UPDATES ON ACETAMINOPHEN TOXICITY

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OBJECTIVES

01 ABOUT ACPC
Brief overview of the Atlantic Canada Poison Centre

02 INCIDENCE + IMPACT
Discuss the incidence and impact of acetaminophen toxicity

03 PATHOPHYSIOLOGY
Review the pathophysiology of Acetaminophen toxicity

04 TREATMENTS
Outline the standard treatments recommended for Acetaminophen toxicity

05 AVAILABLE EVIDENCE
Discuss the available evidence supporting the different IV N-Acetylcysteine regimens

06 "NEWER" TREATMENTS
Evaluate evidence supporting "newer" treatment options emerging for Acetaminophen toxicity

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01

ABOUT ACPC

Brief overview of the **A**tlantic **C**anada **P**oison **C**entre

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OVERVIEW

ATLANTIC CANADA
POISON CENTRE

- The ACPC provides telephone-based poison information service to the public and HCPs to Atlantic Canada (NB – HCPs only)
- Cases managed by pharmacists and RNs with specialized knowledge in toxicology
- On call toxicologist or ED/CC physician available 24/7

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OVERVIEW

COMMUNITY
Patient contact and assessment

EMERGENCY SERVICES
Contact with 911 and paramedics to assist with transport

HEALTH CARE CENTRE
Contact with HCF to provide treatment recommendations

CASE RESOLUTION
Treatment plan updated prn, followed to a known outcome

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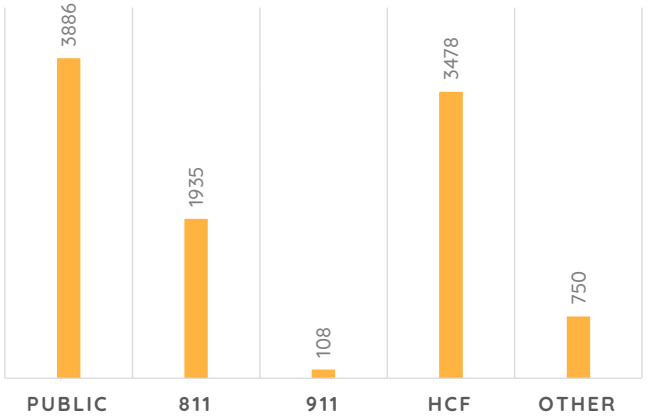
PREVALENCE + OUTCOMES (2022)

CALL SITE



Total Calls	10748
Exposure	10157
Information	428
Animal	163
Non-toxic	114
Minimal effect	4856
Minor effect	2591
Moderate effect	1380
Major effect	242
Death	23

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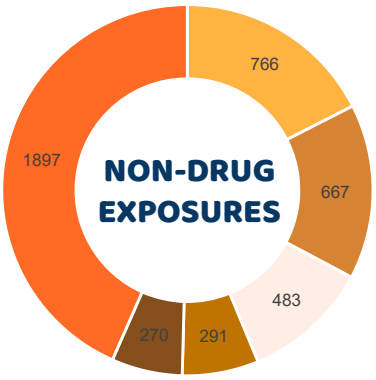
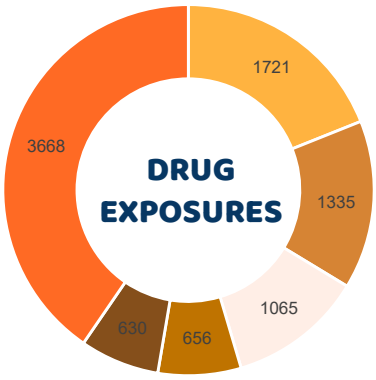
TOP 5's



- CLEANING SUBSTANCES (HOUSEHOLD)
- ALCOHOLS
- COSMETICS/PERSONAL CARE PRODUCTS
- FOREIGN BODIES/TOYS/MISCELLANEOUS
- CHEMICALS
- OTHER



- ANALGESICS
- ANTIDEPRESSANTS
- SEDATIVE/HYPNOTICS/ANTIPSYCHOTICS
- CARDIOVASCULAR DRUGS
- STIMULANTS AND STREET DRUGS
- OTHER

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02

INCIDENCE + IMPACT

Discuss the incidence and impact of acetaminophen toxicity

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13%

Acetaminophen was involved in 13% of the deaths at the Atlantic Canada Poison Centre (2022)

Acetaminophen is commonly taken in overdose either accidentally or intentionally and in most western countries, it is **the most common single compound taken in overdose**.

Several studies show that hepatotoxicity due to APAP accounted for **almost half** the cases of acute liver for the entire 16-year period

A. REUBEN ET AL. (2016)

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03

PATHO-PHYSIOLOGY

Review the pathophysiology of Acetaminophen toxicity

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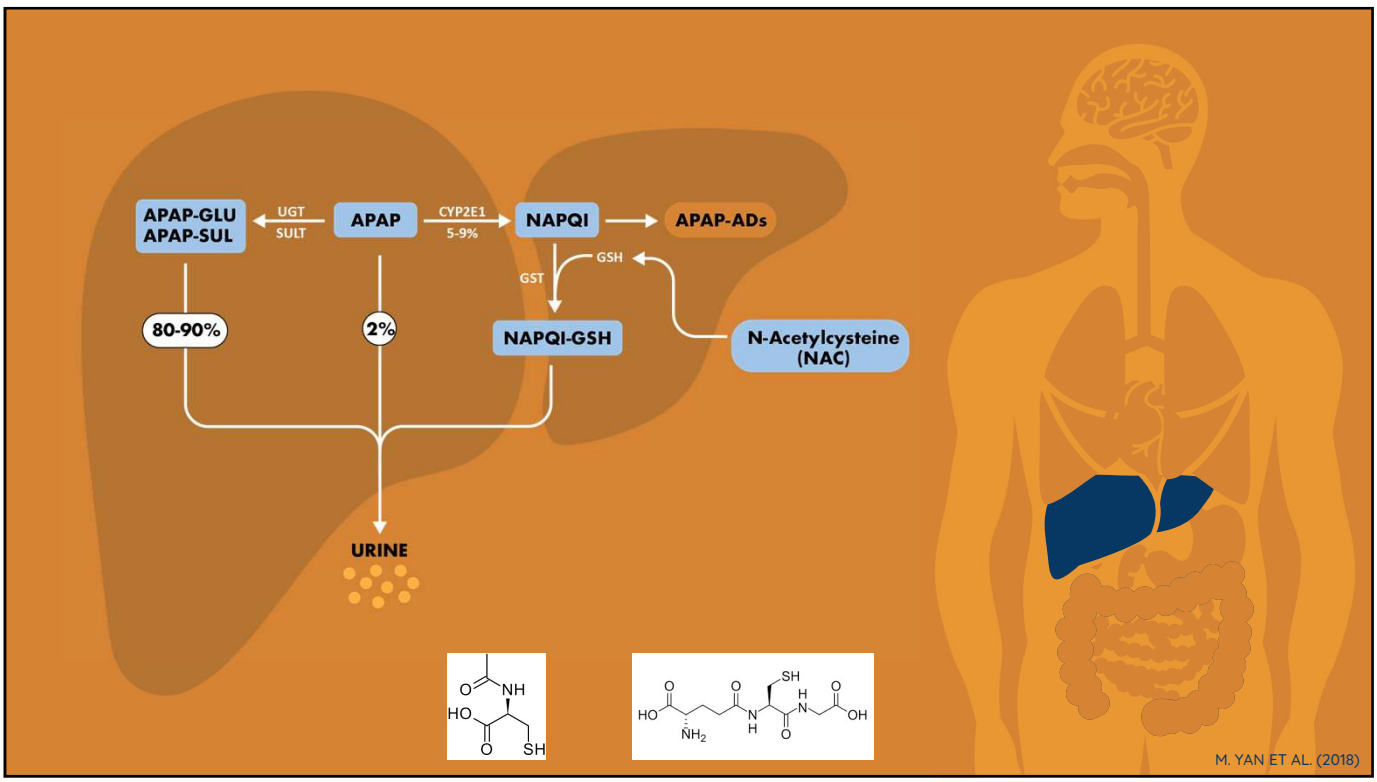

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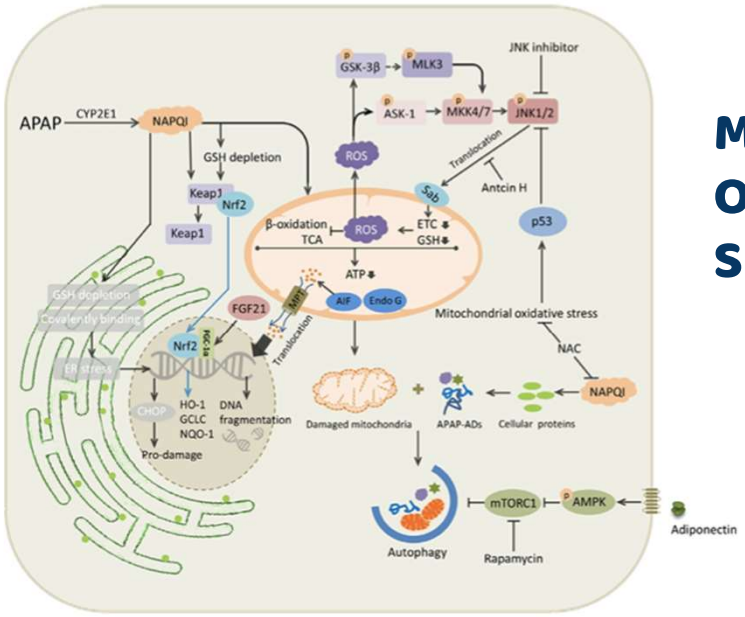

Mitochondrial Oxidative Stress

M. YAN ET AL. (2018)

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TREATMENT

Outline the standard treatments recommended for Acetaminophen toxicity

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TREATMENTS

01 ACTIVATED CHARCOAL

02 N-ACETYLCYSTEINE

03 DIALYSIS

04 LIVER TRANSPLANTATION

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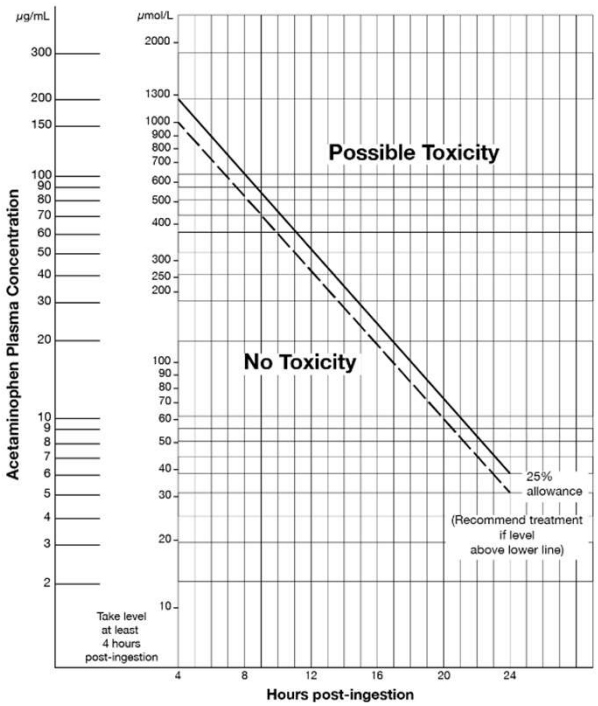
STANDARD TREATMENTS

ACETAMINOPHEN has a volume distribution of about 1 L/kg

The plasma level in mg/L can be "read" as the mg/kg body burden at that time.

Therefore, 200 µg/mL corresponds to a 200-mg/kg-body burden.

Toxic Dose:
200mg/kg or 10,000mg
*whichever is less



B. RUMACK. (2002)

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ACTIVATED CHARCOAL

Children up to 1 year
1 gram/kg

Children 1-12 years
1-2 gram/kg to a maximum of 50 grams

Adolescents and Adults
1-2 gram/kg to a maximum of 100 grams

Activated Charcoal Reduces the Need for *N*-Acetylcysteine Treatment After Acetaminophen (Paracetamol) Overdose

Nicholas A. Buckley, Dr. Nicholas Buckley, Ian M Whyte, Dianne L O'Connell & Andrew H Dawson

Table 1

Proportion of Patients, Ingesting ≥10 g of Acetaminophen and Presenting Within 24 Hours, with Probable or High Risk Concentrations and the Method of Gastrointestinal Decontamination Used

	No GI Decontamination (n = 167)	Charcoal Alone (n = 163)	Lavage & Charcoal (n = 120)	p Value (combined charcoal v none)
Median time to presentation, min (range)	385 (10–1380)	135 (5–885)	120 (14–840)	0.0001
Concentration above the possible risk line	68 (40.7%)	45 (27.6%)	27 (22.5%)	0.0007
Probable or high risk concentration	50 (29.9%)	21 (12.9%)	17 (14.2%)	<0.0001
Median length of stay, hours (range)	22.3 (1–170)	19.2 (2–285)	18.8 (2.7–154)	0.04

Odds ratio need for NAC treatment if charcoal received: Probable or high risk concentration: OR 0.36 (95% CI 0.23–0.58); Possible risk concentration: OR 0.50 (95% CI 0.33–0.75).

N. BUCKLEY ET AL. (1999)

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ACTIVATED CHARCOAL

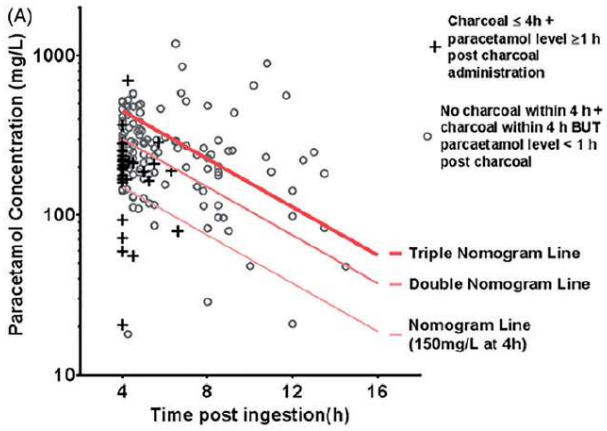
Children up to 1 year
1 gram/kg

Children 1-12 years
1-2 gram/kg to a maximum of 50 grams

Adolescents and Adults
1-2 gram/kg to a maximum of 100 grams

Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2)

Angela L. Chiew, Geoffrey K. Isbister, Katharine A. Kirby, Colin B. Page, Betty S. H. Chan & Nicholas A. Buckley



A. L. CHIEW ET AL. (2017)

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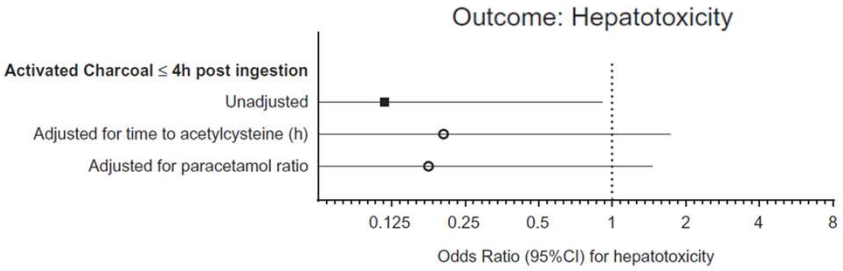

A. L. CHIEW ET AL. (2017)

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N-ACETYL CYSTEINE

INTRAVENOUS 21 HOUR PROTOCOL (TRADITIONAL)

Loading Dose: 150 mg/kg acetylcysteine IV in 200 mL dextrose 5% in water over 60 minutes immediately followed by:

Second Infusion: 50 mg/kg acetylcysteine IV in 500 mL dextrose 5% in water over 4 hours, immediately followed by:

Third Infusion: 100 mg/kg acetylcysteine IV in 1000 mL dextrose 5% in water over 16 hours

INTRAVENOUS 21 HOUR PROTOCOL (SINGLE CONCENTRATION)

This protocol will use one standard concentration: **Acetylcysteine (NAC) 30 mg/mL.** See Administration Section below for preparation instruction.

Dose is calculated using total body weight up to a **maximum of 100 kg**.

Loading Dose: 150 mg/kg acetylcysteine IV over 60 minutes, immediately followed by:

Continuous Infusion: 15 mg/kg/h acetylcysteine IV for a minimum of 20 h (ALERT — verify rate change on pump)

https://atlanticcanadapoisoncentre.ca/acetylcysteine-adult.html

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N-ACETYL CYSTEINE

Predicting the requirement for N-acetylcysteine in paracetamol poisoning from reported dose

S. B. DUFFULL,[1] and G. K. ISBISTER[2,3]

[1]*School of Pharmacy, University of Otago, Dunedin, New Zealand*
[2]*Discipline of Clinical Pharmacology, University of Newcastle, Newcastle NSW, Australia*
[3]*Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle, Waratah NSW, Australia*

Table 1. Comparison of patients with an early (4–7 h) first paracetamol concentration to patients with a late (7–16 h) first paracetamol concentration.

Median and IQR; percentage	All admissions	Early admissions	Late admissions
Number of cases	1571	1241	330
Sex (Female)	1140[a] (72.6%)	919[a] (74.1%)	221[a] (67.0%)
Age (years)[b]	26 (20–39)	26 (20–38)	29 (20–42)
Dose (g)[b]	10 (6–16)	10 (6–15)	11 (6–18)
Time of paracetamol concentration (hours)[b]	4.5 (4–6.6)	4.25 (4–5)	10 (8.5–12.3)
Paracetamol concentration (micromol/L)[b]	288 (102–655)	315 (123–697)	173 (57–451)
SDAC	314 (20.0%)	314 (25.3%)	0
Time of SDAC (hours)[b]	2 (1.33–3)	2 (1.33–3)	
NAC treatment	443 (28.2%)	286 (23.0%)	157 (47.6%)
Alanine transaminase (ALT; I/U)[b]	60 (45–90)	56 (43–80)	70 (49–346)
Hepatotoxicity (ALT > 1000)	23 (1.5%)	5 (0.4%)	18 (5.5%)
Above nomogram line	337 (21.5%)	226 (18.2%)	111 (33.6%)

[a]Number.
[b]IQR (interquartile range).

S. B. Duffull et al. (2013)

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DIALYSIS

Extracorporeal treatment for acetaminophen poisoning: Recommendations from the EXTRIP workgroup

S. Gosselin, D. N. Juurlink, J. T. Kielstein, M. Ghannoum, V. Lavergne, T. D. Nolin, R. S. Hoffman & on behalf of the extrip workgroup

ECTR is recommended:

- If the [APAP] more than 1000 mg/L (6620 µmol/L) and NAC is NOT administered (1D)
- If the patient presents with altered mental status, metabolic acidosis, with an elevated lactate, and an [APAP] is more than 700 mg/L (4630 µmol/L) and NAC is NOT administered (1D)
- If the patient presents with an altered mental status, metabolic acidosis, an elevated lactate, and an [APAP] is more than 900 mg/L (5960 µmol/L) even if NAC is administered (1D)

Intermittent hemodialysis is the preferred ECTR in patients with APAP poisoning

S. GOSSELIN ET AL. (2014)

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LIVER TRANSPLANT

Outcomes in Adults With Acute Liver Failure Between 1998 and 2013:

An Observational Cohort Study

Adrian Reuben, MBBS, Holly Tillman, MS, Robert J. Fontana, MD, Timothy Davern, MD, et al.

Variable	Overall (1998–2013) (n = 2070)		Early (1998–2005) (n = 989)		Later (2006–2013) (n = 1081)		P Value*
	Total Patients, n	Patients, n (%)	Total Patients, n	Patients, n (%)	Total Patients, n	Patients, n (%)	
APAP toxicity							
Listed for transplantation	955	228 (23.9)	450	126 (28.0)	505	102 (20.2)	**0.005**
TFS	955	668 (70.0)	450	286 (63.6)	505	382 (75.6)	**<0.001**
Non-APAP cause							
Listed for transplantation	1106	547 (49.5)	539	304 (56.4)	567	243 (42.9)	**<0.001**
TFS	1106	381 (34.5)	539	160 (29.7)	567	221 (39.0)	**0.001**

Criteria 1	Criteria 2 (all three required)
pH < 7.3, irrespective of grade of encephalopathy	Prothrombin time > 100 seconds AND
	Serum creatinine >3.4 mg/dL (300 micromol/L AND
	Grade III or IV encephalopathy

Figure 1. King's College Criteria for liver transplantation in acetaminophen-induced fulminant hepatic failure.

A. REUBEN ET AL. (2016)

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LIVER TRANSPLANT

Hypoglycemia and lactic acidosis outperform King's College criteria for predicting death or transplant in acetaminophen toxic patients

Michael Levine, Samuel J. Stellpflug, Anthony F. Pizon, David A. Peak, Janna Villano, Timothy Wiegand, Christian Dib & Stephen H. Thomas

Criteria 1	Criteria 2 (all three required)
pH < 7.3, irrespective of grade of encephalopathy	Prothrombin time > 100 seconds AND
	Serum creatinine >3.4 mg/dL (300 micromol/L AND
	Grade III or IV encephalopathy

Figure 1. King's College Criteria for liver transplantation in acetaminophen-induced fulminant hepatic failure.

M. LEVINE ET AL. (2018)

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05

AVAILABLE EVIDENCE

Discuss the available evidence supporting the different IV N-Acetylcysteine regimens

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	SCHMIDT ET AL. (2018) N = 767	MCNULTY ET AL. (2018) N = 476	WONG & GRAUDINS (2016) N = 599	BATEMAN ET AL. (2014) N = 222
INTERVENTION	TWO BAG (N=493) 1) 200MG/KG OVER 4 HR 2) 100MG/KG OVER 16 HR TOTAL DOSE: 300MG/KG	TWO BAG (N=163) 1) 200MG/KG OVER 4 HR 2) 100MG/KG OVER 16 HR TOTAL DOSE: 300MG/KG	TWO BAG (N=210) 1) 200MG/KG OVER 4 HOUR 2) 100MG/KG OVER 16 HR TOTAL DOSE: 300MG/KG	TWO BAG (N=108) 1) 100MG/KG OVER 2 HOUR 2) 200MG/KG OVER 10 HR TOTAL DOSE: 300MG/KG
COMPARATOR	THREE BAG (N=274) 1) 150MG/KG OVER 15MIN 2) 50MG/KG OVER 4 HR 3) 100MG/KG OVER 16 HR TOTAL DOSE: 300MG/KG	THREE BAG (N=313) 1) 150MG/KG OVER 15MIN TO 1HR 2) 50MG/KG OVER 4 HR 3) 100MG/KG OVER 16 HR TOTAL DOSE: 300MG/KG	THREE BAG (N=389) 1) 150MG/KG OVER 1HR 2) 50MG/KG OVER 4 HR 3) 100MG/KG OVER 16 HR TOTAL DOSE: 300MG/KG	THREE BAG (N=109) 1) 150MG/KG OVER 15MIN 2) 50MG/KG OVER 4 HR 3) 100MG/KG OVER 16 HR TOTAL DOSE: 300MG/KG

	SCHMIDT ET AL. (2018) N = 767	MCNULTY ET AL. (2018) N = 476	WONG & GRAUDINS (2016) N = 599	BATEMAN ET AL. (2014) N = 222
SAFETY ADVERSE EVENTS: NON-ALLERGIC ANAPHYLACTIC REACTIONS (NAARS)	4% TWO BAG VS. 17% THREE BAG DIFFERENCE: 13% 95% CI (-17.6%, -8.0%) P<0.001	14% THREE BAG VS 5% TWO BAG DIFFERENCE: 9% 95% CI (4.3%, 14.6%) P=0.002	10% THREE BAG VS 4.3% TWO BAG DIFFERENCE: 5.7%, OR 2.5 95% CI (1.1, 5.8) P=0.02	4.6% TWO BAG VS 31% DIFFERENCE: 26.4% OR 0.23 97.5% CI 0.12, 0.43; P<0.0001
EFFICACY HYPATOTOXICITY	DEFINITION OF HEPATOTOXICITY: ALT >1000 IU/L OCCURRENCE: 4% TWO BAG VS. 4% THREE BAG, DIFFERENCE: 0, 95% CI (-2.9%, 3.0%) P=0.03	DEFINITION OF HEPATOTOXICITY: ALT >1000 IU/L OCCURRENCE: 4.8% THREE BAG VS. 3.7% TWO BAG, DIFFERENCE: 1.1, 95% CI (-2.6%, 4.8%) P=0.58	DEFINITION OF HEPATOTOXICITY: ALT >1000 IU/L OCCURRENCE: 5.2% TWO BAG VS 4.3% THREE BAG, DIFFERENCE 0.9, P=0.68, OR 1.2 95% CI (0.55, 2.63)	DEFINITION OF HEPATOTOXICITY: ALT INCREASE OF 50% OF BASELINE OCCURRENCE: 12.8% THREE BAG VS. 9% TWO BAG DIFFERENCE 3.8, OR 0.60, 97.5% CI (0.20, 1.83)

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Single bag high dose intravenous N-acetylcysteine associated with decreased hepatotoxicity compared to triple bag intravenous N-acetylcysteine in high-risk acetaminophen ingestions

Kartik R. Shah & Michael C. Beuhler

Design: Retrospective observational study from January 1, 2016 to December 31, 2017
Population: 89 high risk acetaminophen ingestions with a multiplication product > 10,000 mg/L IU/L, not having received NAC within 8 hours.
Interventions: 23 patients receiving standard IV NAC; 150 mg/kg over 1 h, 12.5 mg/kg/hour for 4 h, and 6.25 mg/kg/ hour until medical clearance vs 66 patients receiving 150mg/kg over 1h and 15mg/kg/ hour until medical clearance.
Bottom Line: In a high-risk population of patients with acetaminophen ingestions, the single bag IV NAC regimen was associated with lower peak transaminase and fewer patients becoming hepatotoxic as compared to the triple bag IV NAC regimen.

Table 3. Hepatotoxicity and coagulopathy between the two IV NAC regimens.

	Triple Bag IV NAC $N = 23$	PC IV NAC $N = 66$	
Hepatotoxicity[a]	12 (52%)	19 (29%)	$p = .043$
Mean peak transaminase in IU/L (SD)	4481 (5256)	2143 (3853)	$p = .026$
Coagulopathy[b]	10 (43%)	15 (23%)	$p = .057$

[a]Hepatotoxicity was defined as peak transaminase $\geq$ 1000 IU/L.
[b]Coagulopathy was defined as peak INR $\geq$ 2.

S. KARTIK ET AL. (2013)

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06

"NEWER" TREATMENTS

Evaluate evidence supporting "newer" treatment options emerging for Acetaminophen toxicity

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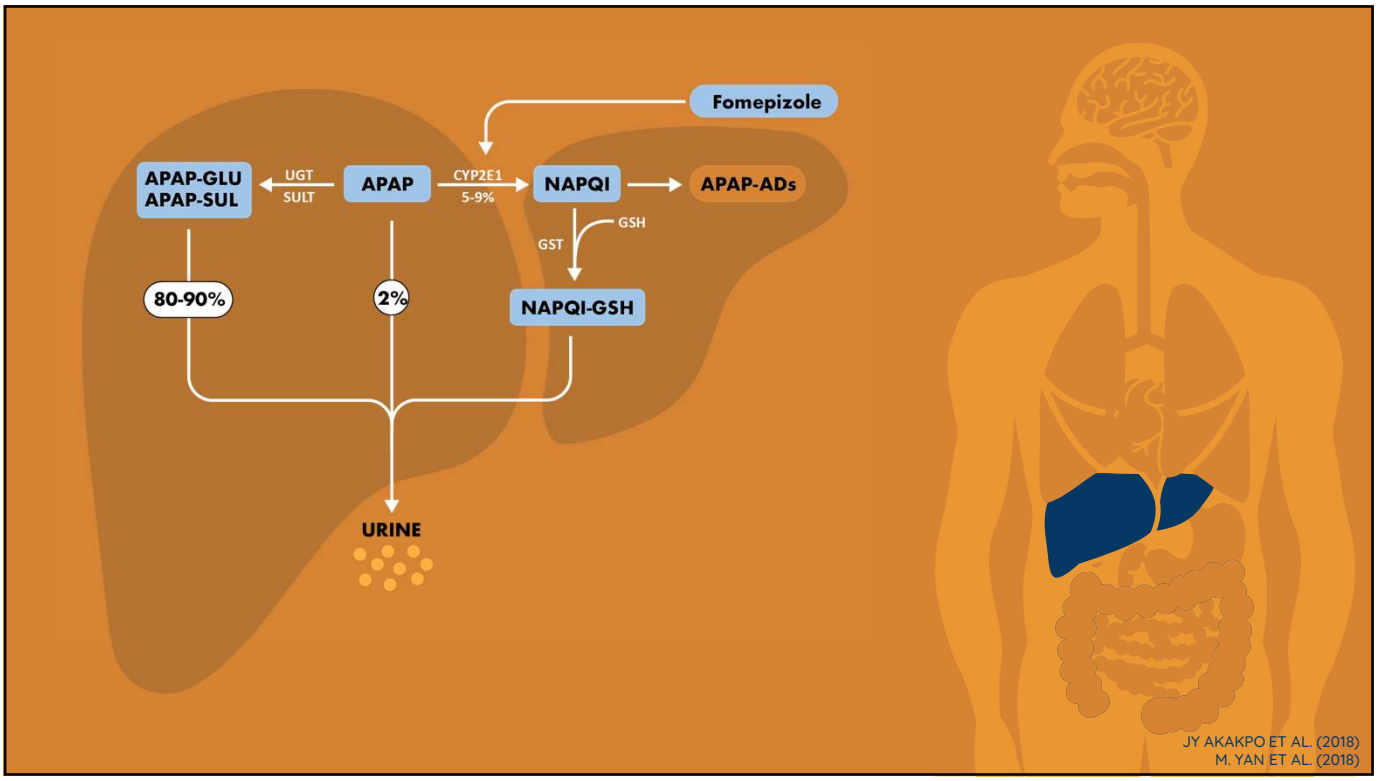
Fomepizole
APAP-GLU
APAP-SUL
UGT
SULT
APAP
CYP2E1
5-9%
NAPQI
APAP-ADs
GSH
GST
80-90%
2%
NAPQI-GSH
URINE
JY AKAKPO ET AL. (2018)
M. YAN ET AL. (2018)

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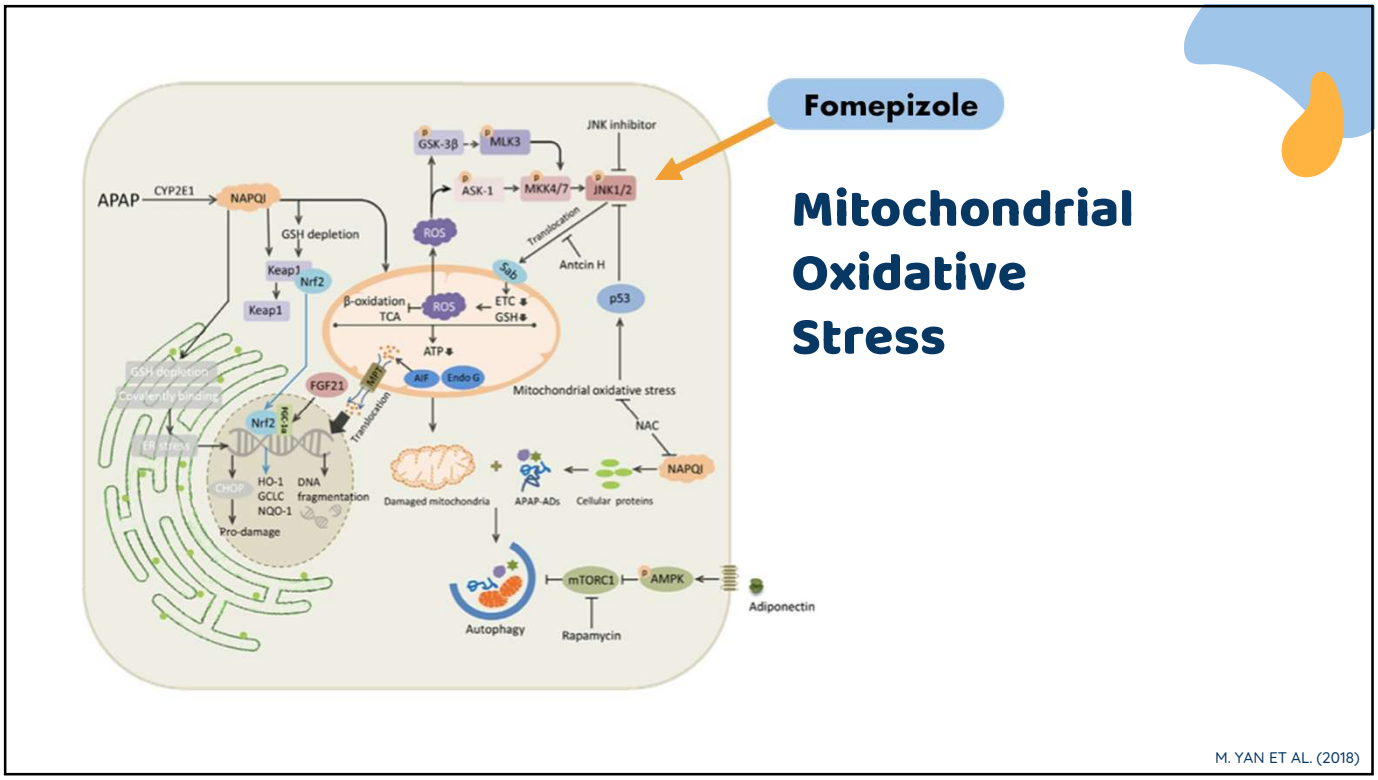
Fomepizole
Mitochondrial Oxidative Stress
APAP
CYP2E1
NAPQI
GSH depletion
Keap1
Nrf2
ROS
GSK-3β
MLK3
JNK inhibitor
ASK-1
MKK4/7
JNK1/2
Translocation
Antcin H
Sab
p53
β-oxidation
TCA
ETC
GSH
ATP
FGF21
AIF
Endo G
Mitochondrial oxidative stress
NAC
HO-1
GCLC
NQO-1
DNA fragmentation
CHOP
Pro-damage
Damaged mitochondria
APAP-ADs
Cellular proteins
Autophagy
mTORC1
AMPK
Rapamycin
Adiponectin
M. YAN ET AL. (2018)

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Fomepizole as an adjunct in acetylcysteine treated acetaminophen overdose patients: a case series

Stephanie L. Link, Garrett Rampon, Stephen Osmon, Anthony J. Scalzo & Barry H. Rumack

Design: Prospective case series
Population: 14 high risk cases with significantly elevated APAP level
Interventions: Fomepizole 15mg/kg +/- repeat dosing (Clinical Judgement)
Bottom Line: This case series demonstrates the safety of fomepizole in acute acetaminophen overdose with better-than-expected outcomes.

Fomepizole as an adjunctive therapy for acetaminophen poisoning: cases reported to the toxicology investigators consortium (ToxIC) database 2015–2020

Ari B. Filip, Sarah E. Berg, Michael E. Mullins, Evan S. Schwarz & On behalf of the Toxicology Investigators Consortium (ToxIC)

Design: Prospective case series (secondary analysis)
Population: 25 cases with severe APAP toxicity.
*median reported lactate = 8mmol/L
Interventions: Fomepizole 15mg/kg +/- repeat dosing (Clinical Judgement)
Bottom Line: Fomepizole is being used increasingly to treat severe APAP toxicity, further data required to support safety and efficacy.

S. LINK ET AL. (2022)
A. FILIP ET AL. (2022)

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Fomepizole

15mg/kg over 30 minutes, repeat dosing rare q12h rarely

GENERAL CRITERIA
Metabolic acidosis
Significantly elevated acetaminophen level
Mental status changes

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THANK YOU

QUESTIONS?

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