

# Acetaminophen Intoxication

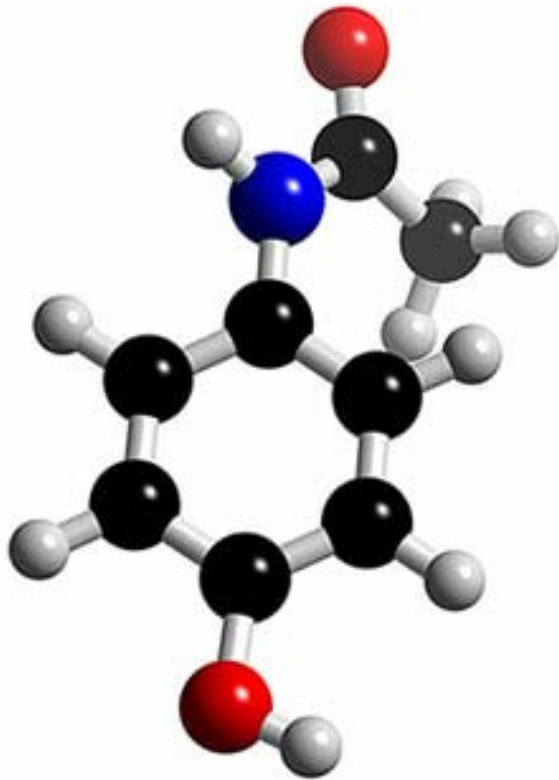
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GI Emergencies Update, Banff  
October 14, 2007  
<http://dr.schaeferville.com>

# Objectives

- Acetaminophen Intoxication Take-Aways
  - it's really common
  - think about it when others don't
  - the cure is in the reduction
  - use NAC liberally

# Case

- 19 year old male presents to ER with nausea and vomiting at 2 am.
- 8 hrs earlier → 'disagreement with girlfriend' at party where he had drank 6 beer
- ingested 50 x 500 mg acetaminophen...
- got worried, called 911.
- PMH: negative
- Examination: embarrassed and scared.
- s(APAP) = 500 ug/l & n-AC protocol started.\
- PROGNOSIS?



- Acetaminophen
  - Tylenol
  - Tylenol #1-4
  - Percocet
  - Anacin
  - Panadol
  
  - N-acetyl-p-aminophenol (APAP)
  - Paracetamol

# Acetaminophen Intoxication

- Most common pharmaceutical implicated in
  - overdose & overdose related deaths
- US 2003 Poison Control Data
  - 147 deaths 23% of all pharm deaths
  - (Poison Control may underestimate → 450 deaths / year)

– Am J Emerg Med 1998;16:443-497

– Semin Liver Dis 2003 Aug;23(3):217-26

## 2003 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System

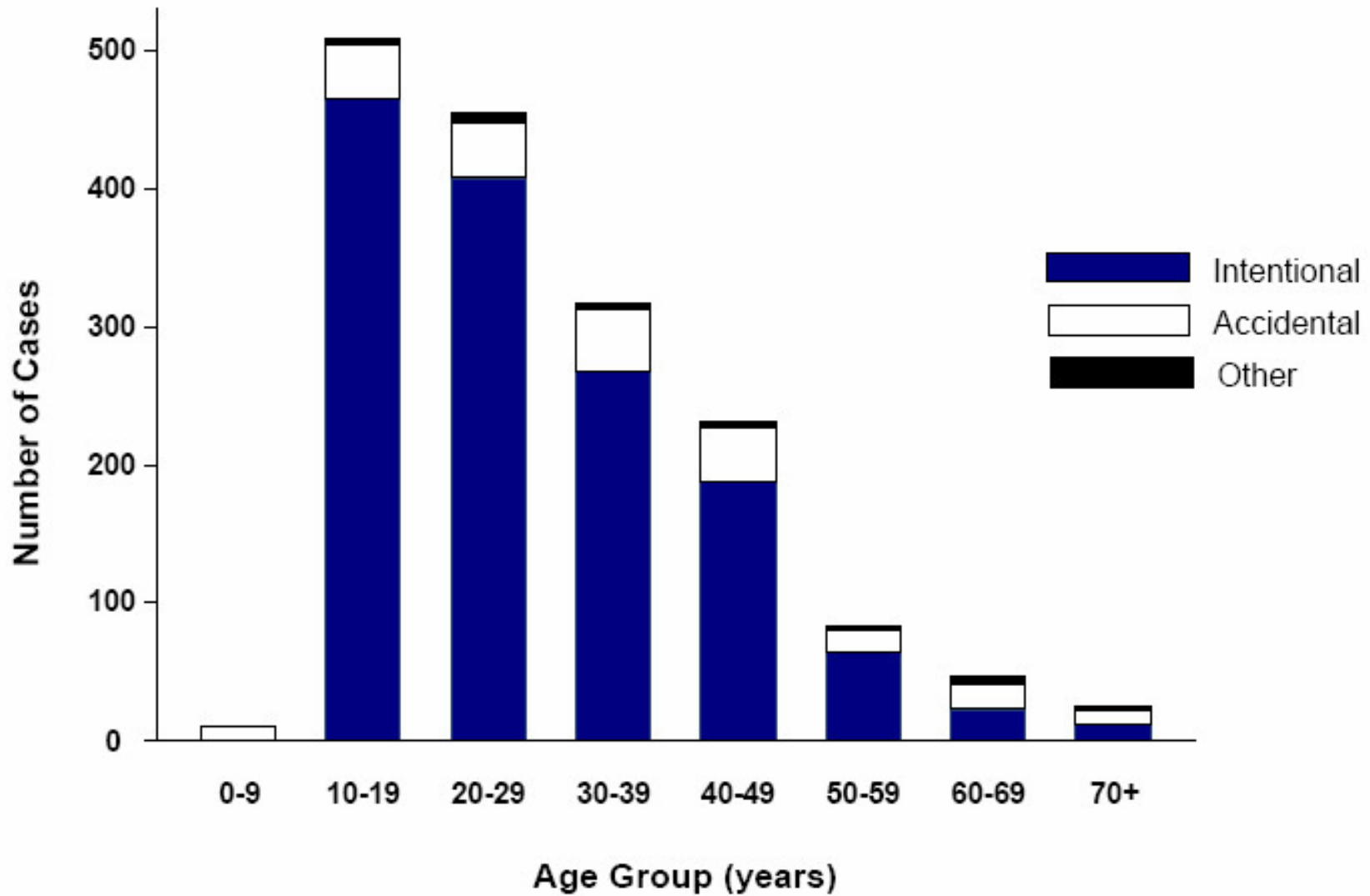
	No. of Exposures	Age			Reason			
		<6	6-19	>19	Unint	Int	Other	Adv Rxn
<b>Analgesics</b>								
Acetaminophen only								
Adult formulation	31,151	7,536	10,303	13,085	15,268	15,338	19	369
Pediatric formulation	22,535	20,201	2,048	244	22,083	308	12	112
Unknown formulation	8,216	1,930	2,486	3,685	3,482	4,467	3	102
Acetaminophen in combination with:								
Aspirin with other ingredient	3,702	1,258	974	1,449	1,973	1,541	1	166
Aspirin without other ingredient	2,788	784	811	1,166	1,287	1,380	1	106
Codeine	5,602	1,048	1,115	3,393	2,362	2,763	3	414
Hydrocodone	19,538	1,777	2,861	14,522	6,625	11,296	15	1,214
Oxycodone	6,078	661	733	4,553	2,281	3,155	5	493
Propoxyphene	5,870	608	803	4,351	2,014	3,472	1	283
Other opioid	517	54	79	376	170	302	1	32
Other drug: adult formulation	21,110	3,075	5,016	12,814	7,006	13,267	8	628
Other drug: pediatric formulation	64	57	6	1	63	0	0	1

# Mortality from acetaminophen toxicity

0.23%

85% intentional  
13% accidental

compared to 50-50 USA

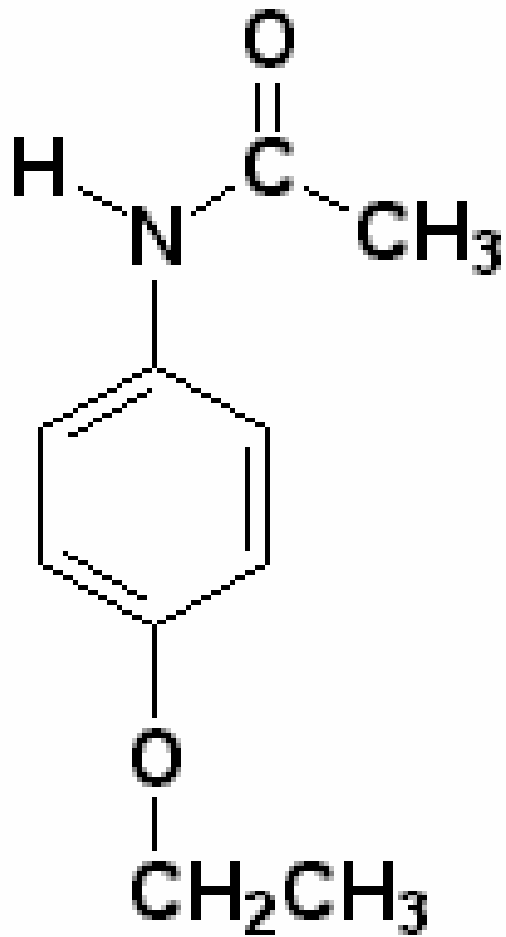


- **Intentional**

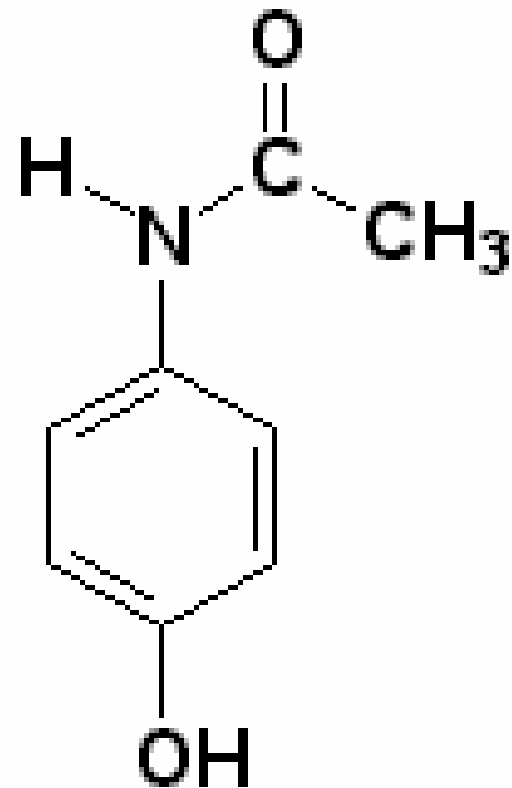
- usually present within 4 hrs
- median: 20 grams over 1 dose

- **Unintentional**

- present after several days
- co-ingest acetaminophen meds (15%)
- impulsive overdosing owing to pain
- median: 34 grams over 3 days



phenacetin



acetaminophen

NO. OF PILLS  
TAKEN IN LIFETIME

CASE  
PATIENTS

CONTROL  
SUBJECTS

UNIVARIATE  
ANALYSIS

ADJUSTED  
ANALYSIS\*

*number (percent)†*

*odds ratio (95% CI)‡*

# Acetaminophen is associated with ESRF

\*Adjusted for age, sex, race, use of the other analgesic drugs shown in the table, and use of analgesic drugs possibly containing phenacetin.

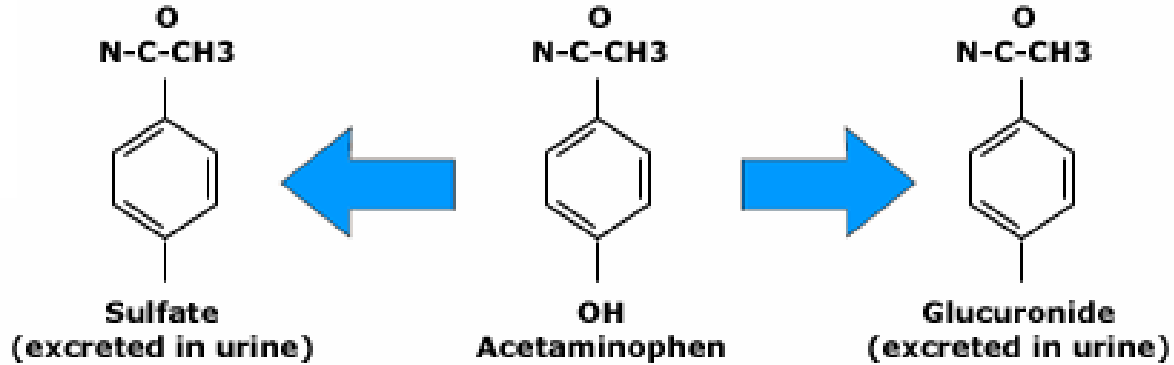
†Because of rounding, not all groups total 100 percent.

‡CI denotes confidence interval.

# Non-Toxic Doses

**90%**

- glucuronide
- sulfate



**5%**

- unchanged urine

Renal excretion

**5%**

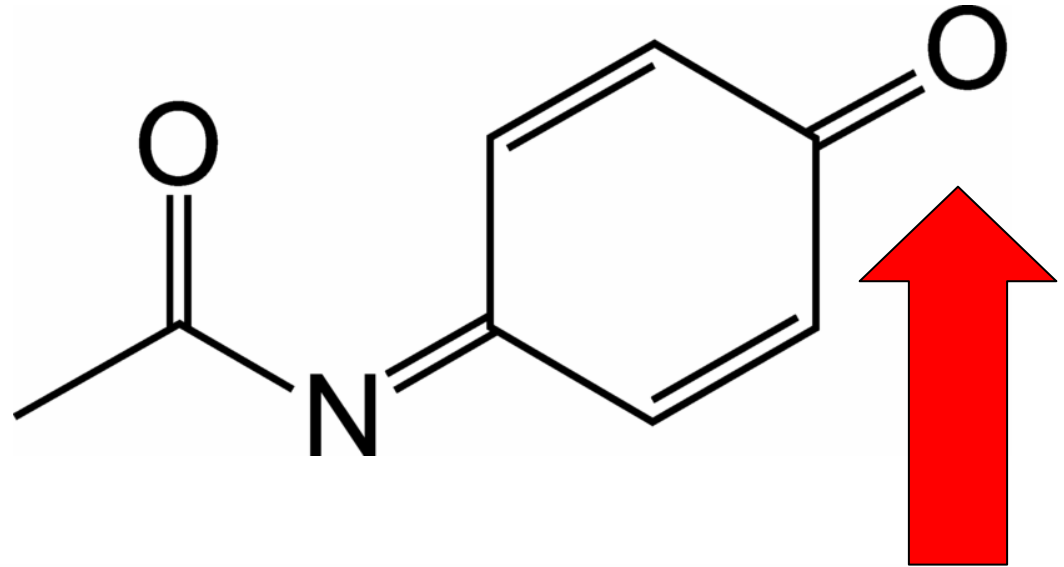
- NAPQI → detoxified

+Glutathione      **Cytochrome P450**  
(CYP2E1, CYP1A2, CYP3A4)

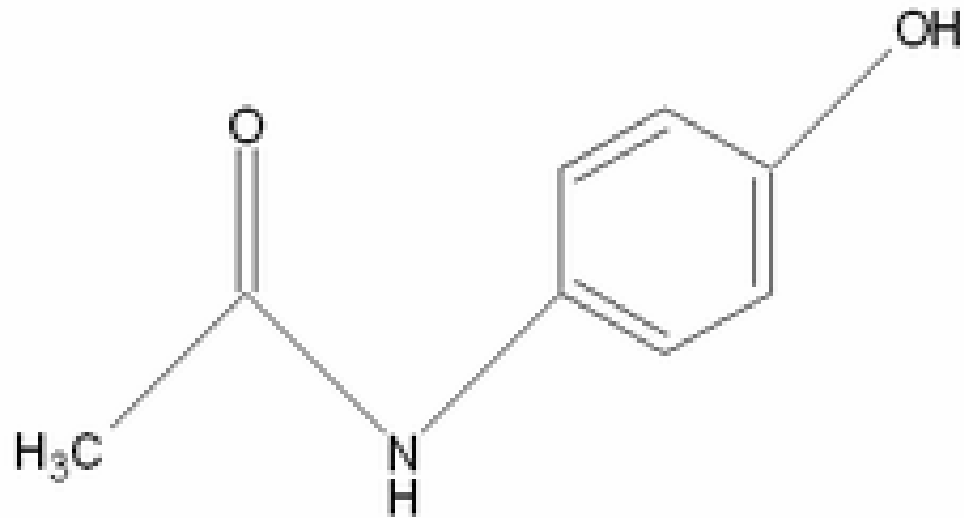
Nontoxic NAPQI  
conjugate  
(excreted in urine)

## NAPQI

N-acetyl-p-benzo-quinone imine

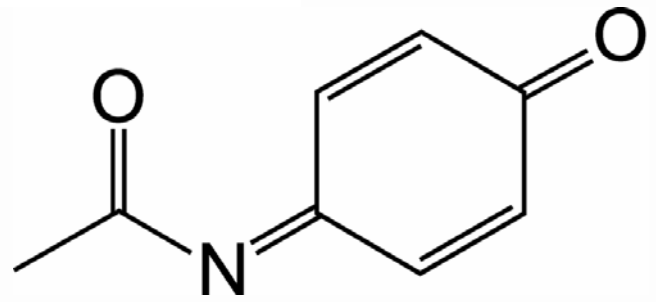
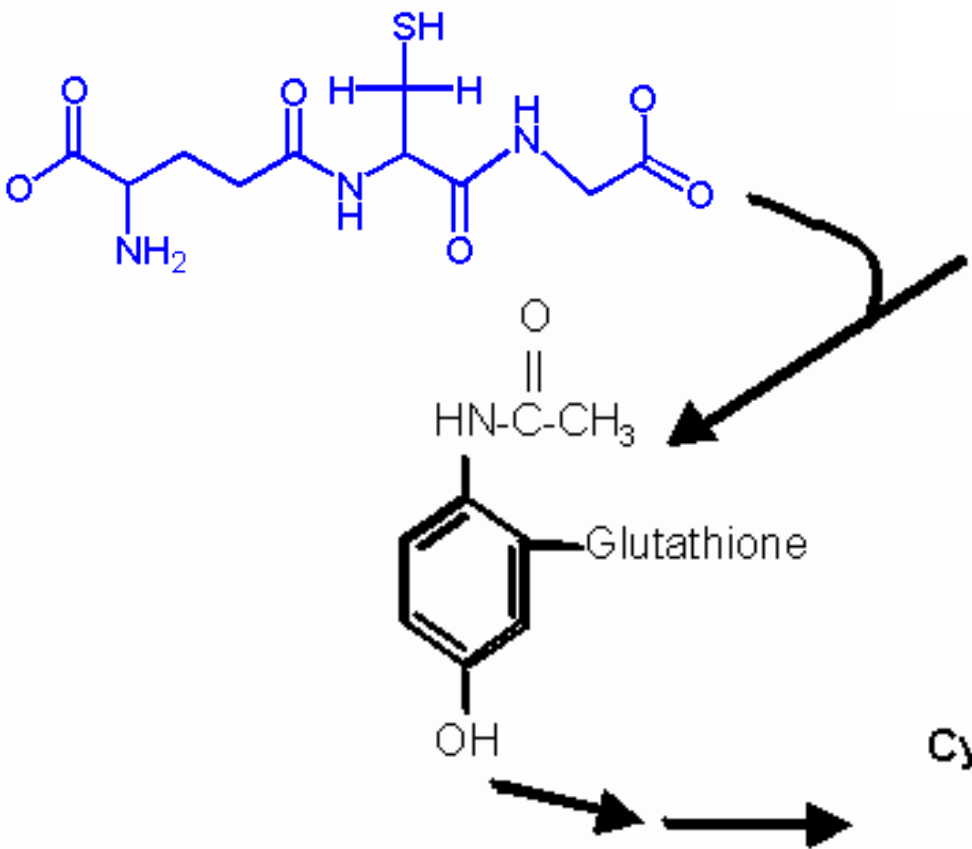


## acetaminophen



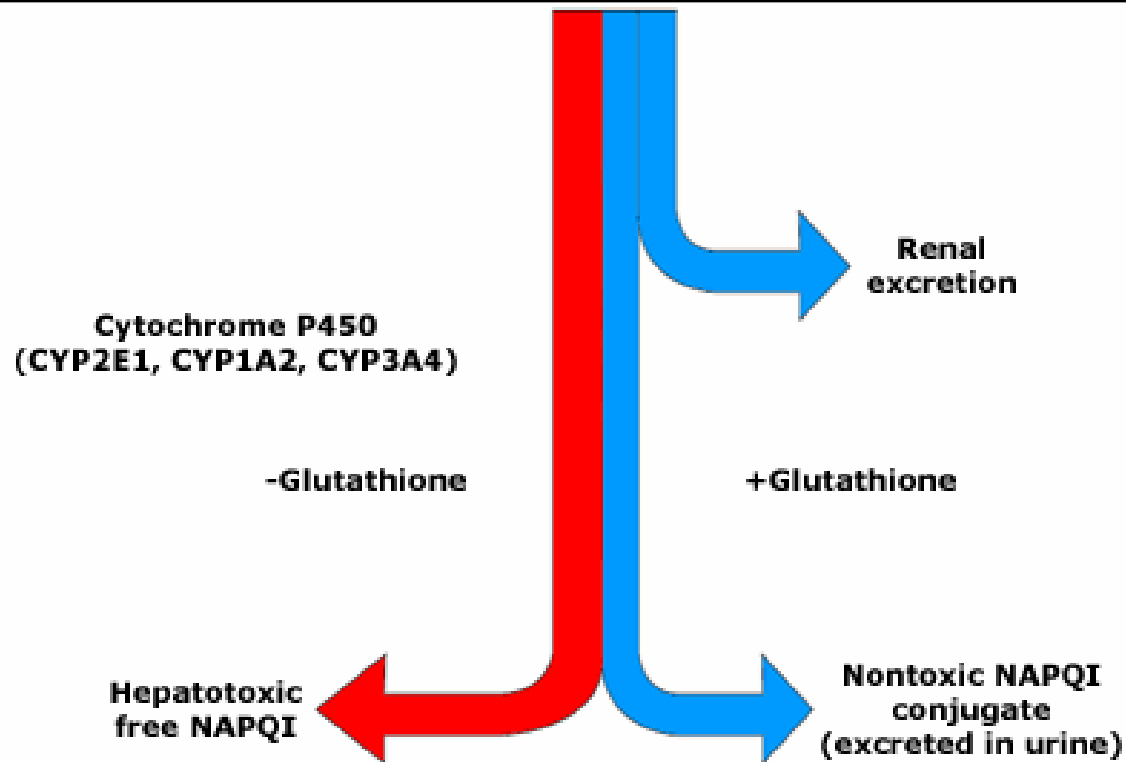
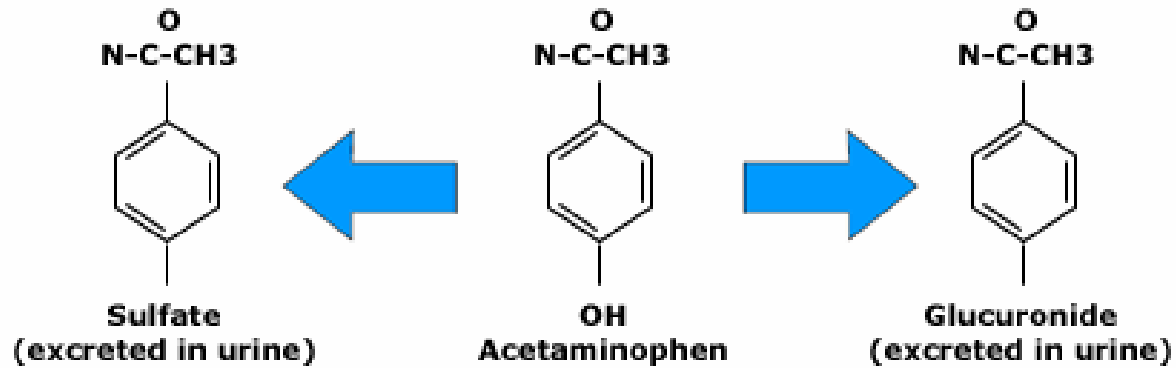
# Glutathione

# NAPQI

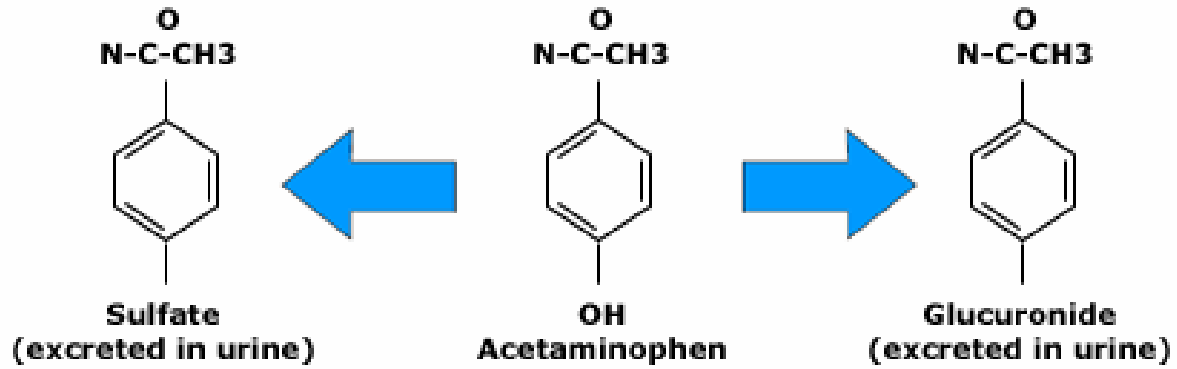


Cysteine & Mercapturic Acid  
Conjugates 5 - 8%

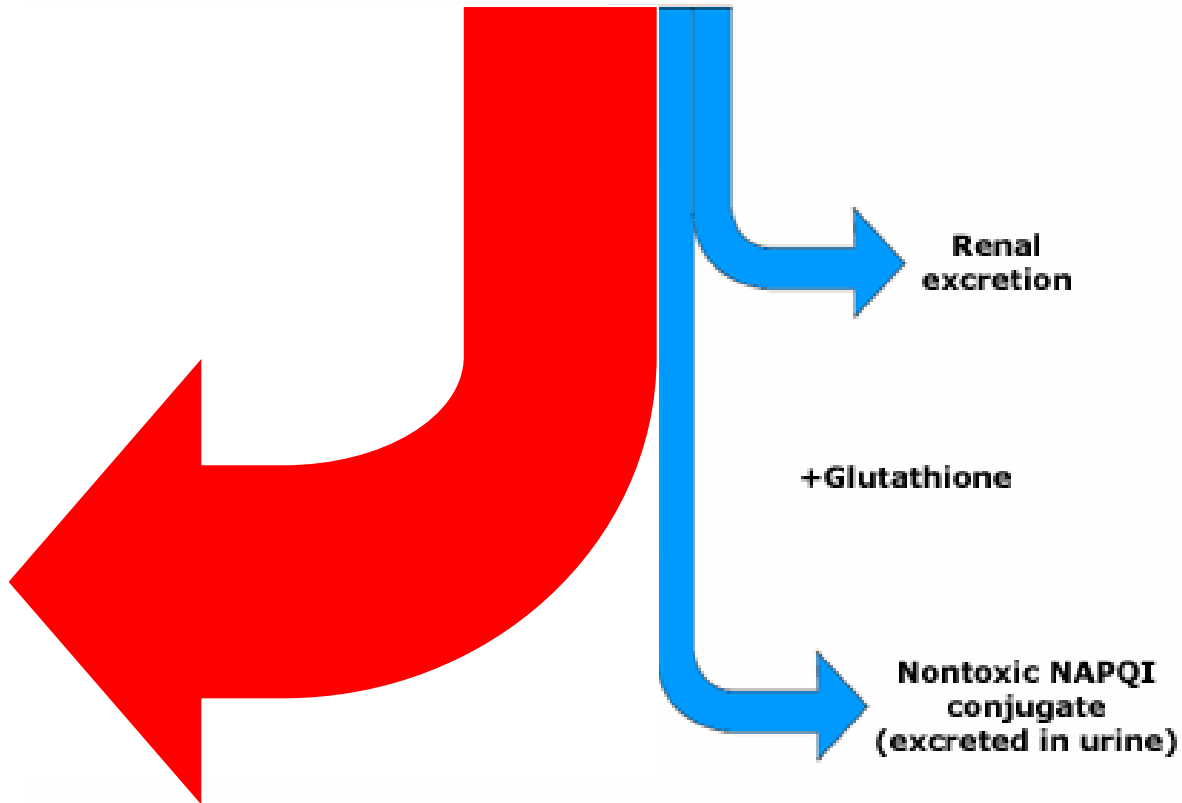
# Toxicity



# Toxicity

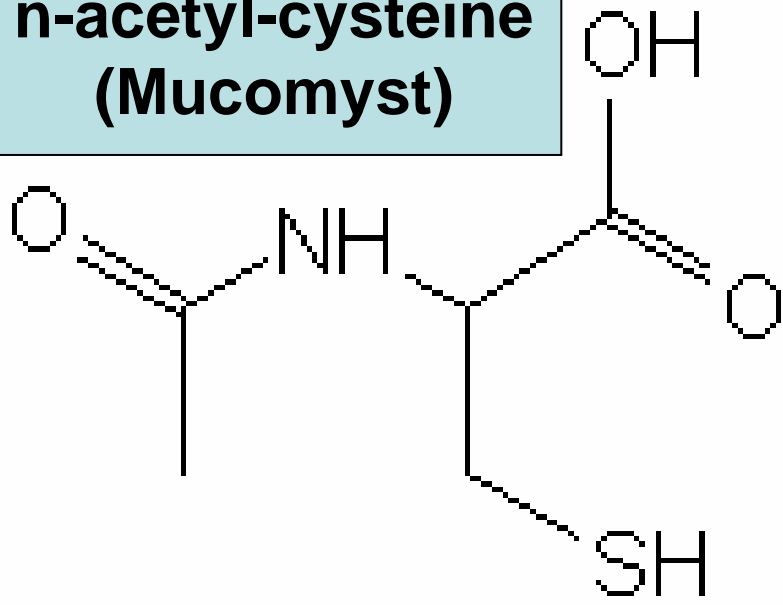


# NAPQI

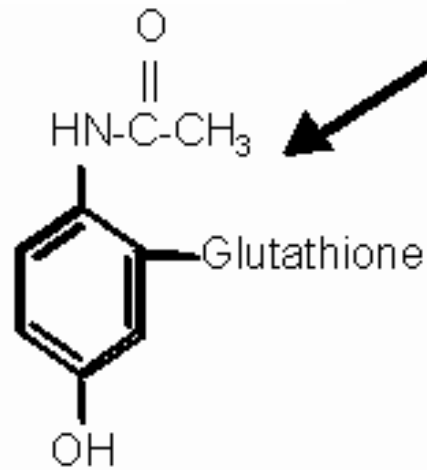
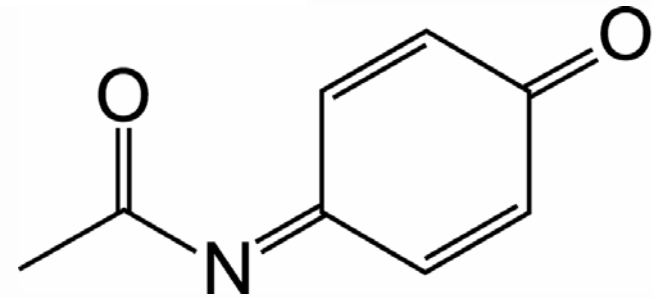


- Pathology Talk

**n-acetyl-cysteine  
(Mucomyst)**



**NAPQI**



**Cysteine & Mercapturic Acid  
Conjugates**      **5 - 8%**

# Predispositions to Toxicity

- Excess acetaminophen intake
- Induction of cytochrome P450
  - chronic alcohol use
  - carbamazepine, phenobarbital, phenytoin, isoniazid, rifampin
- Decreased glucuronidation or sulfation
  - trimethoprim-sulfamethoxazole, zidovudine
  - herbals
- Depletion of glutathione stores
  - malnutrition
  - chronic alcohol ingestion

# How much (adults)?

- Maximum Recommended Dose
  - 1,000 mg qid → 4 g/d
- Toxicity Unlikely:
  - Single Dose of 7½ - 10 g
  - 12 g over 24 hr
- Toxicity Likely (ALT > 1,000 IU/l)
  - 350 mg/kg (28 g / 80 kg)

# Alcohol

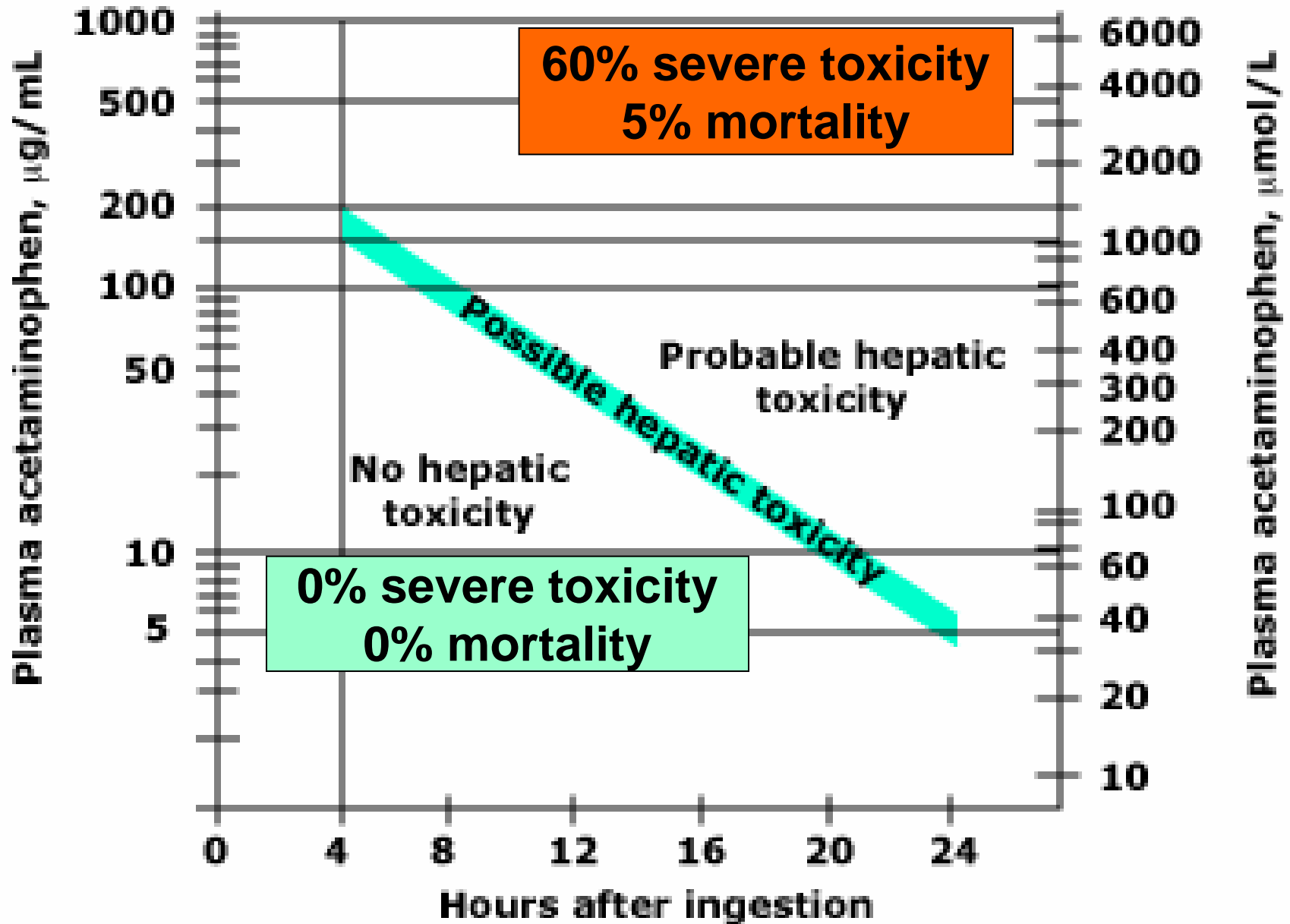
- Acute alcohol
  - no effect or protective
- Regular alcohol use
  - varied observations
  - higher mortality with less drug
  - chronic liver patients, 4 g/d x 2 weeks → no hepatotoxicity

# Four Stages

- Stage I (0.5 to 24 hours)
    - nausea, vomiting, diaphoresis, lethargy, and malaise
  - Stage II (24 to 72 hours)
    - stage I symptoms resolve
    - AST & ALT & INR increases
    - RUQ pain, hepatomegaly, jaundice, oliguria
  - Stage III (72 to 96 hours)
    - Stage I symptoms reappear with encephalopathy
    - ALT & AST > 10,000, INR rises, lactic acidosis, hypoglycemia, renal failure, death
  - Stage IV (4 days to 2 weeks)
    - recovery phase begins on day 4
    - clinically complete in 7 days, histology lags (3 mo)
- recovery is complete

# Diagnosis

- How much?
- What preparation?
- When?
- Pattern?
- Intent?
- Comorbid?
  
- Serum Acetaminophen Concentration
  - 4 hr & 24 hr after presentation
  - < 4 hr may not represent peak values
  - Rumack-Matthew Nomogram



# Therapy

- GI decontamination
- n-Acetyl-cysteine
  
- cimetidine → not effective
- dialysis → not hepato-effective
- transplantation → effective
- bioartificial liver → experimental

# Activated Charcoal

- DOSE
  - single dose of 1 gram / kg
- INDICATION
  - ingestion was < 4 hr prior to presentation
  - consider a dose > 4 hr when
    - sustained release formulation
    - co-ingestants that slow GI transit
- EFFICACY
  - 52% better than ipecac or gastric lavage
  - binds NAC but no need to alter oral dose

# n-acetylcysteine (NAC)

- Treat if anyone of:
  - serum APAP at 4+ hr above R-M line
  - serum APAP unavailable in 8 hr of ingestion
  - ingestion time unknown & APAP > 10 ug/ml
  - any hepatotoxicity & APAP ingestion
  - suspicion of repeat excess APAP ingestions
  - patient has risk factors for APAP-induced hepatotoxicity & serum APAP > 10 ug/ml

# n-acetylcysteine

- IV preferred to Oral
- **Acute Presenters (8-10 h after ingestion)**
  - **Load: 150 mg/kg IV in 250 ml D5W over 1 hr**
  - **Maintenance 1: 50 mg/kg in 500 ml D5W over 4 hr**
  - **Maintenance 2: 100 mg/kg in 1000 ml D5W over 16 hr**
- Later Presenters ( >10 h after ingestion)
  - Load: 140 mg/kg IV in 500 ml D5W over 1 hr
  - Maintenance: 70 mg/kg IV in 250 ml D5W q4h x at least 12 doses (48 hr of treatment)

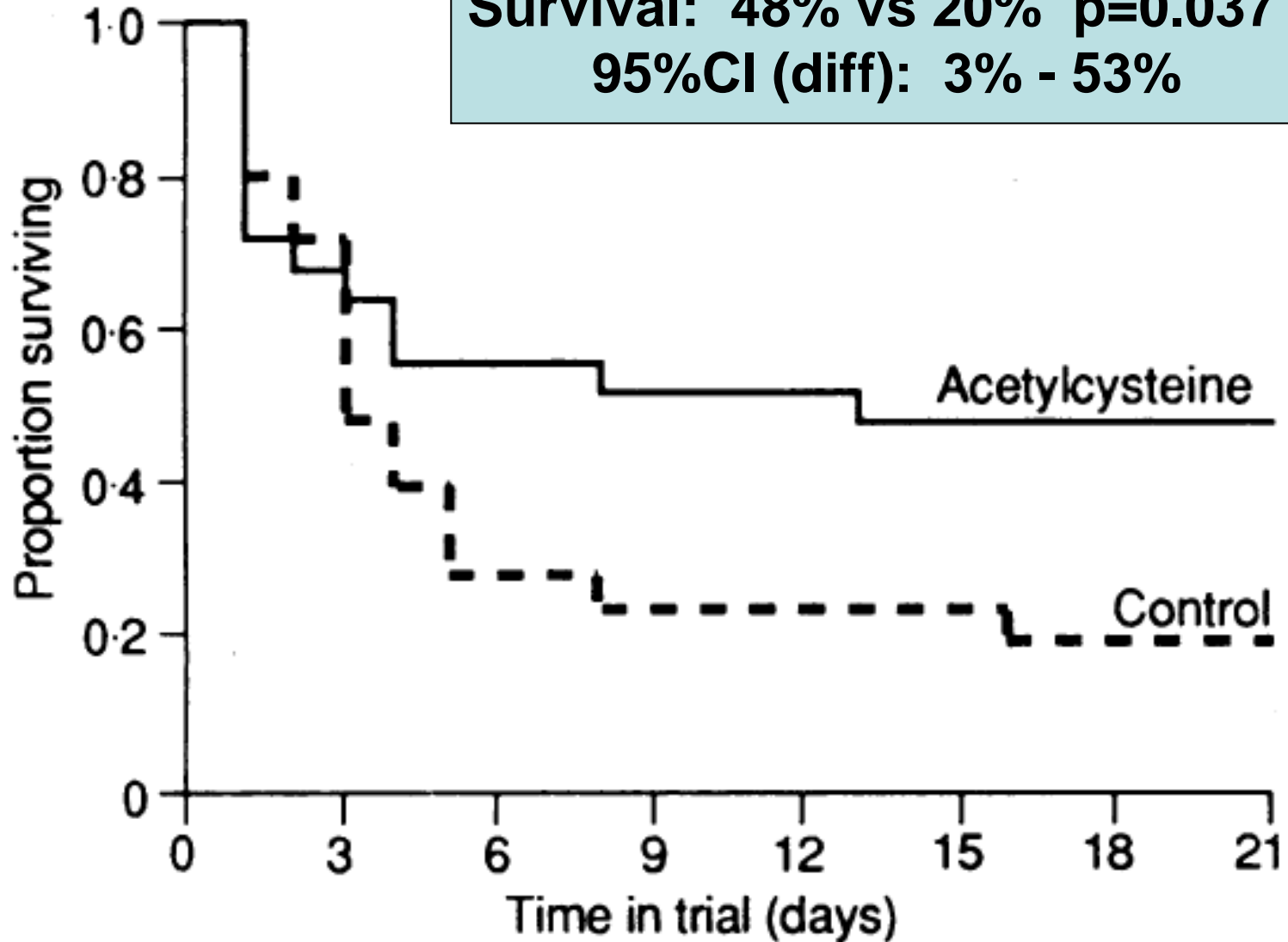
# How late can one start?

## **Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial** BMJ VOLUME 303 26 OCTOBER 1991

R Keays, P M Harrison, J A Wendon, A Forbes, C Gove, G J M Alexander, Roger Williams

	Acetylcysteine	Control
No of patients	25	25
Age (years)	33 (17-60)	34 (16-58)
Sex (M/F)	12/13	9/16
Hours from overdose to presentation to referring hospital	28 (16-36)	32 (16-48)
Hours from overdose to admission to liver failure unit	53 (36-80)	56 (33-96)
Values at entry to trial:		
Serum creatinine ( $\mu\text{mol/l}$ )	246 (86 to 620)	247 (71-574)
Arterial pH	7.39 (6.89 to 7.48)	7.39 (7.08-7.53)
Prothrombin time (s; control time 15 s)	115 (29 to 180)	140 (29 to 180)
No of patients fulfilling criteria for poor prognosis:		
Admission pH <7.30	8	5
Prothrombin time >100 s + serum creatinine >300 $\mu\text{mol/l}$ + grade 3 or 4 coma	9	11
Rise in prothrombin time on day 4 compared with day 3 after overdose	5	5
No of patients fulfilling at least one criterion for poor prognosis	17	18

**Survival: 48% vs 20% p=0.037**  
**95%CI (diff): 3% - 53%**



*Proportions of patients surviving in acetylcysteine treated and control groups on each day after start of trial*

# How long do we persist?

- Until death or recovery (INR < 2.0)

# Prognosis

- At risk patients without NAC
  - mortality 4.3 – 24%
- Time
  - < 1% mortality when NAC within 10 hr ingestion
- PT at day 4
  - rising → 8% survival
  - falling → 82% survival

# Transplant Criteria

## Acetaminophen-Induced ALF

- Arterial pH <7.3 (irrespective of the grade of encephalopathy)

## OR

- Grade III or IV encephalopathy  
AND
- Prothrombin time >100 seconds  
AND
- Serum creatinine >3.4 mg/dL (301 µmol/L)

## All Other Causes of ALF

- Prothrombin time >100 seconds (irrespective of the grade of encephalopathy)

## OR

Any **three** of the following (irrespective of the grade of encephalopathy)

1. Age <10 years or >40 years
2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
3. Duration of jaundice before onset of encephalopathy >7 days
4. Prothrombin time >50 seconds
5. Serum bilirubin >18 mg/dL (308 µmol/L)

# Summary

- Frequent presentation
- Diagnostic pitfall
  - chronic user
  - unintentional overdose
- n-acetyl-cysteine is effective
  - use when in doubt
- Prognosis
  - ingestion to NAC time is most important