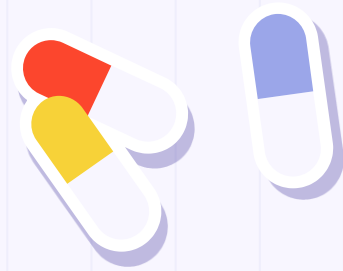


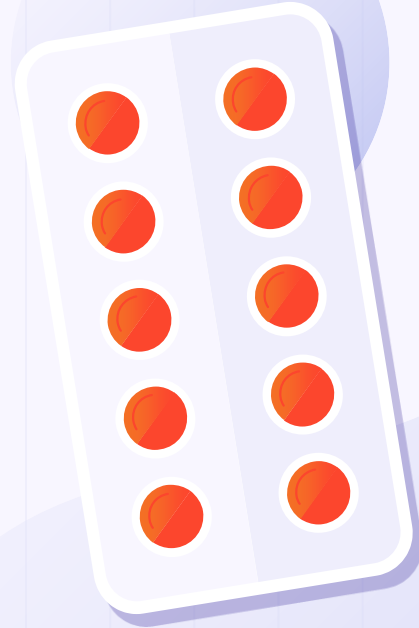
Acetaminophen Toxicity

Zaid Kofahi & Fares Habboub



What is acetaminophen

Acetaminophen (N-acetylp-aminophenol; APAP; paracetamol)



ARACHIDONIC ACID PATHWAY

NSAIDs 



Cyclooxygenase pathway

Constitutive Homeostatic

COX1

COX2

Inducible Pro-inflammatory

PGG2

PGH2

PGD₂

PGE₂

PGF_{2α}

PGI₂

TXA₂

5-Lipoxygenase pathway

5HPETE

5HETE

Leucotriene B4

Leucotriene A4

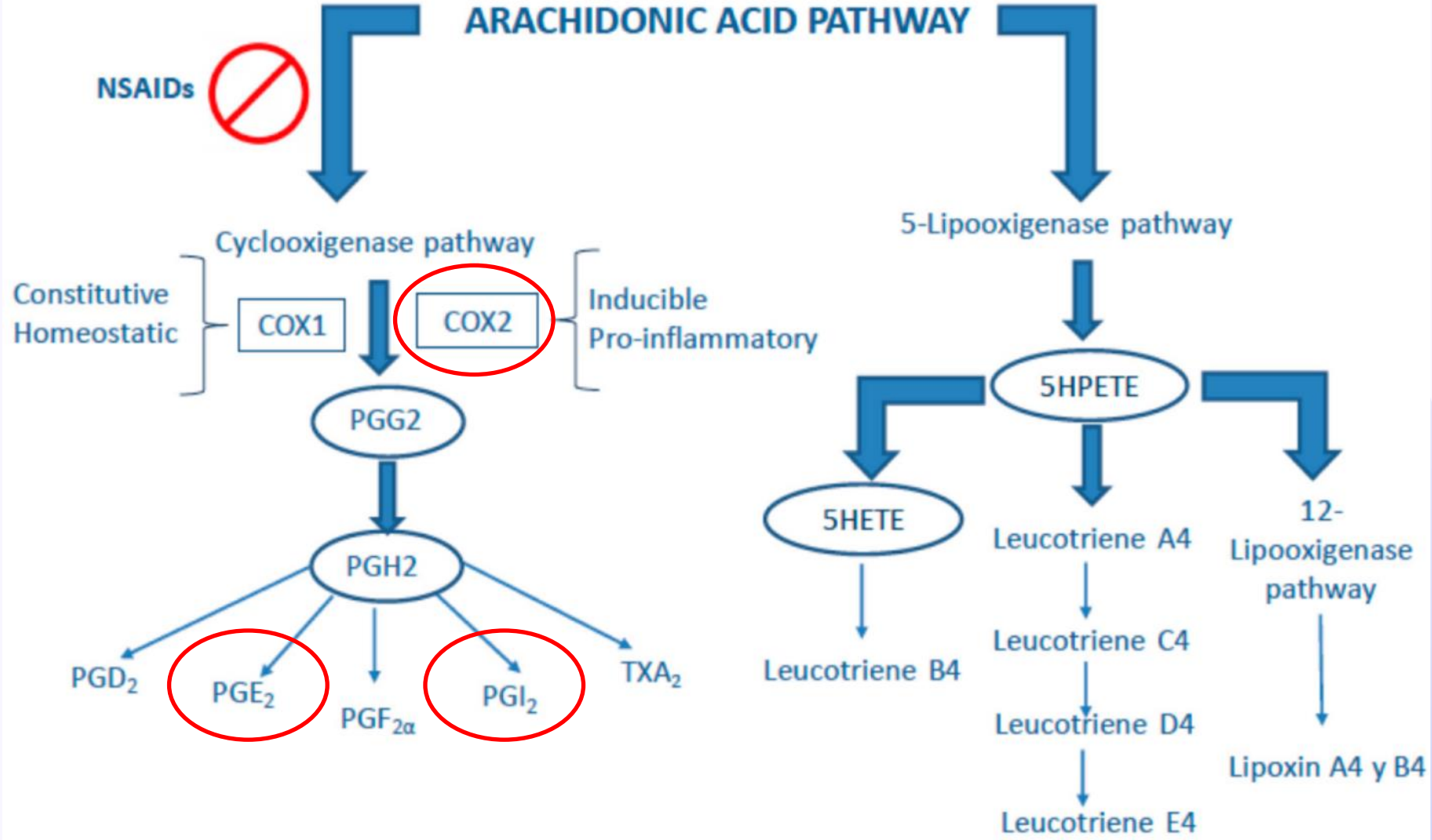
Leucotriene C4

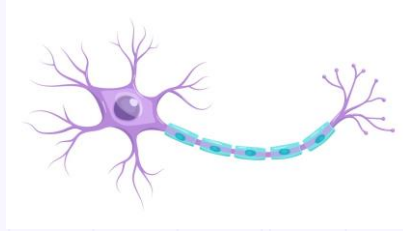
Leucotriene D4

Leucotriene E4

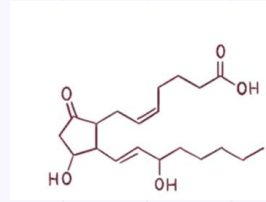
12-Lipoxygenase pathway

Lipoxin A4 y B4

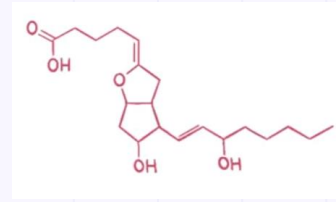




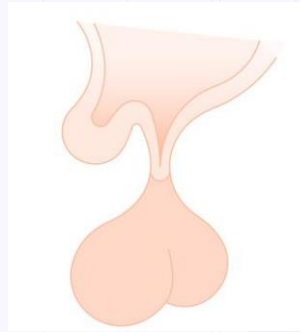
Nociceptors
Lowers threshold for activation



PGE2



PGI2

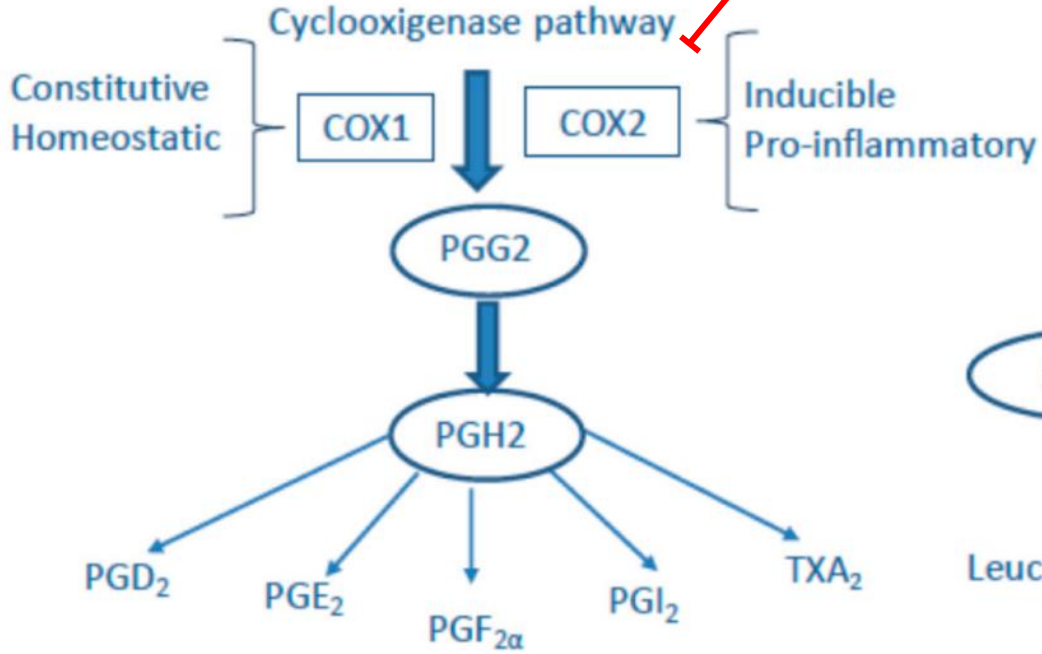


Hypothalamus
Increase body temperature → FEVER

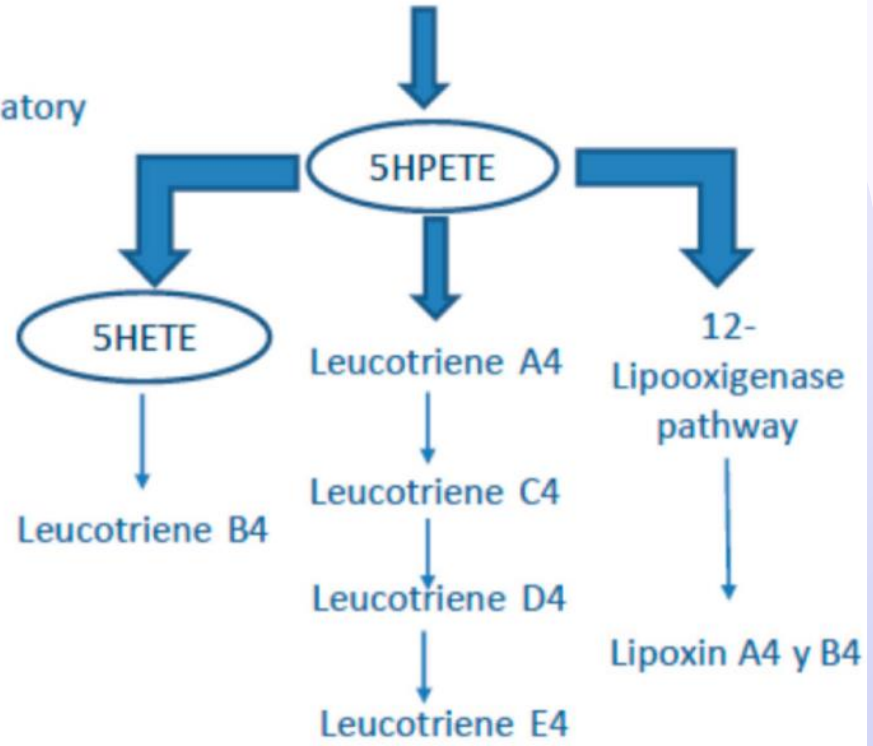
ARACHIDONIC ACID PATHWAY

NSAIDs 

Acetaminophen 



5-Lipoxygenase pathway



```
graph TD; Dosing[Dosing] --- Therapeutic[Therapeutic]; Dosing --- Toxic[Toxic]
```

Dosing

Therapeutic

Toxic

Therapeutic

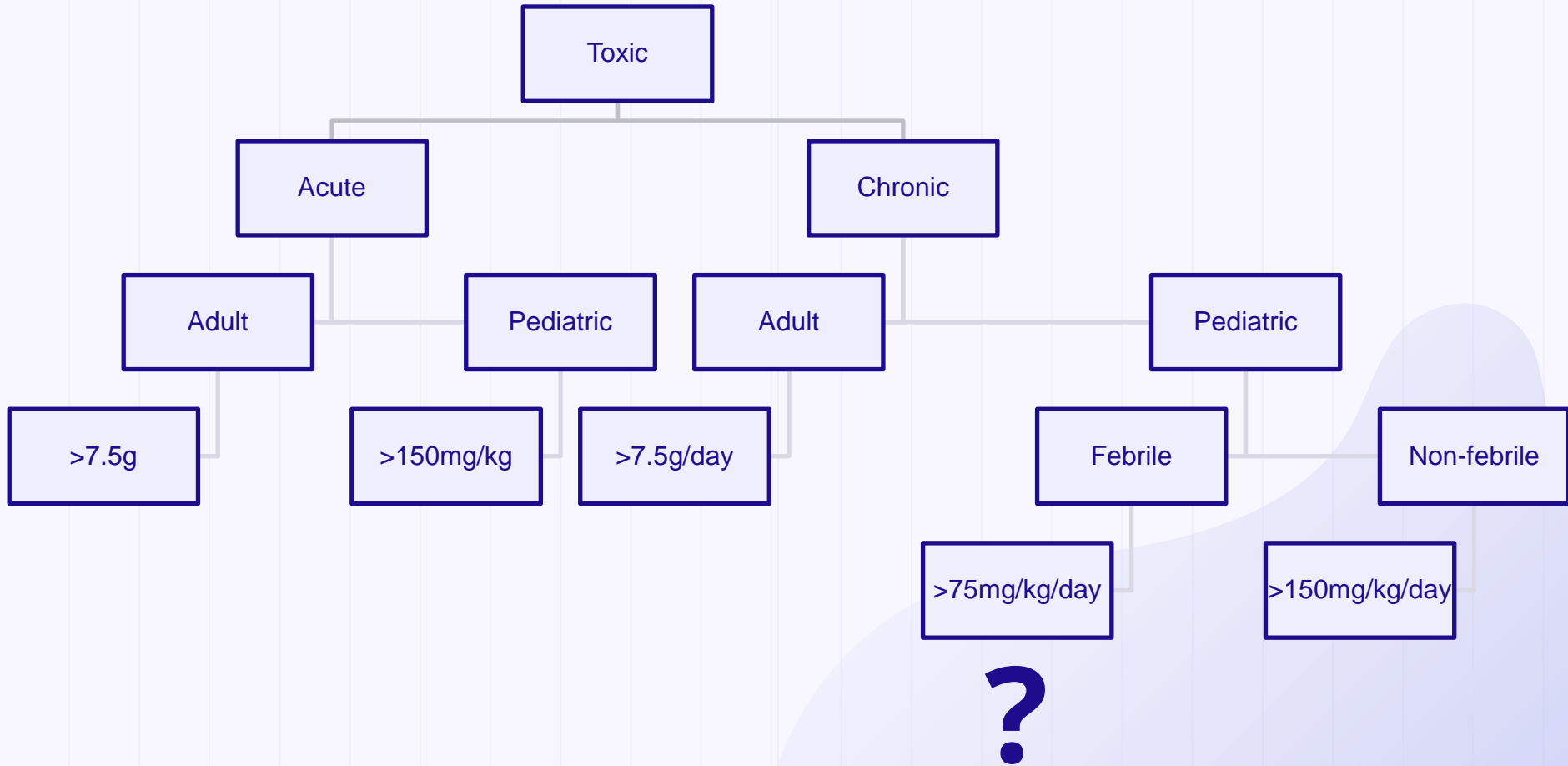
```
graph TD; A[Therapeutic] --> B[Adult]; A --> C[Pediatric]; B --> D["1g every 4 hours, not to exceed 4g per day"]; C --> E["15mg/kg every 4 hours, no more than 5 doses per day"];
```

Adult

1g every 4 hours,
not to exceed 4g
per day

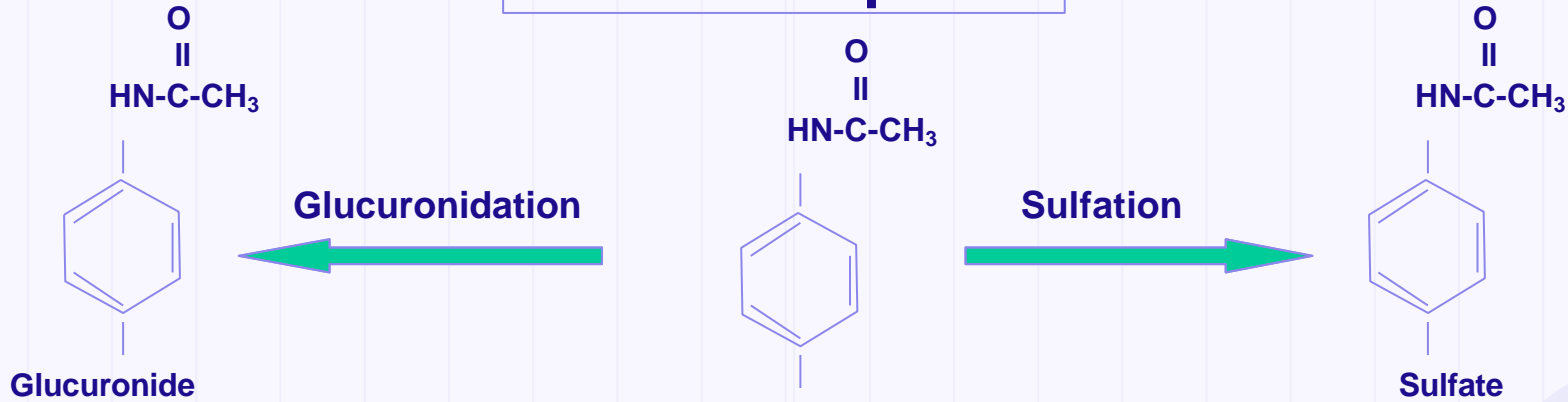
Pediatric

15mg/kg every 4
hours, no more than
5 doses per day



Acetaminophen

Normal acetaminophen metabolism



OH

P450

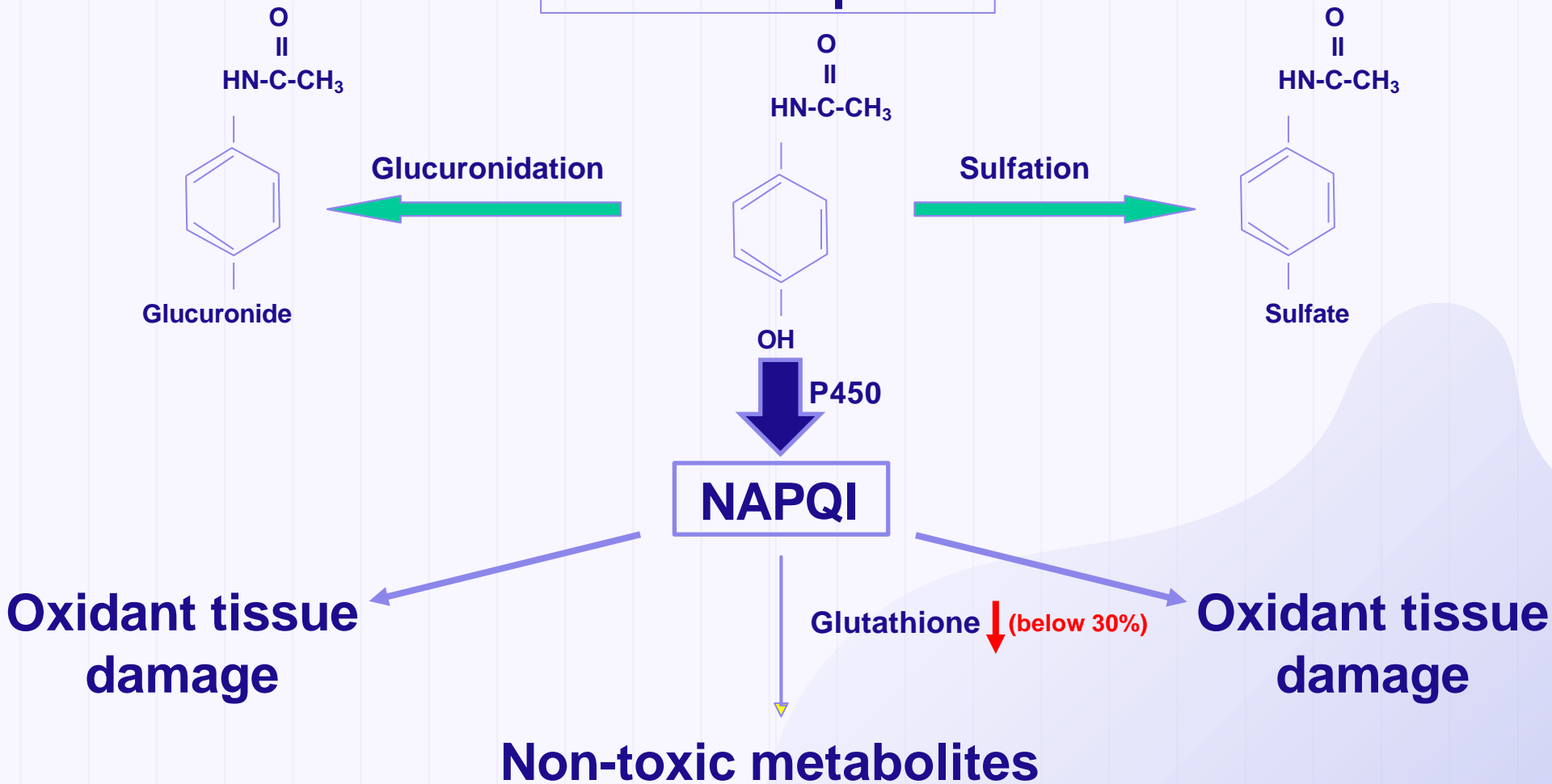
NAPQI

Glutathione

Non-toxic metabolites

Acetaminophen

Acetaminophen toxicity



Phases of toxicity



Phase 1

- First day
- Usually asymptomatic (silent overdose)
- Nausea, vomiting, abdominal pain



Phase 2

- 1-3 days
- Resolution of initial physical symptoms
- Elevation of LFT, PT, Bilirubin



Phase 3

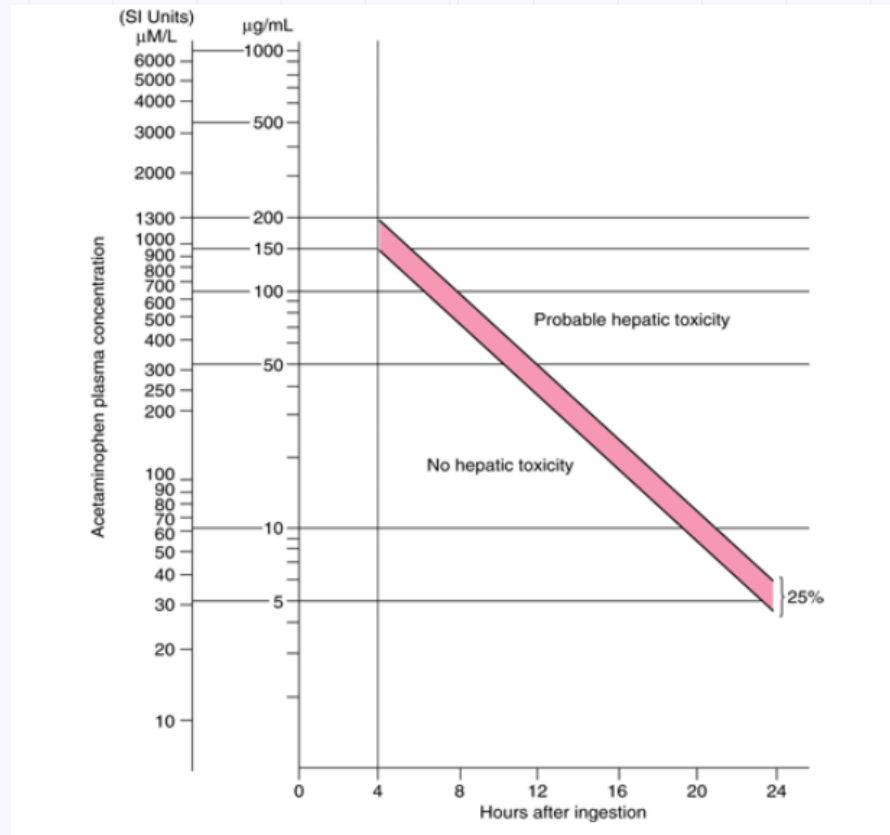
- 3-4 days
- GI symptoms reoccur
- Liver enzymes are in THOUSANDS
- Symptoms of liver failure
- Coma and anuria precede death



Phase 4

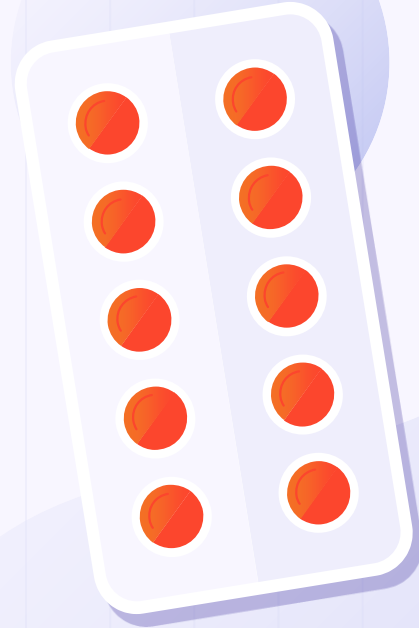
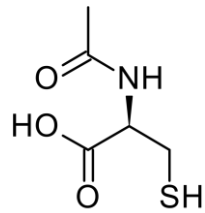
- >4 days
- Recovery phase
- LFTs will decrease but will not normalize (may take several weeks)
- Bilirubin will remain elevated for some time

Rumack-Matthew Nomogram for Acute Acetaminophen Toxicity

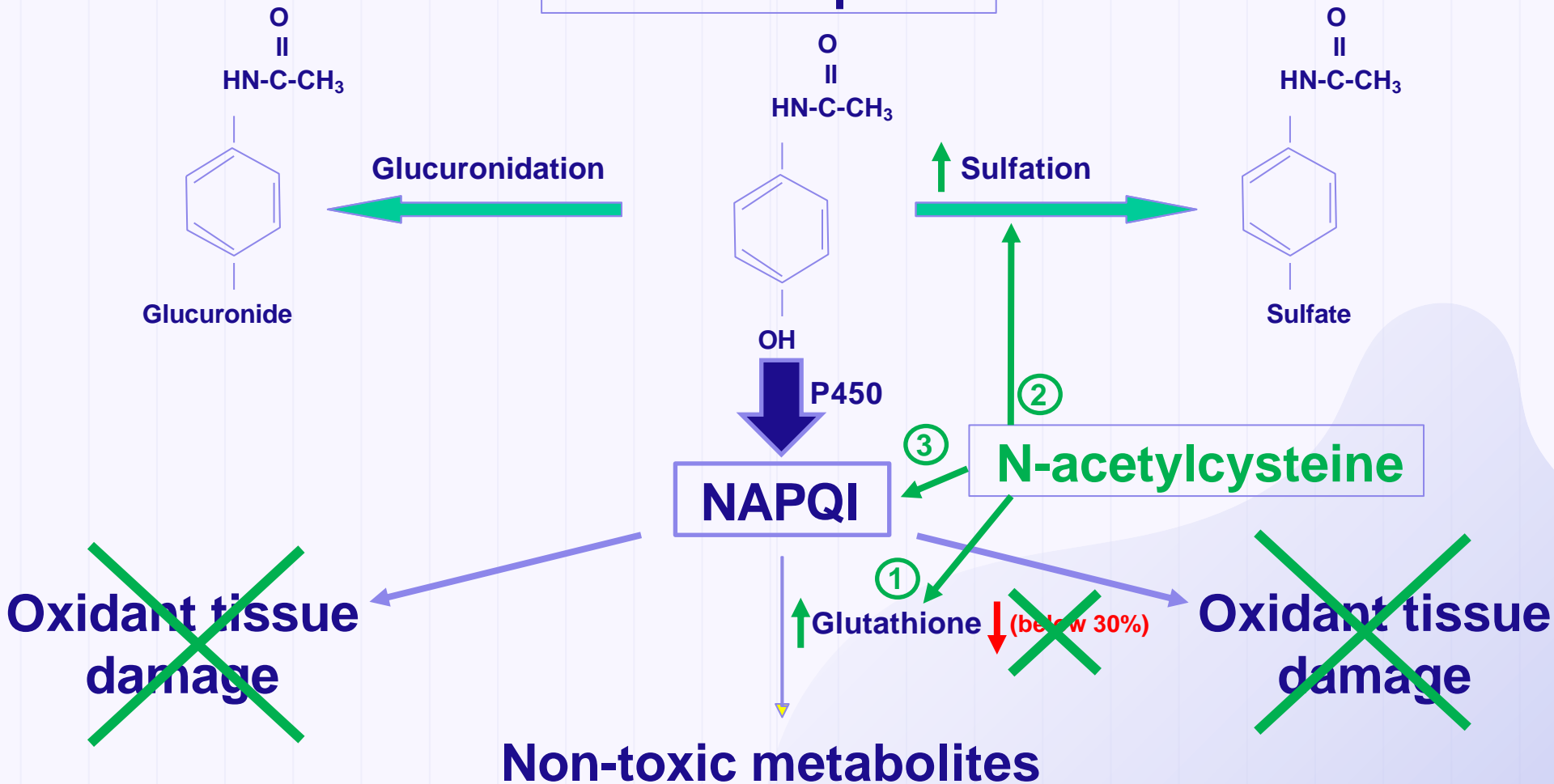


Management

N-acetylcysteine



Acetaminophen



Indications of Treatment (Single dose)

01

Acetaminophen plasma
conc. > 150mcg/ml at 4
hours

03

Ingestion of 7.5g in adults

02

Ingestion of
150mg/kg in children

04

Patient is unreliable
or unconscious

Indications of Treatment (Repeat or chronic ingestion)

01

Signs of hepatotoxicity
(elevated AST)

02

Acetaminophen plasma
conc. >25mcg/ml

03

Symptomatic



Ethanol and Acetaminophen



Ethanol is metabolized to some extent by the P450 system. Chronic ethanol ingestion causes increase in 2E1 P450 activity, and with the increase in P450's activity, more metabolites are produced by metabolism of acetaminophen, thus the lower threshold for toxicity amongst alcoholics (Lower threshold in western societies in contrast to ours)

N-acetylcysteine

Benefits

Oral vs. IV



Take-Home Points

Rule of 150's

>150mg/kg
>150mcg/ml at 4 hours

NAPQI and NAC

Mechanisms

Nomogram

For single acute
ingestions

Treatment

Indications, timing





Thanks