Forensic & Toxicology Team

MED 433

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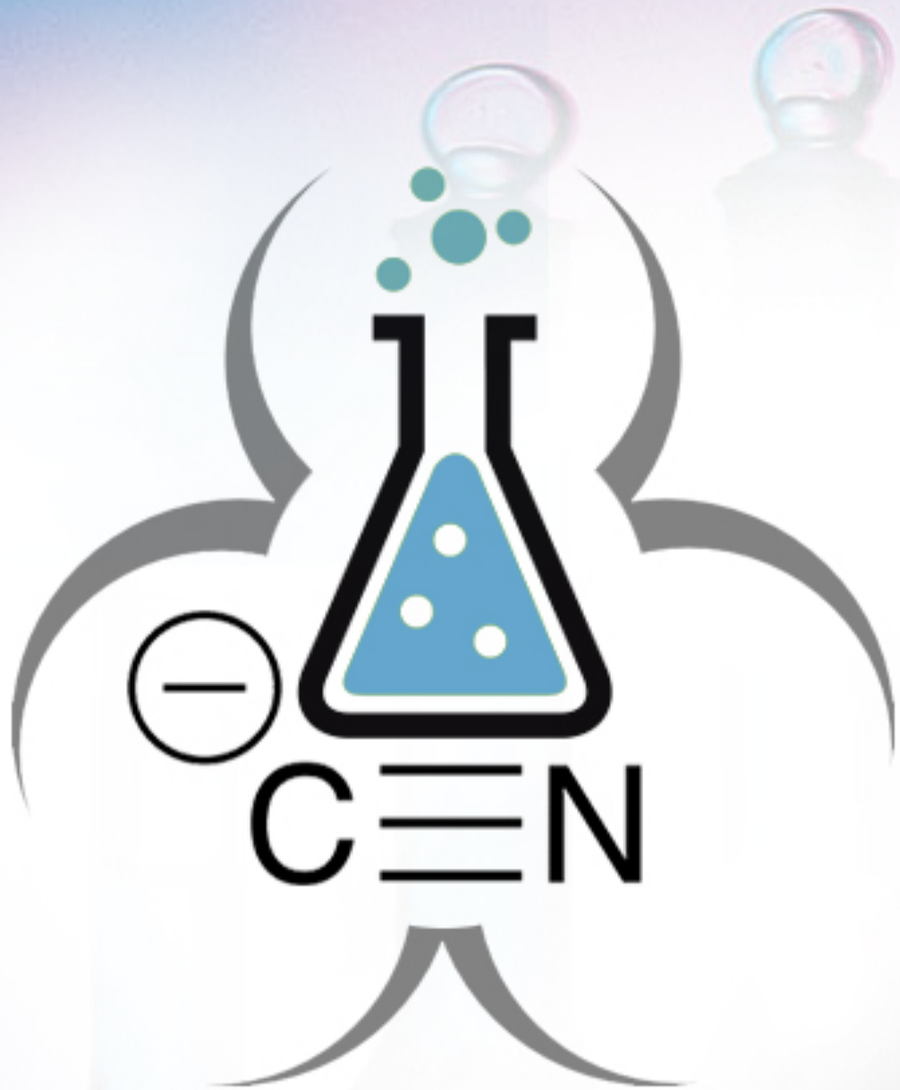



# Lecture 2: Acetaminophen Overdose

# Objectives

I. Know the potential toxic dose of APAP according to age

II. Know the symptoms and signs of APAP OD

III. Know the indications of NAC therapy

# Abbreviations

| | | | |
|---|---|---|---|
| **APAP** | Acetaminophen | **NAC** | N-Acetylcysteine |
| **NAPQI** | N-acetyl-p-benzoquinone imine | **AST** | Aspartate transaminase |
| **GSH** | Glutathione | **ALT** | Alanine transaminase |
| **CYP** | P450 cytochromes | **OD** | Over dose |

# Acetaminophen

- ✓ Also known as Paracetamol or N-acetyl-p-aminophenol (APAP)
- ✓ Trade names: Tylenol - Panadol.
- ✓ Approved as an Over-the-counter (OTC) drug since 1960
- ✓ 1st cases of hepatic damage after APAP OD 1966

## ✪ Therapeutic dose

- **Children:** 10-15 mg/kg/dose
- **Adults:** 325-1000 mg/dose
  - ✓ Every 4-6 hours, with a **maximum of 4g/day**

## ✪ Toxic dose

- **Children:**

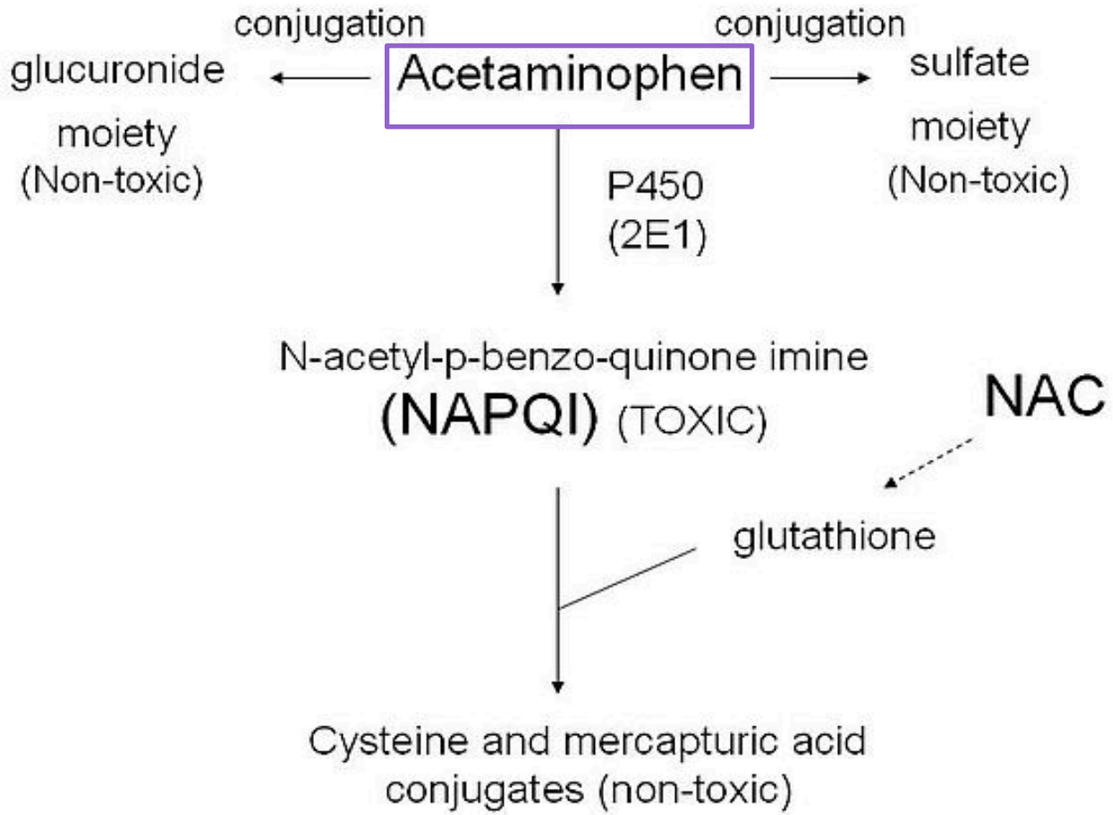
| < 12 months | 1 – 6 y | 1 – 6 y with risk factors | 7 – 12 y |
|---|---|---|---|
| 150 mg/kg | 200 mg/kg | 150 mg/kg | 150 mg/kg |

- **Adults:** More than 6 g (1)

(1) 60% chance of liver damage

## ✪ Normal Metabolic Pathway

| | | |
|---|---|---|
| **90%** | **(40-65%)** | Hepatic glucuronide conjugation |
| | **(20-45%)** | Hepatic sulfate conjugation |
| **5%** | Excreted unchanged in the urine | |
| **5-15%** | Oxidation by P450 cytochromes (CYP 2E1, 1A2, and 3A4) to **NAPQI (TOXIC)** ⬇ Glutathione (GSH) combine with NAPQI (1) ⬇ Cysteine/mercaptate conjugates (NONTOXIC) | |




## ✪ In Over Dose

**<u>Saturation</u>** of glucuronidation and sulfation → P450 takes over hence **NAPQI** increases → Rate and quantity of NAPQI formation overwhelms GSH supply and regeneration → 1- Elimination of NAPQI prolonged; 2- Free NAPQI binds critical cell proteins with sulfhydryl groups

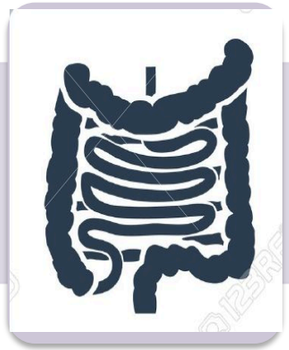
cellular dysfunction and cell death (2) (3)

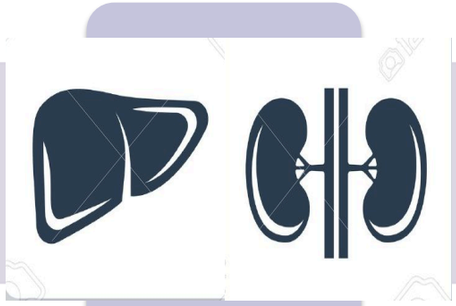
(1) Normally NAPQI is detoxified by reduced GSH (glutathione) and thiol-containing substances
(2) Animal models: hepatotoxicity when GSH stores fall <30% of baseline
(3) Cellular death and hence liver enzymes will increase

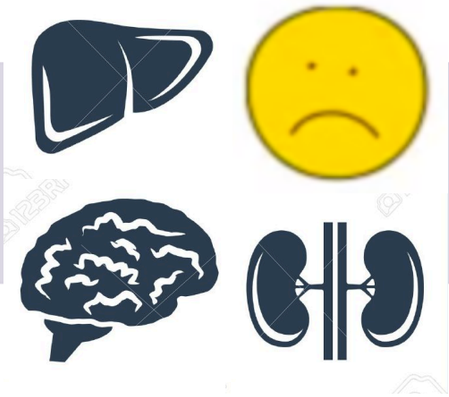
## ✪ Factors which adversely affect APAP metabolism

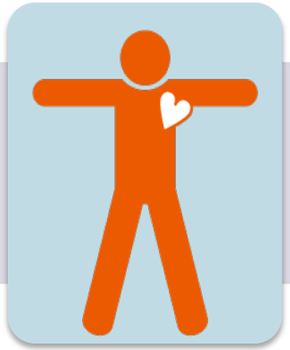
- ✓ Up regulation (i.e. induction) of CYP 2E1 enzyme activity
- ✓ Decreased glutathione stores (How?)  Eating - NAC
- ✓ Frequent dosing interval of APAP
- ✓ Prolonged duration of excessive dosing
- ✓ Smoking, barbituates, rifampin, carbamazepine, phenytoin, INH + ethanol
- ✓ Use of APAP by alcoholics has not been associated with higher risk of liver injury in prospective trials

## ✪ Clinical manifestation









| Stage I | Stage II | Stage III * | Stage IV |
|---|---|---|---|
| 0.5-24 h | 24-48 h | 48-96 h | 4-14 d |
| Nausea/Vomiting, anorexia or asymptomatic | 1- resolution of stage I<br>2- RUQ pain<br>3- elevation of PTT, INR bilirubin+ enzymes. (at the latest by **36h)** | Coagulopathy, peaking of enzymes, Acidosis, Hypoglycemia, Bleeding diathesis, Jaundice / anuria / cerebral edema, Coma, ARF in 25% of pts with hepatotoxicity.<br>* Fulminant hepatic failure. | Resolution |

## ✪ Diagnosis

- ✓ Serum APAP level should be measured between **4 and 24** hours after ingestion.
- ✓ The value obtained should be evaluated according to the Rumack-Matthew nomogram for determining the risk of hepatotoxicity and the need for NAC therapy.

## ✪ The Rumack-Matthew nomogram

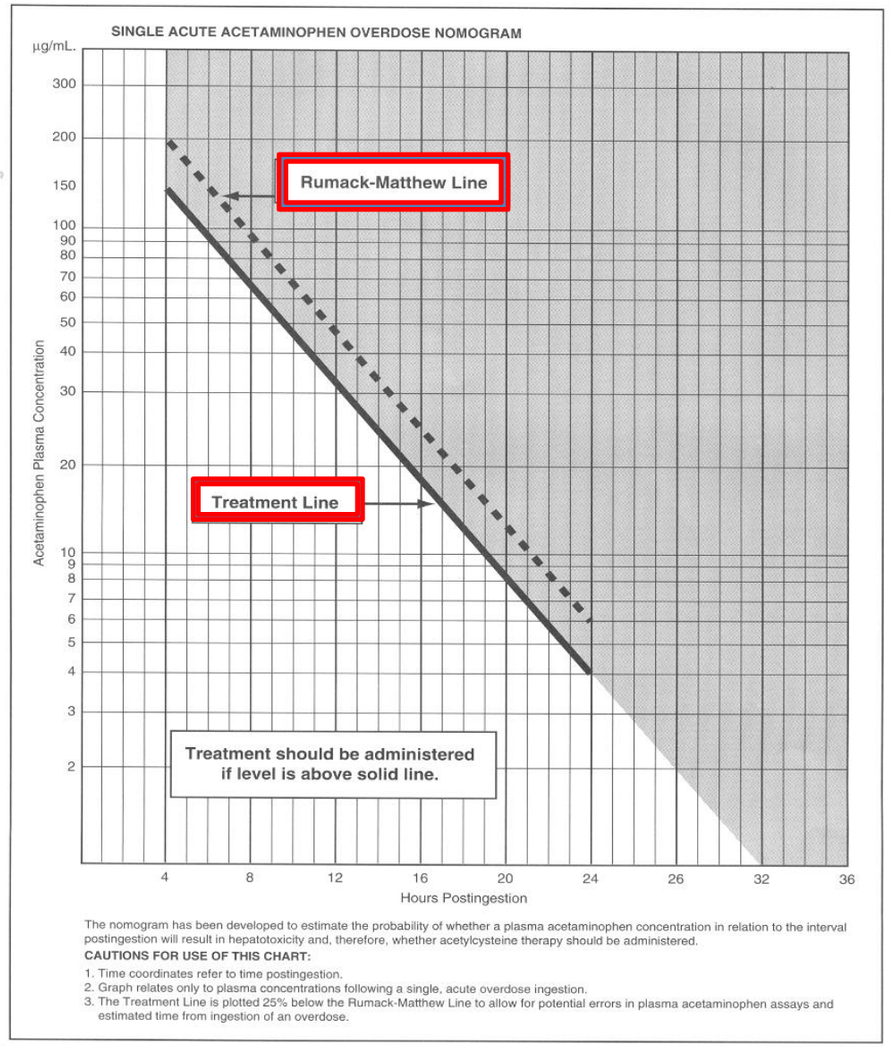
- ✓ APAP level to predict which patients will develop an AST elevation >1000 IU/L **without antidotal treatment (4)**
- ✓ Derived from acute ingestion of immediate release acetaminophen
- ✓ Begins at 4 h post ingestion
- ✓ Recommended line of treatment has been lowered by 25% to increase its sensitivity and safety.

**What percent of pts whose APAP level falls above the upper line of the Rumack-Matthew nomogram will develop hepatotoxicity? (1)**

**60%**

**Which lab test is the most sensitive for early detection of hepatotoxicity?**

**AST**




(1) defined as elevation of the plasma transaminases above 1,000 U/L
(2) We can't measure the drug level before **4 hours**
(3) Any patient that comes after 24hrs of ingestion with symptoms or any detectable APAP you start him on NAC
(4) If you already started NAC the Rumack-Matthew-nomogram becomes useless

## ✪ Toxicology History

- ✓ Often incomplete, unreliable or unobtainable
- ➥ Source: Patient, friends, family, EMS or pill containers
- ➥ Past medical history: liver/renal disease, concurrent medications, previous overdoses, psychiatric hx, substance abuse
- ➥ 5 W's of toxicology:

| WHO | WHAT | WHEN | WHERE | WHY |
|---|---|---|---|---|
| • Age, weight, relation to others. | • Name and dose of medication, coingestants and amount ingested | • Time of ingestion, single vs. multiple ingestions. | • Route of ingestion, geographical location (1) | • Intentional vs. unintentional |

## ✪ Management Guidelines(3):

**A**irway → **B**reathing → **C**irculation → **D**econtamination (Activated Charcoal) (2) → **F**ind antidote (NAC)

- ✓ NAC should optimally be given within 8 to 10 hours after ingestion
- ✓ More delayed therapy is associated with a progressive increase in hepatic toxicity
- ✓ Some benefit may still be seen 24 hours or later after ingestion

**(1) Location may be important for environmental or occupational exposures**
**(2) Activated Charcoal will ADSORBE the drug**
**(3) When the patient comes late There is no indication for Elimination of the drug from the systemic circulation in case of Acetaminophen toxicity**

## ✪ N-Acetylcysteine (NAC) (Antidote)

### ➥ Action

| Early | Late (12-24 h) |
|---|---|
| 1. Prevents binding of NAPQI to hepatocytes<br>2. GSH precursor → increases GSH stores<br>3. Increases sulfation metabolism of APAP → less NAPQI formed<br>4. Reduces NAPQI back to APAP (at least in animal models)<br>5. Sulfur group of NAC binds and detoxifies NAPQI to cysteine and mercaptate conjugate (= GSH substitute) | 1. Modulates the inflammatory response<br>2. Antioxidant, free radical scavenger<br>3. Reservoir for thiol groups (i.e. GSH)<br>4. Impairs WBC migration and function → anti-inflammatory<br>5. Positive inotropic and vasodilating effects (NO) → improves microcirculatory blood flow and O2 delivery to tissues<br>6. Decreases cerebral edema formation, prevents progression of hepatic encephalopathy and improves survival |

### ➥ Indications for NAC

- ✓ APAP level above the treatment line
- ✓ History of significant APAP ingestion presenting close to **8h**(1) (give while waiting for level)
- ✓ All APAP ingestions who present late >24h with either **detectable APAP** or **elevated transaminases**
- ✓ Chronic ingestions (>4g/day in adult, >120mg/d in child) with elevated transaminases
- ✓ History of exposure and Fulminant Hepatic Failure (FHF)

## ✪ Poor prognostic indicators

- ✓ pH <7.3 (2 days after OD, after fluids)
- ✓ Hepatic encephalopathy
- ✓ PT >1.8 times normal.
- ✓ Serum creatinine >300mmol/L
- ✓ Coagulation factor VIII/V ratio of >30

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1) **Optimally it should be given 8-10 hours after the ingestion and if the patient came after that period you should give NAC while waiting for the drug level when the patient is symptomatic or if APAP overdose is confirmed by clinical assessment.**
2) **NAC is also given in case of Fulminant Hepatic Failure outside the context of APAP toxicity due to its anti-inflammatory action (e.g. in hepatitis)**

## ✪ Paracetamol (acetaminophen) poisoning Vale, JA, Proudfoot, AT. *Lancet 1995; 346:547*

| | Treatment delay below 10 hours | Treatment at 10 to 24 hours |
|---|---|---|
| **Mortality** | ✓ No deaths | ✓ 200 patients had a 2.0 to 7.4 percent mortality,<br>✓ 5.3 to 10.7 mortality in 85 patients who received only supportive care. |
| **liver damage (defined as a plasma ALT or AST level above 1000 IU/L)** | ✓ 1.6 to 10 percent incidence | ✓ 27 to 63 per cent in patients treated at 10 to 24 hours<br>✓ 58 to 89 percent in those receiving supportive care |

## ✪ Improved outcome of Paracetamol-induced fulminant hepatic failure by late administration of NAC Lancet 1990 Jun 30;335(8705):1572-3]

The influence of NAC, administered at presentation to hospital, on the subsequent clinical course of 100 patients who developed APAP-induced fulminant hepatic failure was analyzed retrospectively

- ✓ Mortality was 37% in patients who received NAC 10-36 h after the overdose, compared with 58% in patients not given the antidote
- ✓ In patients given NAC, progression to grade III/IV coma was significantly less common than in those who did not receive the antidote (51% vs 75%)

## ✪ XR tablets

- ✓ Several studies show that elimination of extended and immediate-release acetaminophen are nearly identical after 4 hours.
- ✓ Some case reports APAP levels falling above the treatment nomogram line as late as 11-14 hours post ingestion of the extended-release preparation

# Clinical Cases

| 1- 15 month old child (wt. 10 kg) accidentally took full bottle of Tylenol 60cc(120mg/5cc) 30 mint ago. Clinically looked well. What will be your treatment plan: |
|---|
| A. Give Ipecac STAT |
| B. Give 1g/kg activated charcoal |
| C. Insert OGT and perform gastric lavage |
| D. Should be observed for 4h then to do drug level |
| **E. None of the above** |

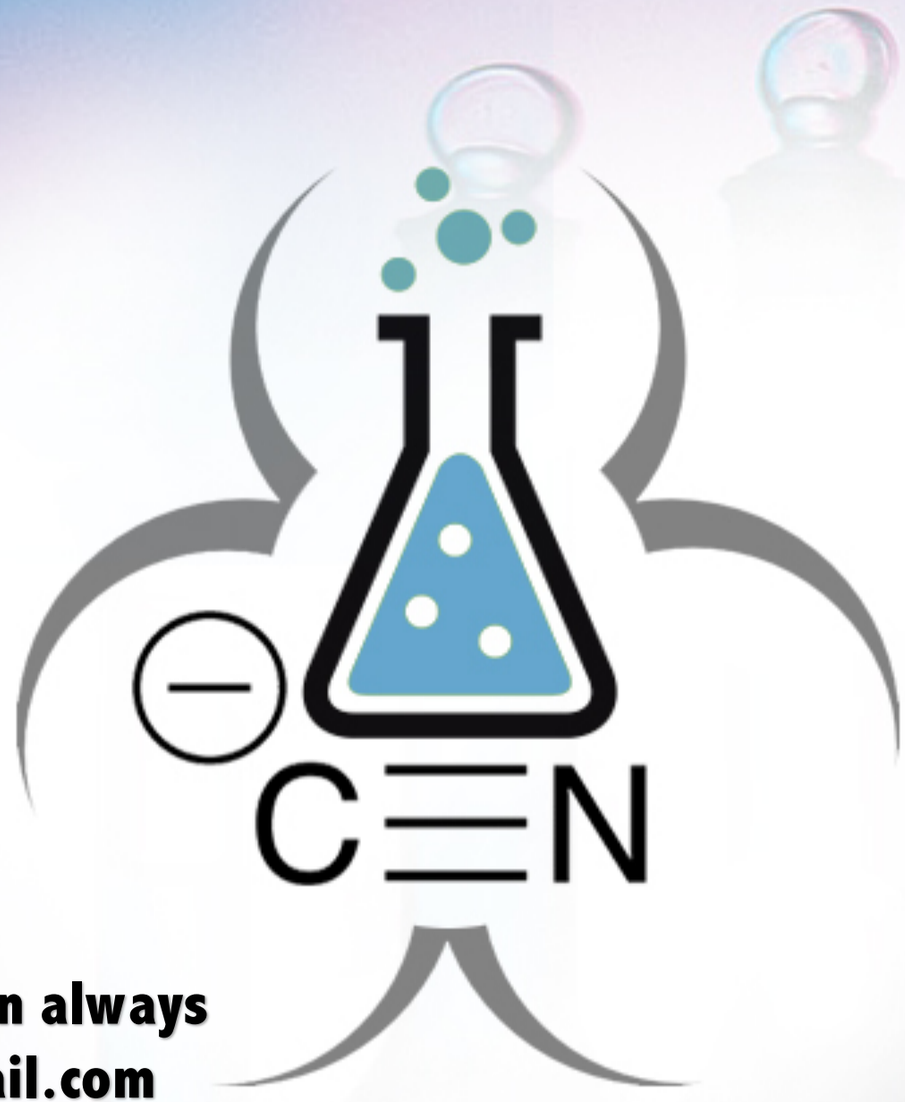
[ (120÷5) × 60 ] ÷ 10 = **he took 144 mg**
*Toxic dose is 200 mg for his age group

| 2- A mother brought her 4 M (5 kg) old son who was febrile for the last 3 days . She was giving him Tylenol (120mg/5 ml) 7ml every 4 h for the last 3 days, she found him today more lethargic, vomiting occasionally, clinically, ill looking slightly jaundiced, afebrile, no meningeal signs, mild injected throat, CSF was obtained & was not suggestive of meningitis. What will be your next step: .2 |
|---|
| **A. Obtain CBG, LFT, PT, PTT, INR, drug level if abnormal start NAC** |
| B. Give activated charcoal immediately |
| C. Admit for observation |
| D. D/C home, most likely it is related to current URTI |

| 3- 19 years old girl brought to ED with GCS 8 following drug ingestion (empty bottle of Tylenol was found in her room). What will be your first response .3 |
|---|
| A. 1g/kg activated charcoal STAT |
| **B. Orotracheal intubation** |
| C. Observation for 4 h |
| D. Do CBC, CBG, PT, PTT, INR, Drug level |
| E. NAC loading dose followed by infusion over 24 h |

| 4- 3 y old boy with accidental Tylenol ingestion on NAC for high drug level, after 48 h course LFT ,INR are high. What will be your recommendation: .3 |
|---|
| A. D/C NAC if drug level undetectable |
| B. D/C NAC and repeat LFT, INR, drug level after 4h |
| **C. Continue on NAC until all his labs become normal** |
| D. D/C NAC, most likely it is secondary to concurrent viral illness |

| 5- 20 yr old pregnant girl ingested 20g of Tylenol in a suicidal gesture 36h ago because she found out it is too late for her to have an abortion. Her APAP is <10 and her AST is 90 |
|---|
| How will you manage her medically? |
| **Management is the same in case of APAP toxicity.** |



**If you have any questions You can always contact us at : forensic433@gmail.com**

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