both intentional and unintentional
- Acetaminophen level should be done on all overdose patients
- Patients may be asymptomatic initially
- Death from severe liver failure can be delayed, prolonged
  - Most common cause of acute liver failure in North America and the UK
- N-acetylcysteine is useful in early as well as late presentations

PEARLS FOR SALICYLATES:

- Work up all anion gaps
- Glucose may correct salicylate delirium
- If you cannot get the urine alkaline, check potassium
- Get nephrology involved early
- Get a second level
- Monitor levels, gases, lytes closely
- BE AFRAID !!!