Acetaminophen overdose

N -acetyl-p-aminophenol (APAP)

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Objectives

- By the end of this lecture, participants should be able to:
- Know the potential toxic dose of APAP according to age
- Know the symptoms and signs of APAP OD
- Know the indications of NAC therapy

APAP

- Acetaminophen has been approved for OTC use since 1960
- 1st cases of hepatic damage after APAP OD 1966
- Therapeutic dose of acetaminophen is 10-15 mg/kg/dose in children and 325-1000 mg/dose every 4-6 hours in adults, with a maximum of 4g/day

Toxic dose of APAP

- Children:
  - < 12 months 150 mg/kg
  - 1 – 6 y 200 mg/kg
  - 1 – 6 y with risk factors 150 mg/kg
  - 7 – 12 y 150 mg/kg
- Youth & Adult
  - 7.5 - 10 g

Metabolic Pathways

- Hepatic glucuronide conjugation(40-65%)
- Hepatic sulfate conjugation(20-45%)

90%

→ inactive metabolites excreted in the urine.

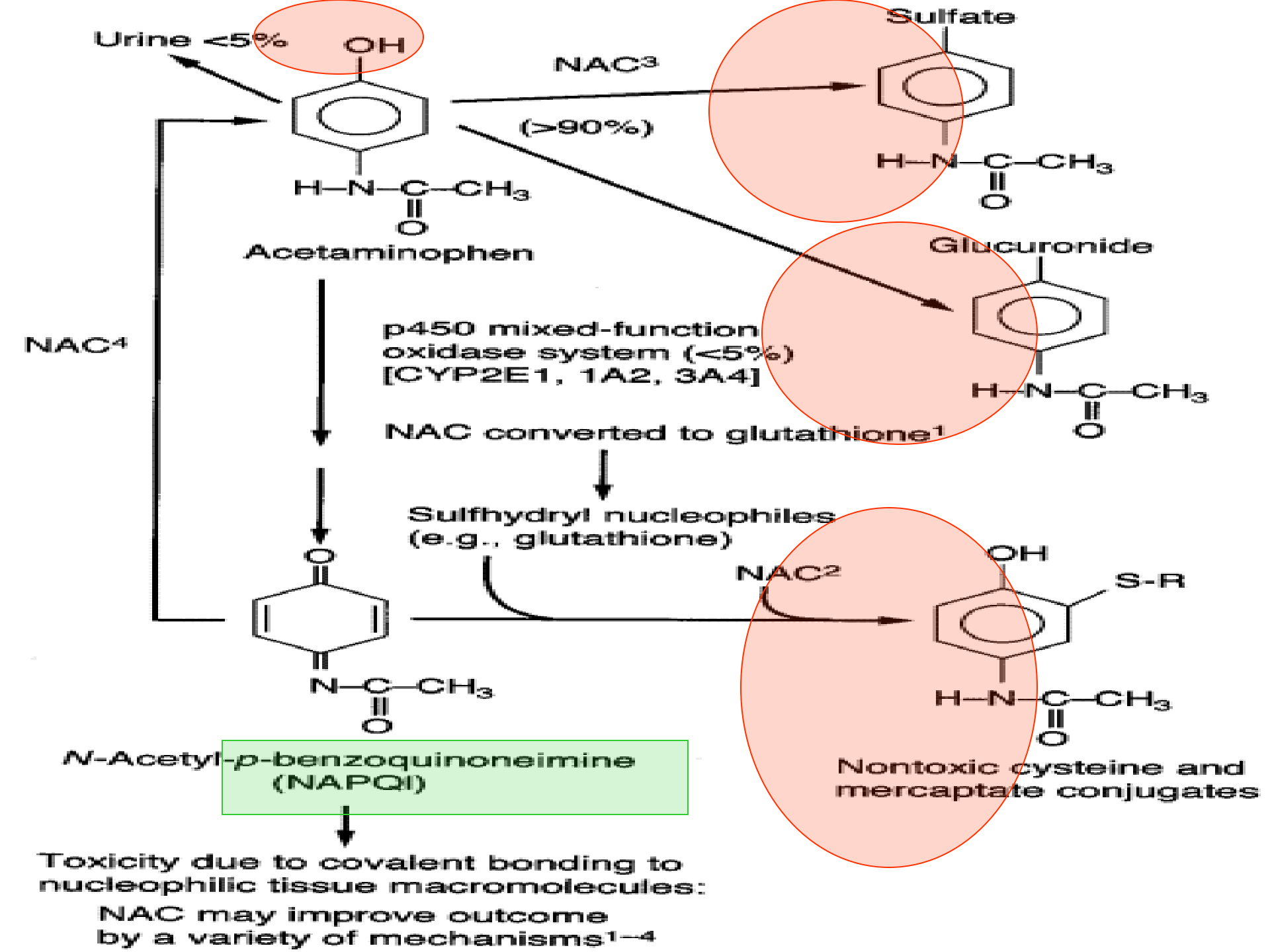
- Excretion of unchanged APAP in the urine (5%).

- Oxidation by P450 cytochromes (CYP 2E1, 1A2, and 3A4) to **NAPQI** (5-15%)

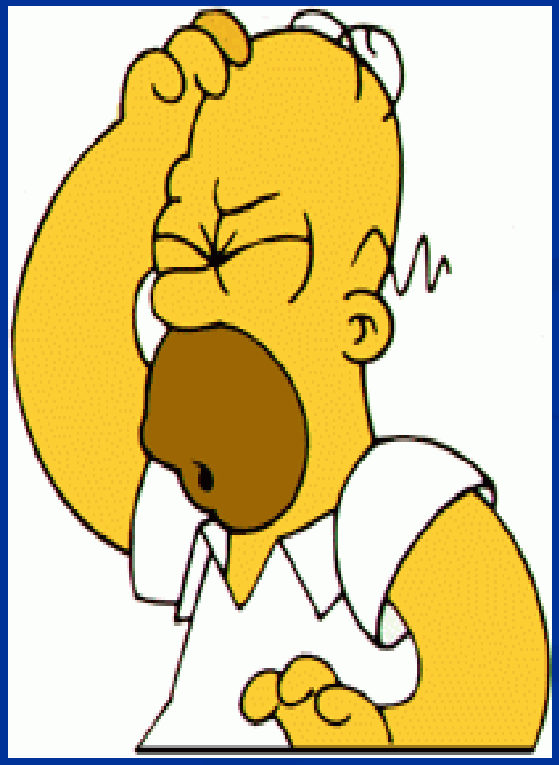
  → GSH combines with NAPQI

  → nontoxic cysteine/mercaptate conjugates

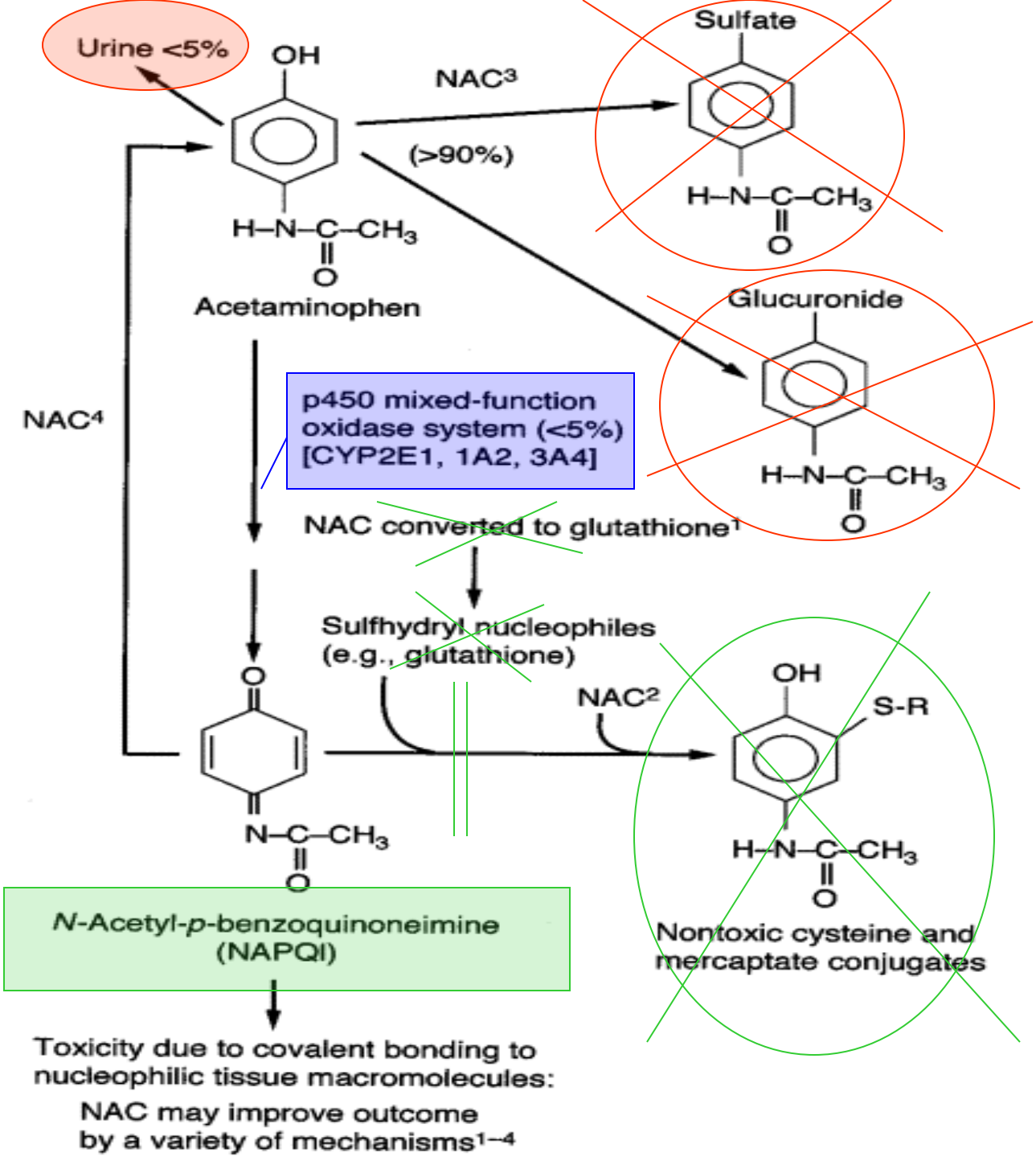
  → excreted in urine.


Urine <5%
OH
NAC3
(>90%)
Sulfate
H–N–C–CH3
O
Acetaminophen
Glucuronide
NAC4
p450 mixed-function
oxidase system (<5%)
[CYP2E1, 1A2, 3A4]
NAC converted to glutathione1
Sulfhydryl nucleophiles
(e.g., glutathione)
NAC2
S-R
N–C–CH3
N-Acetyl-p-benzoquinoneimine
(NAPQI)
Nontoxic cysteine and
mercaptate conjugates
Toxicity due to covalent bonding to
nucleophilic tissue macromolecules:
NAC may improve outcome
by a variety of mechanisms1–4

What happens in OD ?



- Saturation of glucuronidation and sulfation pathways
- Amount of APAP metabolized by p450 cytochromes to **NAPQI** increases
- Normally NAPQI is detoxified by reduced **GSH** (glutathione) and **thiol-containing substances**
- In OD: rate and quantity of NAPQI formation overwhelms GSH supply and regeneration:
  - → elimination of NAPQI prolonged
  - → free NAPQI binds critical cell proteins with sulfhydryl groups
  - → cellular dysfunction and cell death.
- Animal models: hepatotoxicity when GSH stores fall <30% of baseline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Factors which adversely affect APAP metabolism

- Up regulation (i.e. induction) of CYP 2E1 enzyme activity
- Decreased glutathione stores
  - Eating
  - NAC
- Frequent dosing interval of APAP
- Prolonged duration of excessive dosing

(Kuffner et al. 2001)

Clinical manifestation

- I 0.5-24h — n/v, anorexia, asymptomatic
- II 24-48 h — resolution of stage I sxs
  RUQ pain, elevation of PTT, INR, bili + enzymes (at the latest by **36h**)
- III 48-96h — coagulopathy, peaking of enzymes, acidosis, hypoglycemia, bleeding diathesis, jaundice, anuria, cerebral edema, coma. ARF in 25% of pts with hepatotoxicity
- IV 4-14d — resolution

Diagnosis

- In the patient with a history of APAP overdose, a 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

Toxicological History

- Often incomplete, unreliable or unobtainable
- Sources – Patient, friends, family, EMS,or pill containers
- PMHx, liver/renal disease, concurrent medications, previous overdoses, PΨHx, substance abuse

The 5W's of toxicology

- Who – pt's age, weight, relation to others
- What – name and dose of medication, coingestants and amount ingested
- When – time of ingestion, single vs. multiple ingestions
- Where – route of ingestion, geographical location
- Why – intentional vs. unintentional

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

AST

Management Guidelines

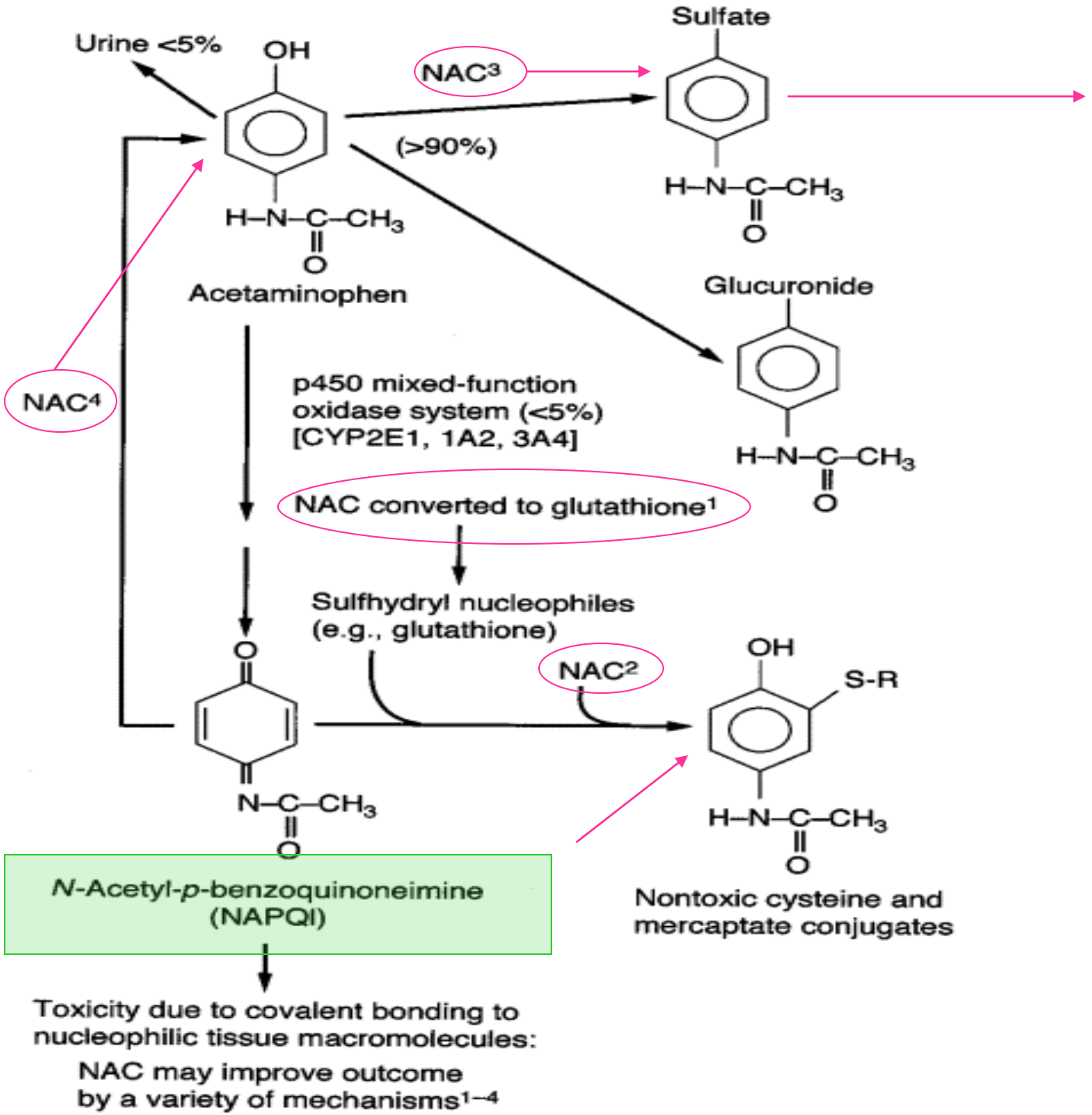
- Airway
- Breathing
- Circulation
- Decontamination
  - AC
- Find antidote
  - NAC

NAC

- Early → Prevents binding of NAPQI to hepatocytes
- GSH precursor → increases GSH stores
- Increases sulfation metabolism of APAP → less NAPQI formed
- Reduces NAPQI back to APAP (at least in animal models)
- Sulfur group of NAC binds and detoxifies NAPQI to cysteine and mercaptate conjugate (= GSH substitute)

NAC

- Late (12-24h) → Modulates the inflammatory response
- Antioxidant, free radical scavenger
- Reservoir for thiol groups (i.e. GSH)
- Impairs WBC migration and function → antiinflammatory
- Positive inotropic and vasodilating effects (NO) → improves microcirculatory blood flow and O2 delivery to tissues
- Decreases cerebral edema formation, prevents progression of hepatic encephalopathy and improves survival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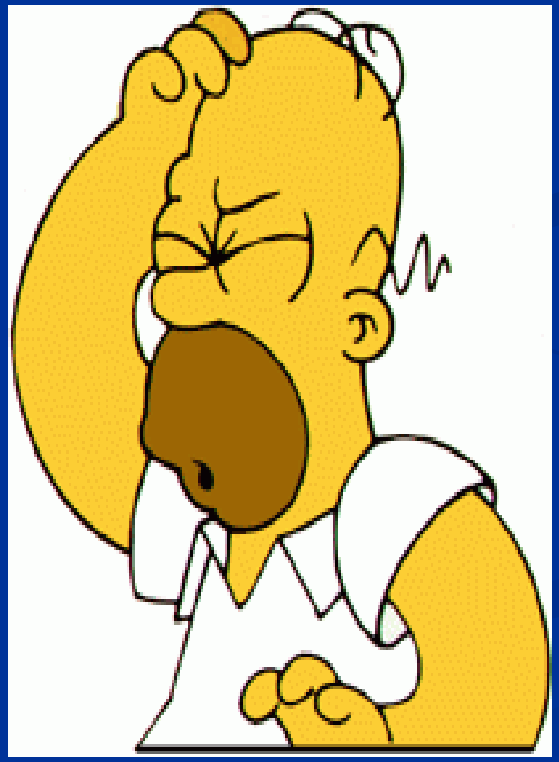
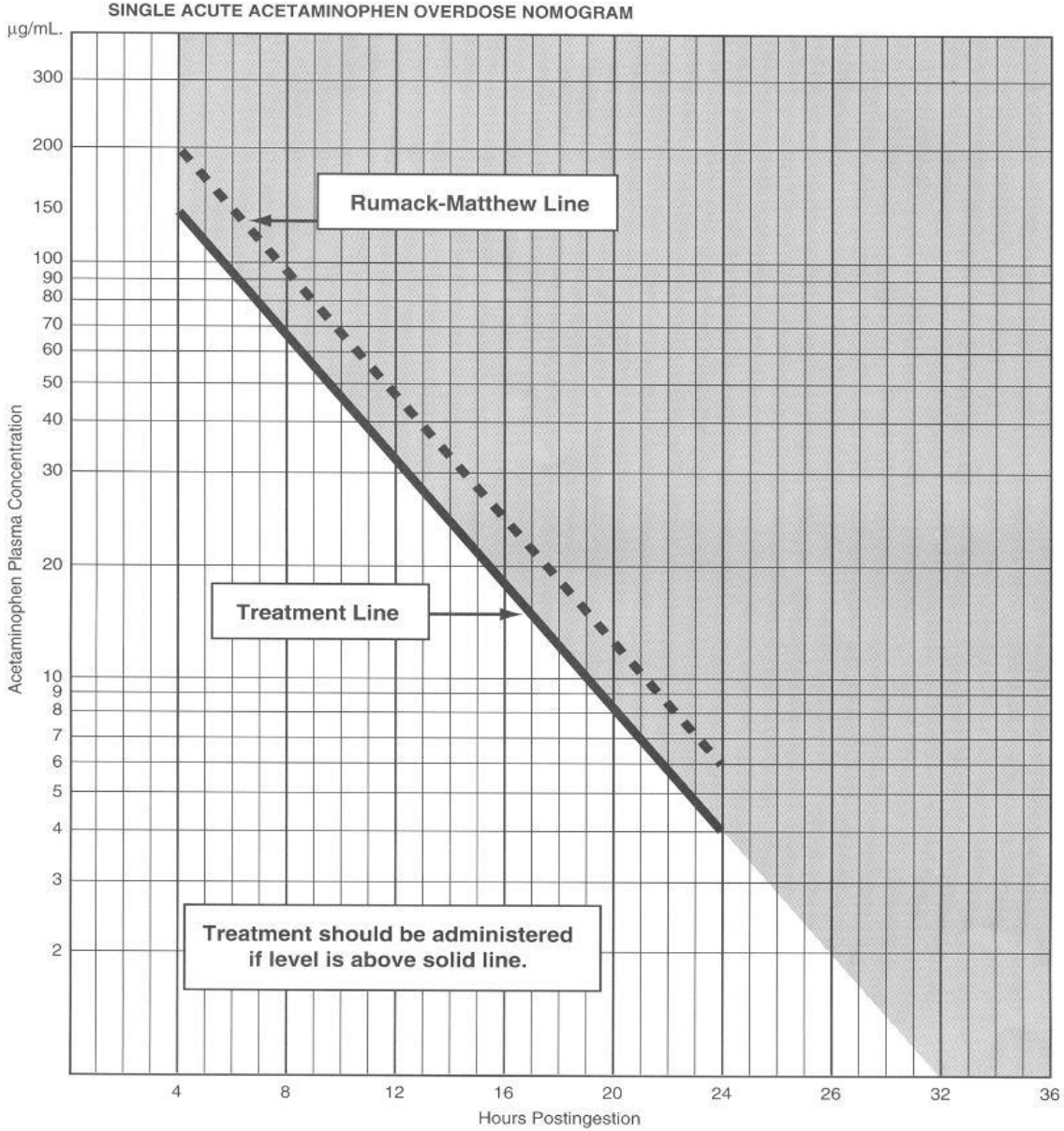
NAC

- 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

What is the Rumack-Matthew nomogram?



SINGLE ACUTE ACETAMINOPHEN OVERDOSE NOMOGRAM



The nomogram has been developed to estimate the probability of whether a plasma acetaminophen concentration in relation to the interval postingestion will result in hepatotoxicity and, therefore, whether acetylcysteine therapy should be administered.

CAUTIONS FOR USE OF THIS CHART:

1. Time coordinates refer to time postingestion.
2. Graph relates only to plasma concentrations following a single, acute overdose ingestion.
3. The Treatment Line is plotted 25% below the Rumack-Matthew Line to allow for potential errors in plasma acetaminophen assays and estimated time from ingestion of an overdose.

Rumack-Matthew nomogram

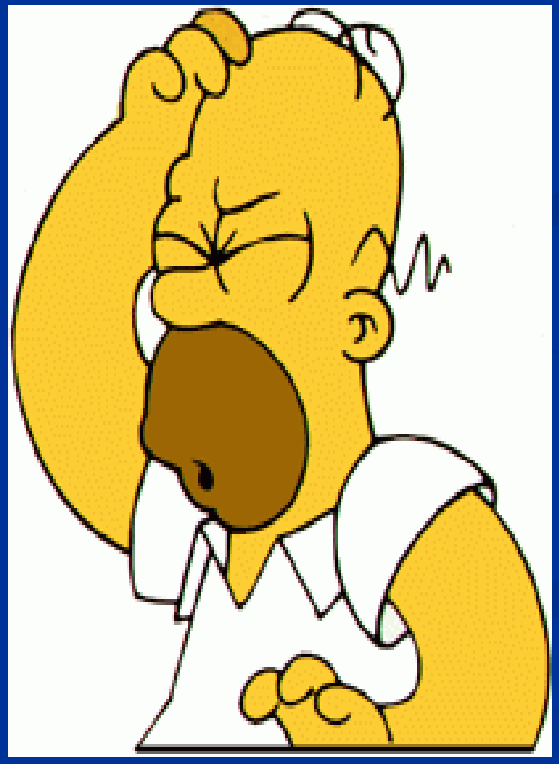
- APAP level to predict which patients will develop an AST elevation >1000 IU/L with out antidotal treatment
- Derived from acute ingestion of immediate release acetaminophen
- Begins at 4 h post ingestion
- Recommended line of treatment has been lowered by 25% to increase its sensitivity

What percent of pts whose APAP level falls above the upper line of the Rumack-Matthew normogram will develop hepatotoxicity?

(defined as elevation of the plasma transaminases above 1,000 U/L)

60%

When to give NAC?



Indication for NAC

- APAP level above the treatment line
- Hx of significant APAP ingestion presenting close to 8h (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
- Hx of exposure and FHF

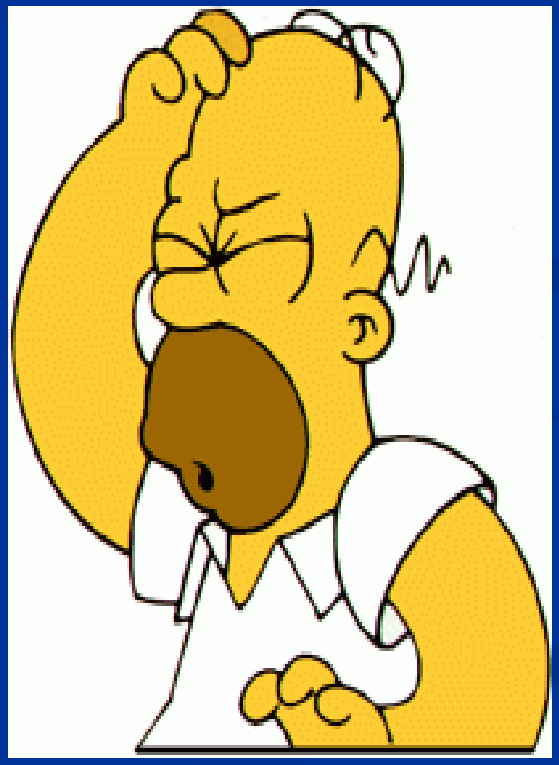
Poor prognostic indicators

- 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

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 normogram line as late as 11-14 hours post ingestion of the extended-release preparation

Short cases



- 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

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- 19 y 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

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

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- 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:

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

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- 20 yr old pregnant girl ingested 20g of Tylenol in a suicidal gesture 36h ago. Her APAP is <10 and her AST is 90
- How will you manage her medically?
- She asks you whether her baby will have any defects?

Questions ??


WE HAVE TWO OPTIONS. EITHER AN EVIDENCE-BASED TREATMENT OR AN EXCITING, RISKY ALTERNATIVE.
Christin Almer

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

- No deaths in 169 patients with a treatment delay below 10 hours
- In contrast, 200 patients treated at 10 to 24 hours had a 2.0 to 7.4 percent mortality, which was still lower than the 5.3 to 10.7 mortality in 85 patients who received only supportive care.
- There was a 1.6 to 10 percent incidence of liver damage (defined as a plasma ALT or AST level above 1000 IU/L) when the treatment delay was less than 10 hours
- Comparable values were 27 to 63 percent in patients treated at 10 to 24 hours and 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%)