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Management of Acetaminophen Poisoning in the US and Canada: A Consensus Guideline

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Meet the Faculty

- Richard C. Dart, MD, PhD
- Lee Cantrell, PharmD

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Relevant Financial Relationship Disclosure

The following persons in control of this activity's content have relevant financial relationships:

- **Richard Dart: Johnson & Johnson, PI/named investigator of research grant from ineligible companies**

All other persons in control of content do not have any relevant financial relationships with an ineligible company.

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Competing Interests

This work supported by an educational grant from Johnson & Johnson Consumer, Inc. Johnson & Johnson had no influence on the methodology, process, or results of the study.

Panel:

- Dr. Dart has received research support from J&J outside the submitted work.
- Dr. Burns reported receiving royalties from UpToDate outside the submitted work.
- Dr. Heard reported receiving royalties from UpToDate outside the submitted work.
- Dr. Funk reported serving on the board of trustees of AACT.
- Dr. Cole reported serving as an elected board member of the AACT.

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Learning Objectives

- Describe the processes involved in acute care management of acetaminophen overdose in the U.S. and Canada.
- Evaluate expert panel developed consensus guidelines for acetaminophen overdose.
- Identify opportunities for further research and novel applications of consensus guideline methodology in acetaminophen overdose.

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Participating Organizations

AMERICA'S POISON CENTERS
Treatment • Education • Prevention

AACT
American Academy of Clinical Toxicology

ACMT American College of Medical Toxicology
"Advancing the toxicologic care of patients and populations"

Canadian Association for Poison Centres and Clinical Toxicology

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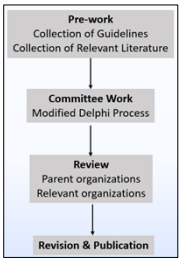
Consensus Guidelines on the Management of Acetaminophen Poisoning in the US and Canada

Richard C. Dart, MD, PhD
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Project Overview




JAMA Network Open.

Consensus Statement | Emergency Medicine

Management of Acetaminophen Poisoning in the US and Canada
A Consensus Statement

Abstract

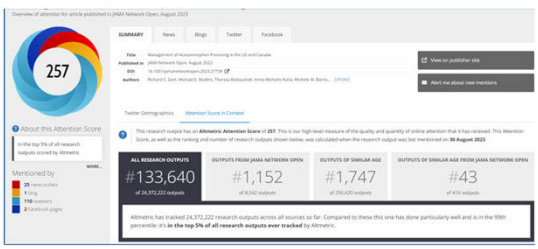
Key Points

JAMA Netw Open. 2023;6(8):e2327739.
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Publication in JAMA Network Open



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Panel and Team

North American Consensus Guidelines for Acetaminophen Poisoning (NAC-GAP) Panelists		
Maryann Amirshahi	Kennon Heard	Steve Seifert
Bill Banner	Rob Hendrickson	Marco Sivilotti
Michael Beuhler	Scott Lucyk	Andrew Stolbach
Michelle Burns	Theresa Matoushek	Christine Stork
Lee Cantrell	Michael Mullins	Karen Simone
Jon Cole	Lewis Nelson	Mark Su
Ally Funk	Michelle Ruha	Shawn Varney

RMPDS (Non-Voting)	
Richard Dart, Non-Voting Chair	Alicia Dalton, Project Management
Barry Rumack, Special Advisor	Ellie Fox, Project Management

Speakers

Richard C. Dart, MD, PhD	• Acute and Repeated Ingestions • Emergency Department Management Guideline • High-Risk Ingestions • Repeated Supratherapeutic Ingestions

Lee Cantrell, PharmD	• Dosing Regimen and Stopping Criteria for NAC
	• Special Issues
	  • Extended-Release Formulations
	  • Pregnancy
	  • Patients Weighing >100 kg
	  • Children
	  • IV Acetaminophen

Acute and Repeated Ingestions

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison & Drug Safety
Professor of Emergency Medicine, University of Colorado School of Medicine

What Type of Ingestion?

Past Definition

- Acute Ingestion
  - Variable - 1, 2, 4, 8, 12 hours
- Repeated (Chronic) Ingestion
  - Multiple doses amounting to more than 7.5 grams over 24 hours
    - Took a handful last every 6 – 8 hours for 2 days.

New Definition

- **Acute Ingestion**
  - **Anything LESS than 24 hours duration**
- **Repeated (Chronic) Ingestion**
  - **Anything OVER 24 hours duration**



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Background on Acute Ingestion

History of known or suspected acute ingestion of 7.5 g or more of acetaminophen *within 24 hours of admission.*

- 1981: Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med*. 1981;141:380-385.

N-acetylcysteine therapy was recommended in all cases of acute acetaminophen ingestion (and when N-acetylcysteine therapy could be initiated within 24 hours of the acetaminophen ingestion)

- **(1) when the *plasma acetaminophen concentration measured between 4 and 24 hours* after ingestion was about the study treatment nomogram line or**
- (2) if plasma concentrations were not available, when the estimated ingestion of acetaminophen exceeded either 7.5 g in and adult or 140 mg/kg in a child.

- 1988: Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med*. 1988;319(24):1557-1562

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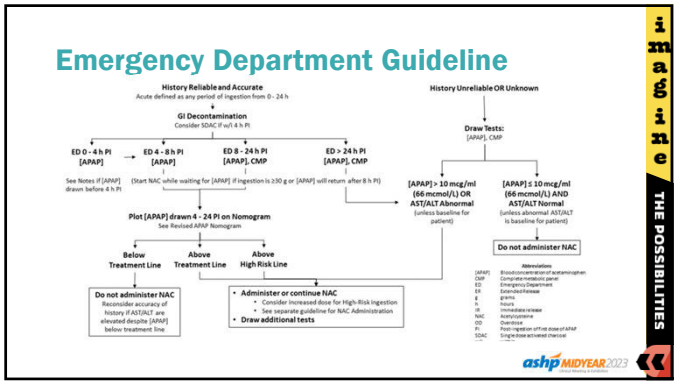
Emergency Department Guideline

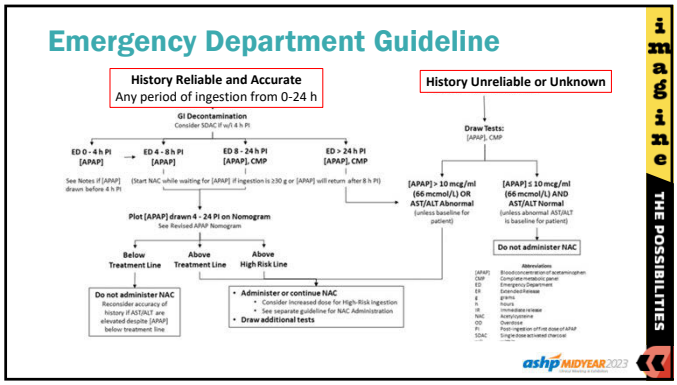
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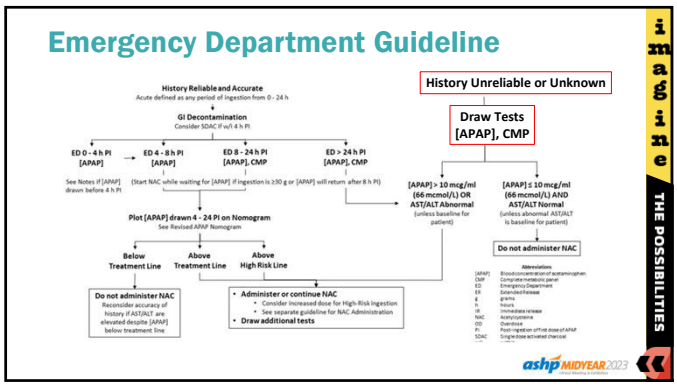
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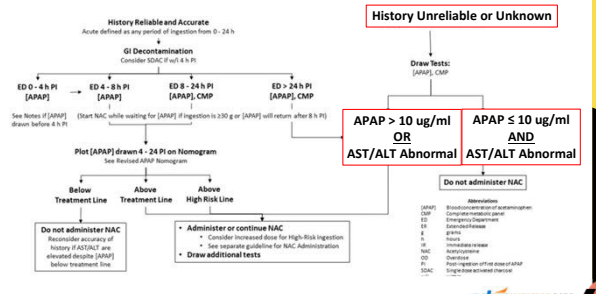




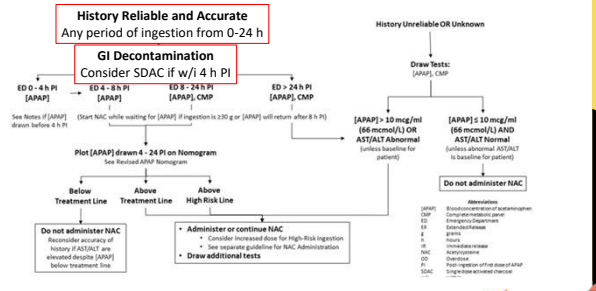


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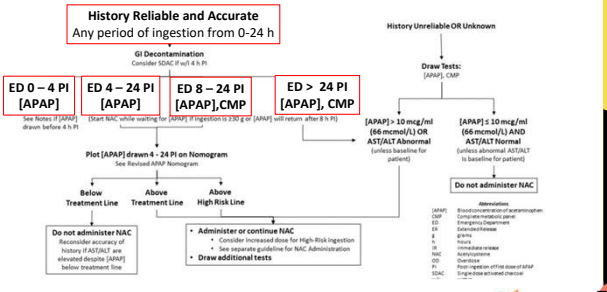
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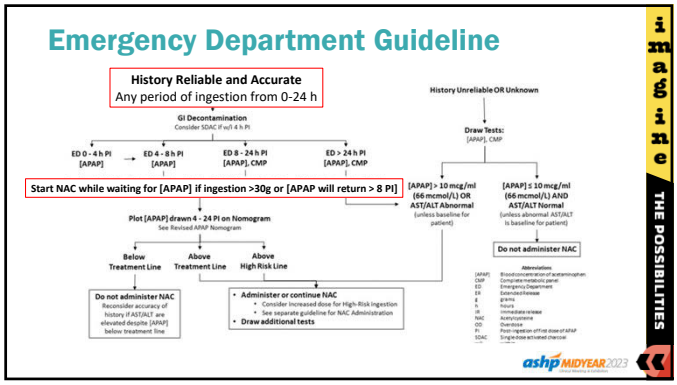
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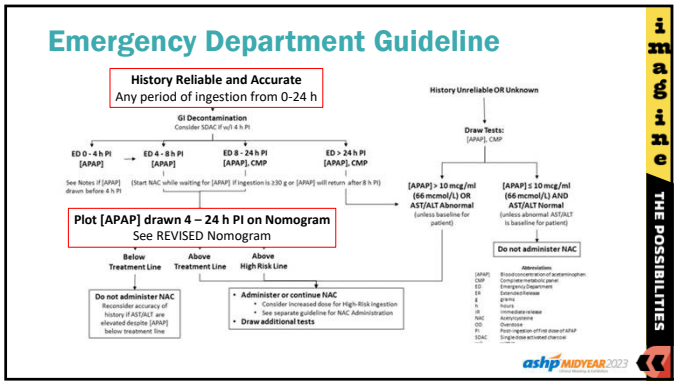


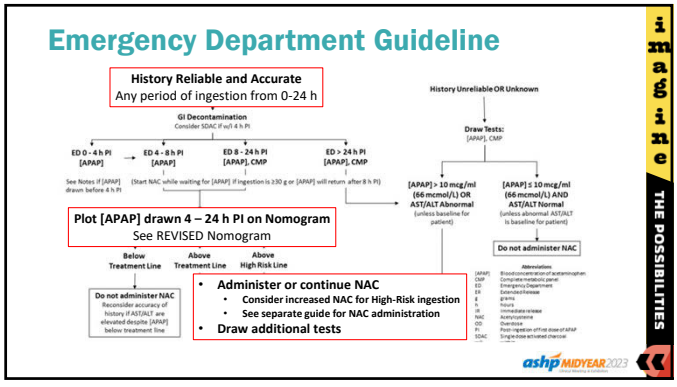
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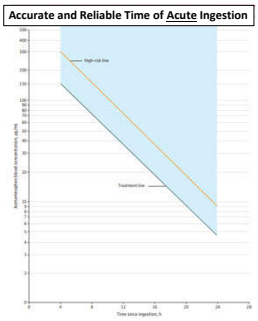
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High-Risk Ingestions

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Revised Rumack- Matthew Nomogram for Assessment of *Acute Ingestion* of APAP



High-Risk Ingestion of Acetaminophen: Key Points

Definition:

- An acute acetaminophen (APAP) ingestion of at least 30 grams OR an ingestion that results in a blood [APAP] above the High-Risk Line on Revised Nomogram.
- High-Risk Ingestions are managed in the same manner as acute ingestion of any acetaminophen product with the following modifications

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High-Risk Ingestion of Acetaminophen: Key Points - Continued

- SDAC may be indicated if there is evidence of APAP in the stomach or GI tract after 4 hours.
- Additional labs may be warranted if the patient has developed signs of mitochondrial dysfunction such as altered level of consciousness (ALOC), metabolic acidosis, or hyperlactatemia. Evaluation of other causes of ALOC is recommended.
- Increased dosage of acetylcysteine may be warranted if [APAP] falls above High-Risk Line on the Revised APAP Nomogram. Consultation with a poison center or clinical toxicologist is recommended.
- Enhanced elimination and referral for transplant evaluation are the same.
  - Enhanced elimination guideline in line with EXTRIP criteria

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Repeated Supratherapeutic Ingestions

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Repeated Supratherapeutic Ingestion (RSTI)

- Just draw APAP concentration and AST/ALT
  - If APAP is > 20 mcg/ml OR AST/ALT is elevated → NAC
  - If APAP is < 20 mcg/ml AND AST/ALT are normal → Do Not Treat



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Dosing Regimen for Acetylcysteine and Stopping Criteria

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Clinical Professor of Pharmacy, UC San Francisco School of Pharmacy
Clinical Professor of Pharmacy, UC San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences

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Acetylcysteine Administration (NAC)

Bottom Line:

- *Use NAC the same way your institution does now!*





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Administration of Acetylcysteine

Decision to administer NAC for any acetaminophen poisoning

↓

Administer NAC for 20-24 h depending on regimen chosen

- Use FDA-approved or published IV or oral protocol that delivers a minimum of 300 mg/kg over 20-24 h
- If >30 g was ingested or in acetaminophen concentration will return after 8 h postingestion, start NAC
- If 150 mg/kg loading dose is used, it should be given over at least 1 h

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Acetylcysteine Stopping Criteria

Decision to administer NAC for any acetaminophen poisoning

Administer NAC for 20-24 h depending on regimen chosen
- Use FDA-approved or published IV or oral protocol that delivers a minimum of 300 mg/kg over 20-24 h
- If >30 g was ingested or in acetaminophen concentration will return after 8 h post-ingestion, start NAC
- If 150 mg/kg loading dose is used, it should be given over at least 1 h

Measure acetaminophen concentration, AST/ALT, PT/INR, and assess NAC stopping criteria before end of infusion:

NAC Stopping Criteria
- Acetaminophen concentration < 10 mcg/ml
- INR <2.0
- AST/ALT normal for patient if if elevated have decreased from peak (25%-50%)
- Patient is clinical well

STOP

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What if Stopping Criteria Are NOT met?

NAC Stopping Criteria
- Acetaminophen concentration < 10 mcg/ml
- INR <2.0
- AST/ALT normal for patient if if elevated have decreased from peak (25%-50%)
- Patient is clinical well

STOP

Continue NAC until stopping criteria are met
- Continue IV NAC at a rate of at least 6.25 mg/kg/h
- Draw [APAP], AST/ALT, and PT/INR every 12-24 h
- Assess NAC stopping criteria are met

Criteria met
Do not administer further NAC

Criteria not met
Continue NAC treatment
Continue IV NAC at rate of at least 6.25 mg/kg/h

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Special Issues
Extended-Release Formulations, Pregnancy, Patients >100kg, Children, IV Acetaminophen

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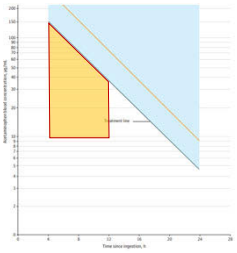
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Extended-Release Acetaminophen Products

- Definition: Acetaminophen products available in the US or Canada and labeled for use on an 8-hour basis.
- Management is the same as other acetaminophen products except:
  - Activated charcoal may be useful longer than 4 hours after ingestion if evidence of ongoing absorption is present (e.g., increasing [APAP]).
  - Acetylcysteine
    - If [APAP] from samples drawn 4 to 24 hours after ingestion is above the nomogram treatment line, acetylcysteine is needed.
    - If the concentration from samples drawn 4 to 12 hours after ingestion is below the treatment line but above 10 µg/mL, it should be measured again 4 to 6 hours after the first measurement.

Extended Release Formulations



Orange zone is where a repeat [APAP] level should be obtained 4 to 6 hours later for Extended Release Formulation ingestions after the first [APAP].

Pregnancy

- The standard evaluation and management of acetaminophen poisoning are the same in the pregnant patient except
  - Some clinicians prefer the IV route for acetylcysteine administration. However, no data are available to demonstrate that the oral route is less effective in the pregnant patient.

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Patients Weighing More Than 100 Kg

- Management of poisoning in patients who weigh more than 100 kg is the same as that for ingestion of any acetaminophen product.
  - The exception is that calculation of acetylcysteine dose should be capped at 100 kg of body weight.

Patients Younger Than 6 Years

- Management in patients younger than 6 years is the same as for older patients except
  - IV APAP:
    - Single IV APAP dose of 90 mg/kg body weight or a cumulative dose of greater than 150 mg/kg body weight during 24 hours → contact a clinical toxicologist or poison center.
  - With some regimens, administration of acetylcysteine requires weight based adjustment to avoid hyponatremia for patients who weigh less than 41 kg. This is addressed in the package labeling or through the poison center.

IV Acetaminophen

Definition

- Acetaminophen (APAP) for injection (10 mg/ml).

Diagnosis and Assessment

- A poison center or clinical toxicologist should be contacted if a patient <~~-~~less than 6 years of age receives IV APAP single dose of 90 mg/kg or a cumulative dose of >~~-~~greater than 150 mg/kg over 24 hours.
- Assessment in patients of any age includes ~~an~~ blood acetaminophen concentration ([APAP]) and AST/ALT.

Treatment with acetylcysteine

- The use of acetylcysteine is the same as other ~~acetaminophen~~ APAP ingestions-(see guidelines for acetylcysteine administration and age < less than 6 years)

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Self-Assessment Question

By definition, an acute ingestion in acetaminophen must begin and end within what period of time?

1. 24 hours
2. 4 hours
3. 8 hours
4. 12 hours
5. 48 hours

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Self-Assessment Question

What is the dose of IV acetylcysteine for adults and children?

1. A minimum of 300 mg/kg infused over 20 t0 21 hours.
2. 150 mg/kg followed by additional doses as prescribed by health care provider
3. 200 mg/kg infused over 12 hours and followed by additional doses as prescribed by health care provider.
4. 600 mg/kg infused over 20 to 21 hours.
5. 10-15mg/kg over 20 to 21 hours

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Key Takeaways

1. Acute ingestion is defined as any ingestion pattern that spans < 24 hrs.
2. The 150 mg/kg IV loading dose should be infused over 1 hr rather than 15 min.
3. Use acetylcysteine the same way your hospital currently uses it!
4. The choice of route and dose for acetylcysteine is left up to the health care provider as long as it delivers at least 300/mg/kg in the first 20-21 hours.

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Questions?

Please send questions/comments to Richard.Dart@RMPDS.org

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