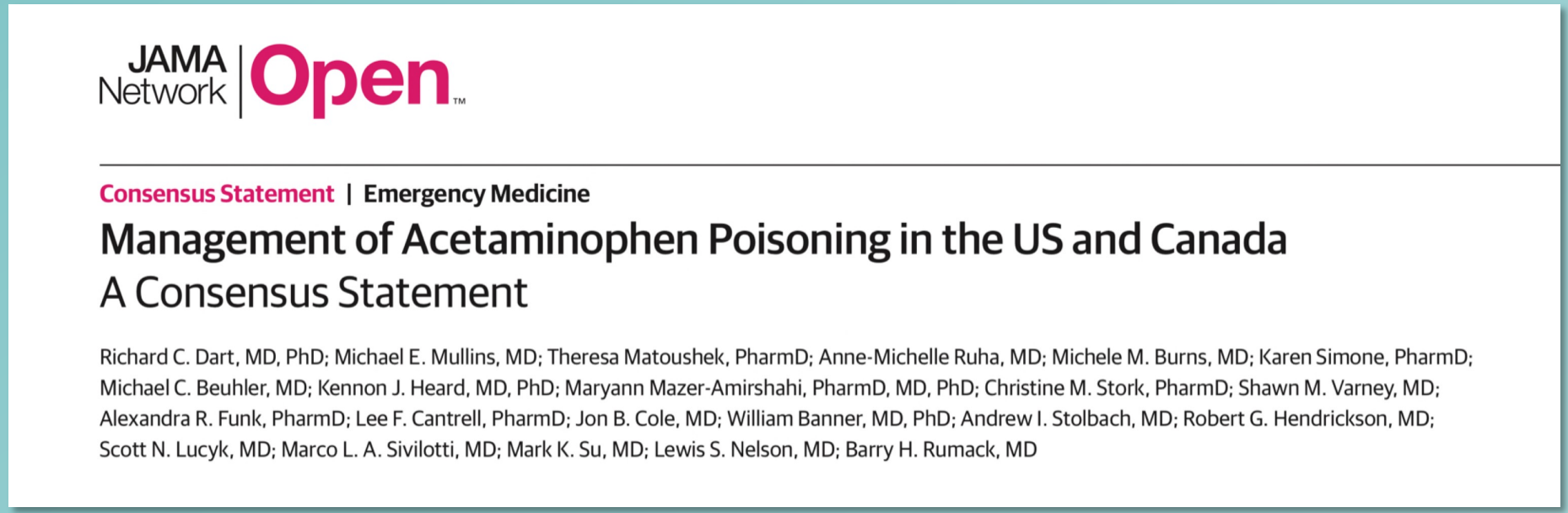
Management of Acetaminophen Poisoning 2023



JAMA Network | Open

Consensus Statement | Emergency Medicine

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

Richard C. Dart, MD, PhD; Michael E. Mullins, MD; Theresa Matoushek, PharmD; Anne-Michelle Ruha, MD; Michele M. Burns, MD; Karen Simone, PharmD; Michael C. Beuhler, MD; Kennon J. Heard, MD, PhD; Maryann Mazer-Amirshahi, PharmD, MD, PhD; Christine M. Stork, PharmD; Shawn M. Varney, MD; Alexandra R. Funk, PharmD; Lee F. Cantrell, PharmD; Jon B. Cole, MD; William Banner, MD, PhD; Andrew I. Stolbach, MD; Robert G. Hendrickson, MD; Scott N. Lucyk, MD; Marco L. A. Sivilotti, MD; Mark K. Su, MD; Lewis S. Nelson, MD; Barry H. Rumack, MD

Nattawit Kaewkomot MD.

References

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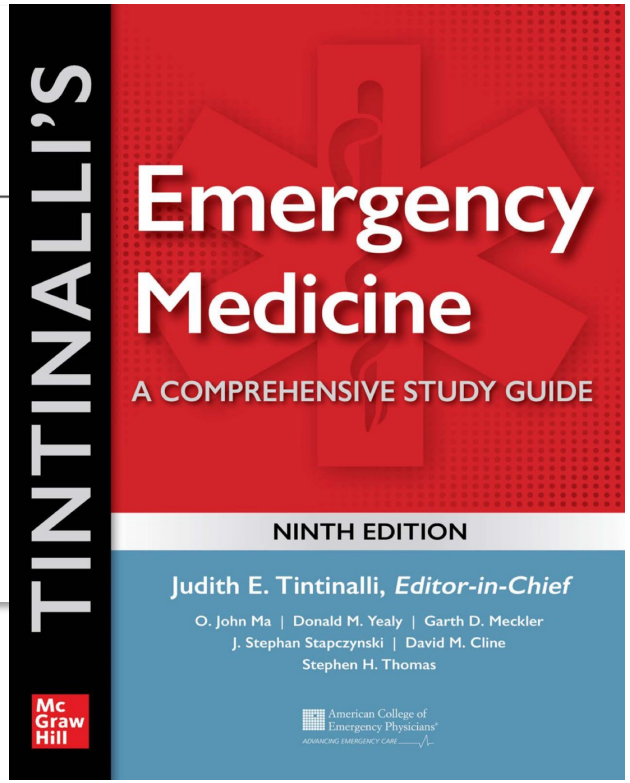


Abstract

IMPORTANCE

The US and Canada currently have **no** formal published nationwide guidelines for the management of acetaminophen poisoning, resulting in significant variability in management.

OBJECTIVE

To develop consensus guidelines for the management of acetaminophen poisoning in the US and Canada.

Abstract

EVIDENCE REVIEW

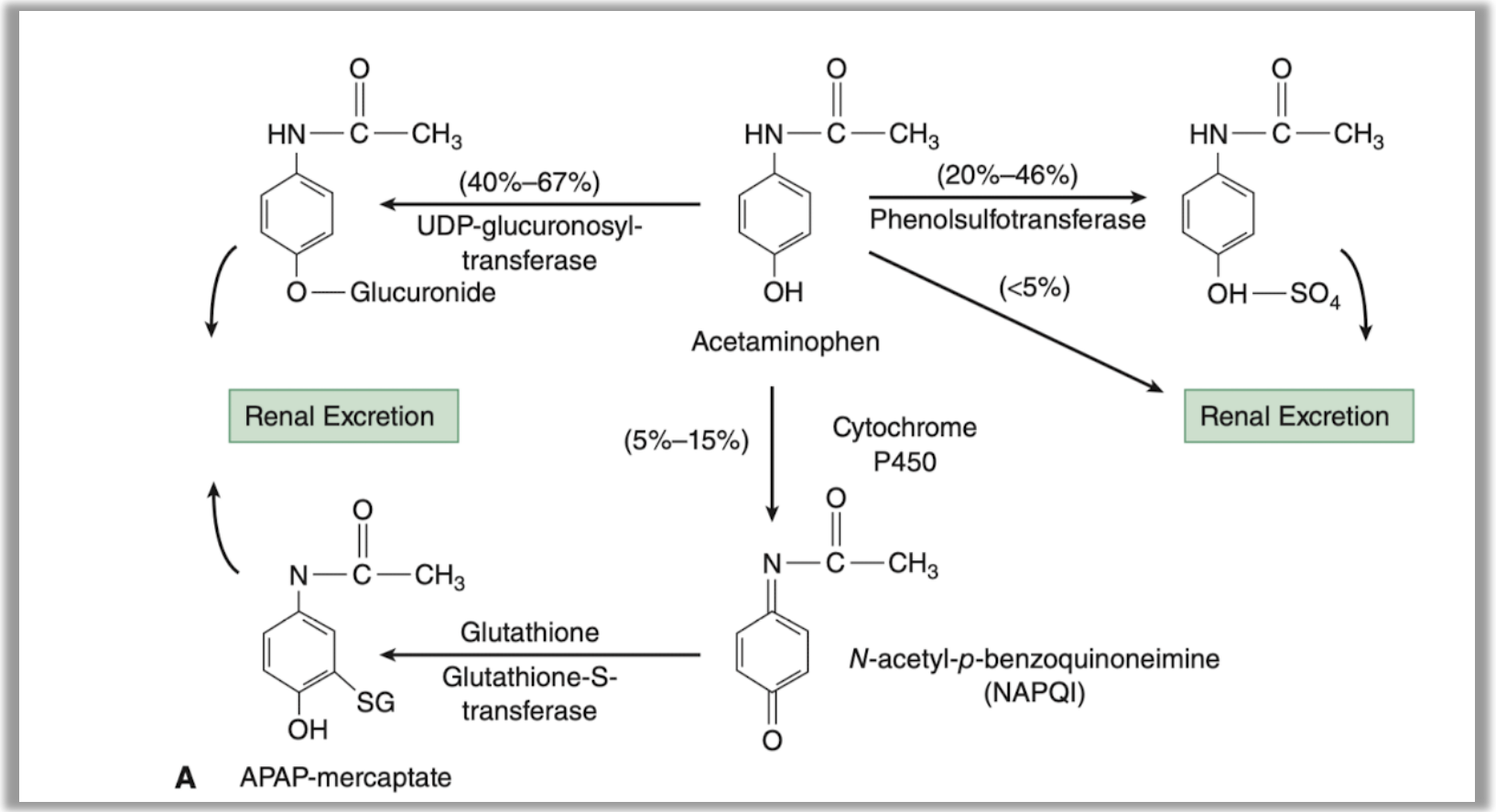
- Selected participants (n = 21) from Four clinical toxicology societies
- March 2021 - March 2023

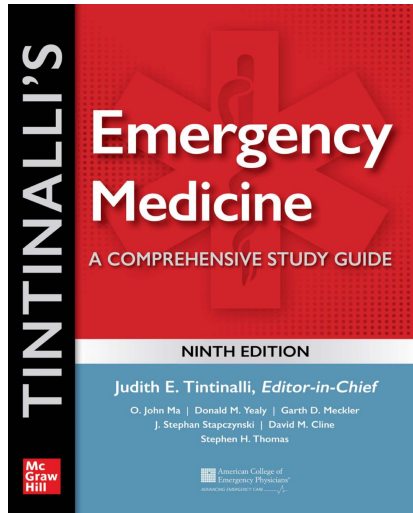
America's Poison Centers
American Academy of Clinical Toxicology
American College of Medical Toxicology
Canadian Association of Poison Control Centers

FINDINGS

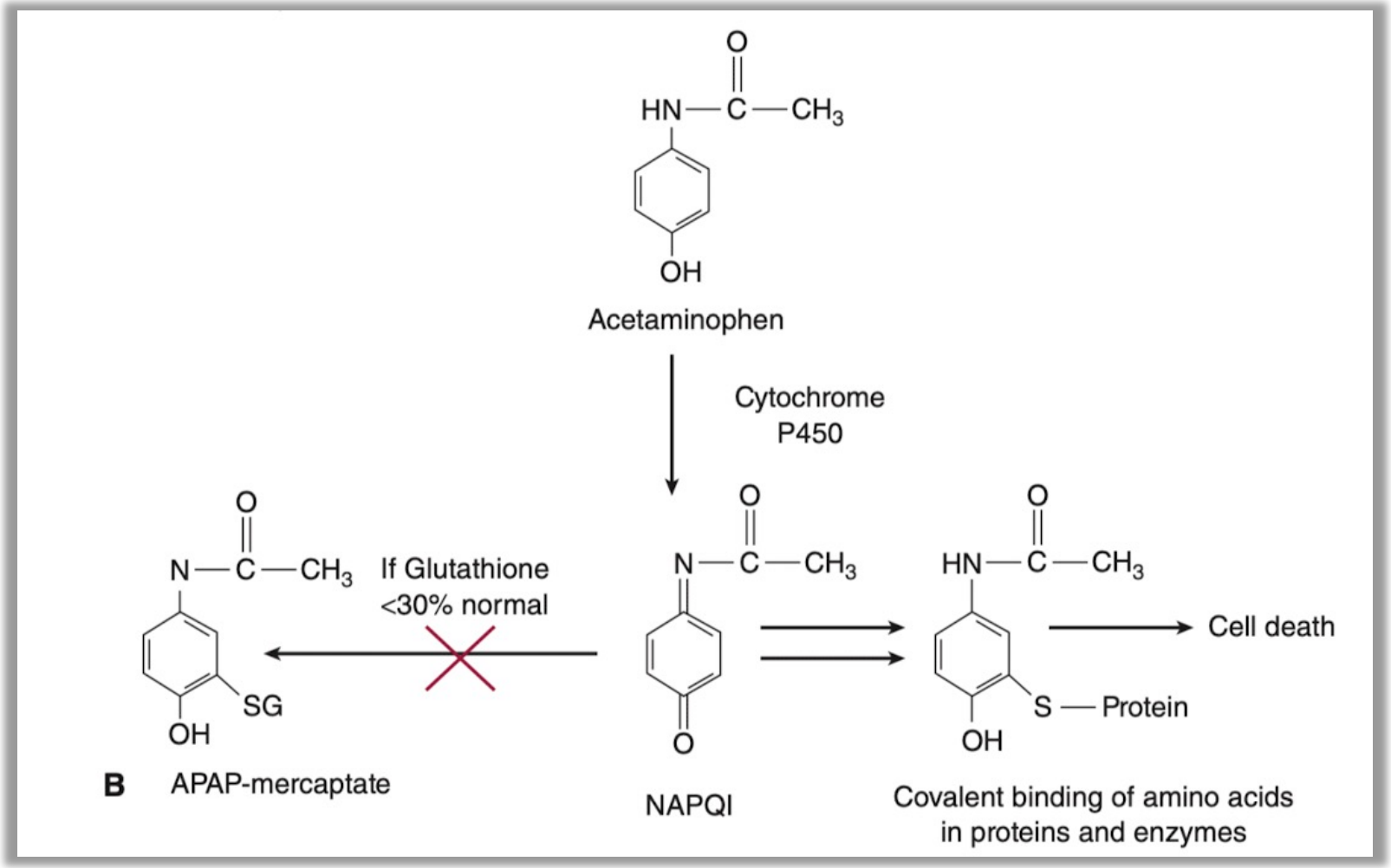
- 84 guidelines and 278 publications retrieved → **5 guidelines** and **7 publications** met evidence quality

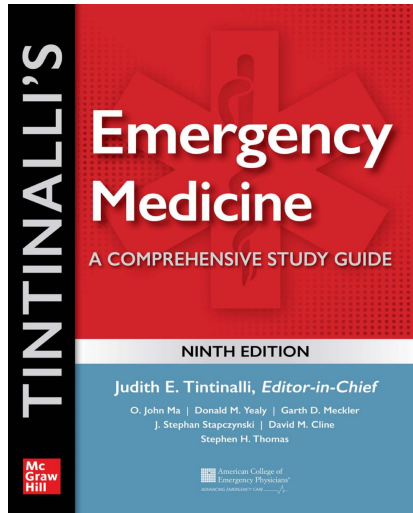
Introduction





Introduction





Introduction

TABLE 190-1 Clinical Stages of Acute Acetaminophen Toxicity

	Stage 1	Stage 2	Stage 3	Stage 4
Approximate timing	First 24 h	Days 2–3	Days 3–4	After day 5
Clinical manifestations	Anorexia Nausea Vomiting Malaise	Improvement in anorexia, nausea, and vomiting Abdominal pain Hepatic tenderness	Recurrence of anorexia, nausea, and vomiting Encephalopathy Anuria Jaundice	Clinical improvement and recovery (7–8 d) *or* Deterioration to multiorgan failure and death
Laboratory abnormalities		Elevated serum transaminases Elevated bilirubin and prolonged prothrombin time if severe	Hepatic failure Metabolic acidosis Coagulopathy Renal failure Pancreatitis	Improvement and resolution *or* Continued deterioration

Outline

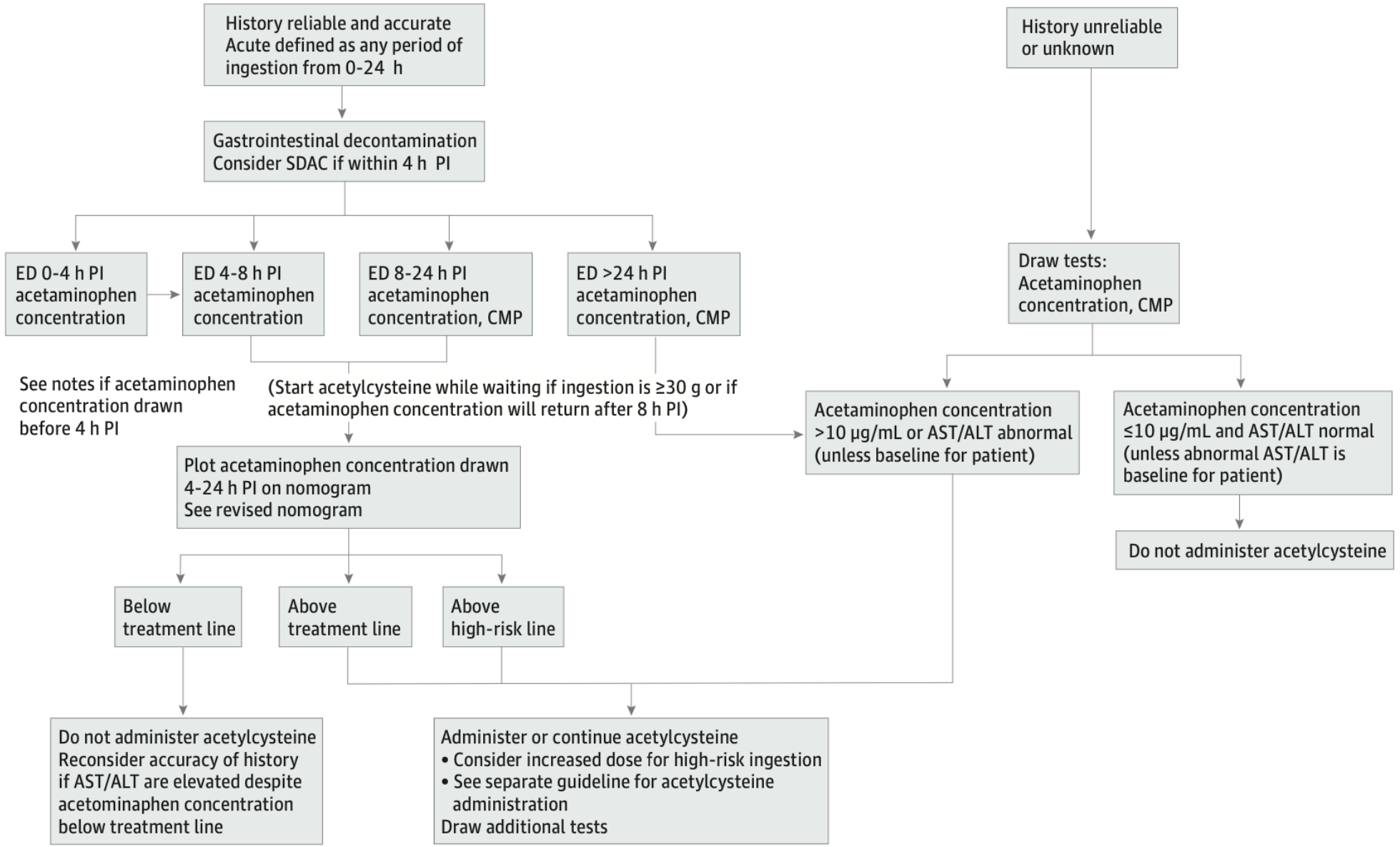
1. Management of Suspected Acute Ingestion of Immediate-Release Acetaminophen Products
2. Administration of Acetylcysteine
3. Special conditions

Outline

1. **Management of Suspected Acute Ingestion of Immediate-Release Acetaminophen Products**
2. Administration of Acetylcysteine
3. Special conditions

Management of Suspected Acute Ingestion of Immediate-Release Acetaminophen Products

Figure 1. Management of Acetaminophen Poisoning in a Medical Facility



High-Risk Acetaminophen Ingestion

High-risk ingestion

- Ingestion of **at least 30 grams** of acetaminophen
- or acetaminophen concentration **above the high-risk line** on the nomogram

Additional laboratory testing

- Indicated if developed **signs of mitochondrial dysfunction**; altered level of consciousness, metabolic acidosis, or hyperlactatemia.
- should include evaluation of **other causes of altered level of consciousness**

Increased dosage of acetylcysteine(NAC)

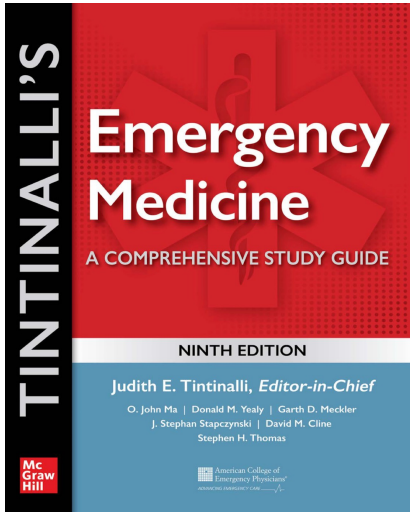
may be warranted in consultation with a Poison Center(PC) or clinical toxicologist

Diagnosis Acetaminophen poisoning

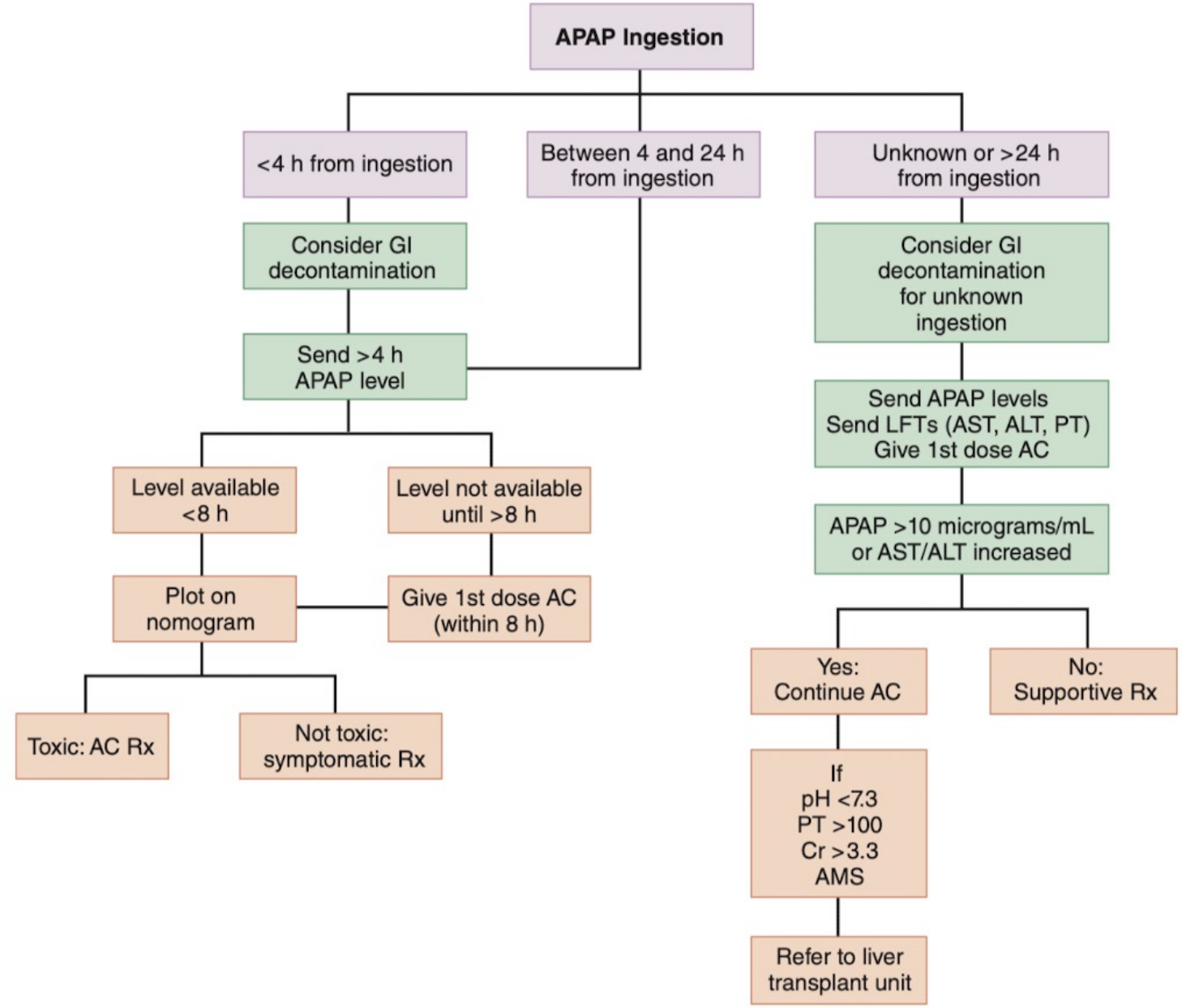
- A patient **≥6 years old** ingests
  1. >10 grams or 200 mg/kg as a single ingestion
  2. >10 grams or 200 mg/kg over a 24-hour period
  3. >6 grams or 150 mg/kg per 24-hour period for at least 2 consecutive days

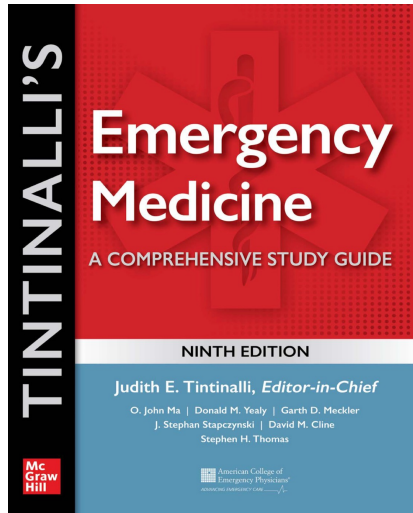
- For children **<6 years old** ingests
  1. > 200 mg/kg of acetaminophen as a single ingestion or over an 8-hour
  2. >150 mg/kg per 24-hour period for the preceding 48 hour

- **Massive Acetaminophen Overdose**: >40 grams or 500 mg/kg



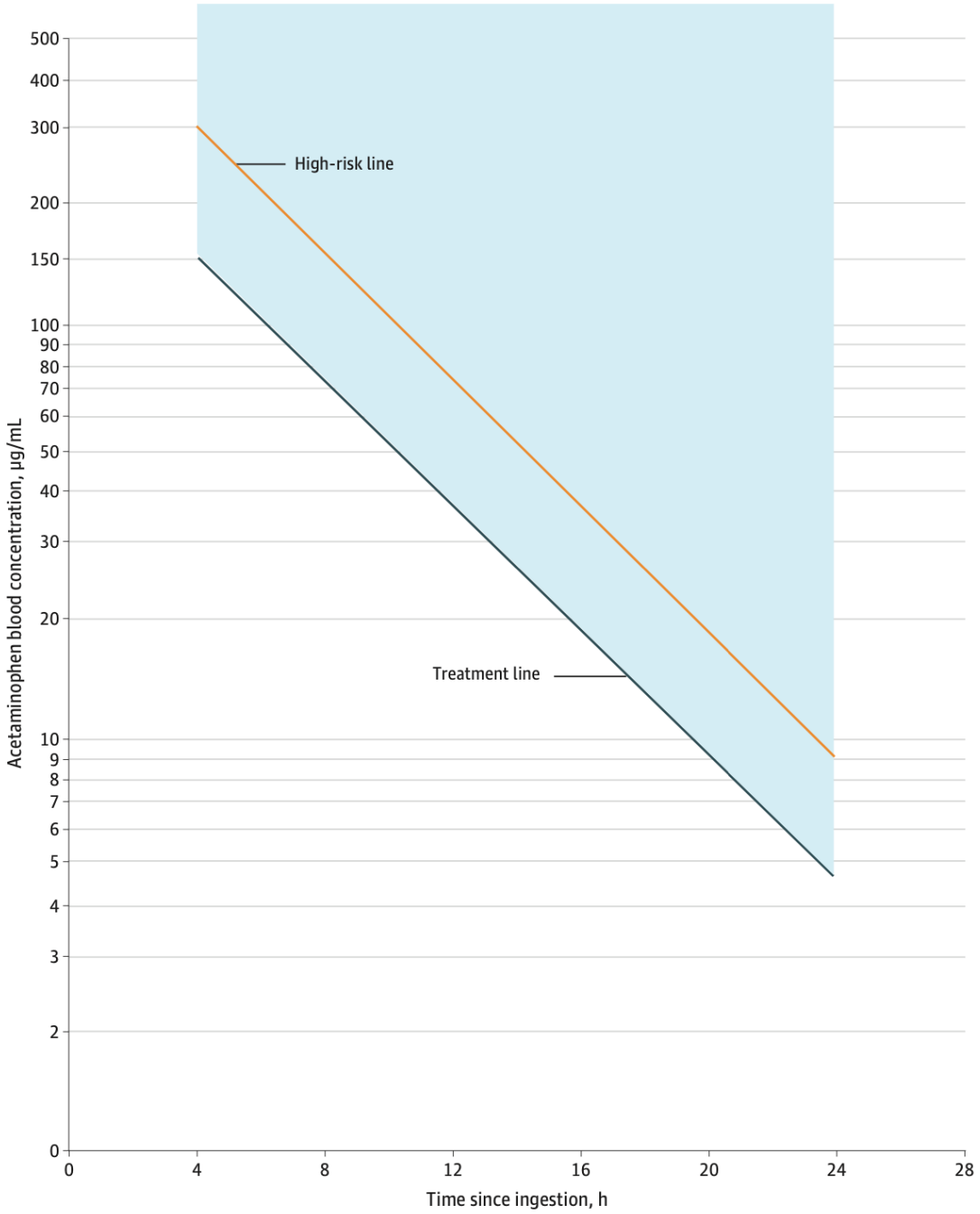
Management of Suspected Acute Ingestion of Immediate-Release Acetaminophen Products





Nomogram

Figure 2. Revised Rumack-Matthew Nomogram for the Acute Ingestion of Acetaminophen



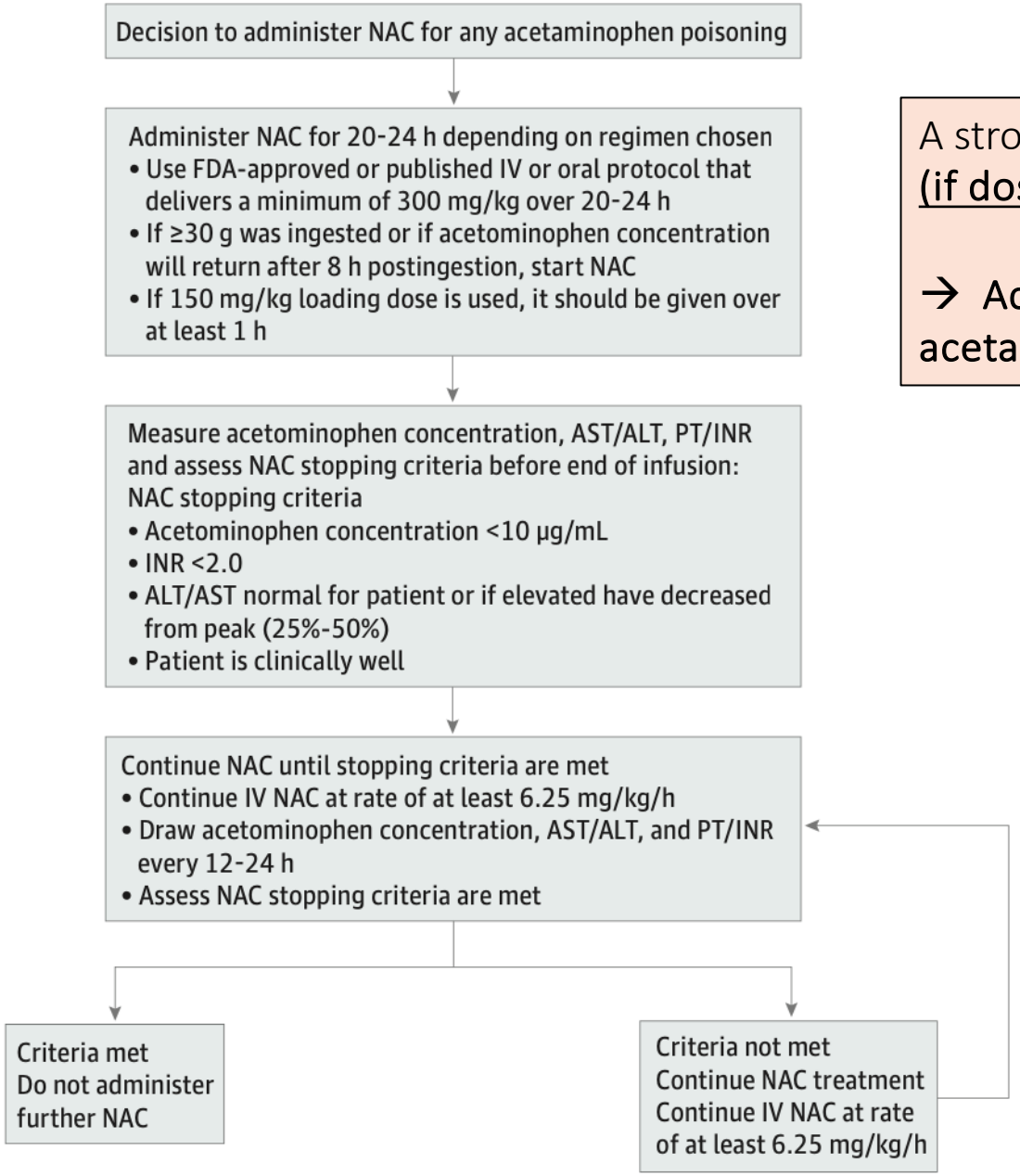
Outline

1. Management of Suspected Acute Ingestion of Immediate-Release Acetaminophen Products
2. **Administration of Acetylcysteine**
3. Special conditions

Administration of Acetylcysteine

- administered **orally** or **intravenously**
- administered **initial dose as soon as the need for treatment becomes evident**
- >15 different regimens identified, but the comparative **effectiveness** has **not** been evaluated
- Recommended use of **at least 300 mg/kg orally** or **IV** during **the first 20 to 24 hours of treatment**
- Calculation of acetylcysteine dose should be **capped at 100 kg of body weight**

Figure 3. Administration of Acetylcysteine in the Management of Acetaminophen Poisoning



A strong clinical concern of acute overdose
(if dose was >200 mg/kg or >10 g)

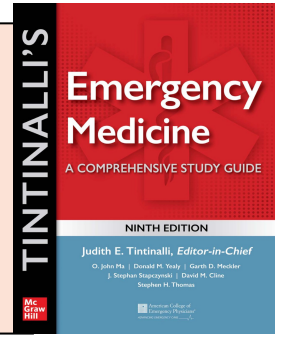
→ Acetylcysteine should be administered before the acetaminophen concentration is available

TABLE 190-2 Acetylcysteine Dosing Regimens

	PO	IV Adult	IV Pediatric (21–40 kg)	IV Pediatric (5–20 kg)
Preparation	Available as 10% and 20% solutions. Dilute to 5% solution for PO administration.	Available as 20% solution. Dilution required.	Available as 20% solution. Dilution required.	Available as 20% solution. Dilution required.
Loading dose	140 milligrams/kg	150 milligrams/kg in 200 mL 5% dextrose in water infused over 60 min	150 milligrams/kg in 100 mL 5% dextrose in water infused over 60 min	150 milligrams/kg in 3 mL/kg 5% dextrose in water infused over 60 min
Maintenance dose	70 milligrams/kg every 4 h for 17 doses	50 milligrams/kg in 500 mL 5% dextrose in water infused over 4 h (12.5 milligrams/kg per hour) *followed by* 100 milligrams/kg in 1000 mL 5% dextrose in water infused over 16 h (6.25 milligrams/kg per hour)	50 milligrams/kg in 250 mL 5% dextrose in water infused over 4 h (12.5 milligrams/kg per hour) *followed by* 100 milligrams/kg in 500 mL 5% dextrose in water infused over 16 h (6.25 milligrams/kg per hour)	50 milligrams/kg in 7 mL/kg 5% dextrose in water infused over 4 h (12.5 milligrams/kg per hour) *followed by* 100 milligrams/kg in 14 mL/kg 5% dextrose in water infused over 16 h (6.25 milligrams/kg per hour)
Duration of therapy	72 h*	21 h*	21 h	21 h
Comments	Dilute with powdered drink mix, juice, or soda. Serve chilled. Drink through a straw to reduce disagreeable smell.	Monitor for drug-related adverse effects and anaphylactoid reactions.	Monitor for drug-related adverse effects and anaphylactoid reactions.	Monitor for drug-related adverse effects and anaphylactoid reactions.

*Check with your institution or poison control center for alternative dosing protocols and for management of adverse effects.

Given the volume and hypotonicity of fluid required, specific acetylcysteine weight-based fluid volume guidelines should be followed <u>for children and small adults (<40 kg)</u>, and these patients should be carefully monitored to avoid <u>fluid overload and hyponatremia</u> during treatment.



Updated guidelines for the management of paracetamol poisoning in Australia and New Zealand

Angela L Chiew[1,2], David Reith[3], Adam Pomerleau[3], Anselm Wong[4,5], Katherine Z Isoardi[6,7], Jessamine Soderstrom[8,9], Nicholas A Buckley[2,10]

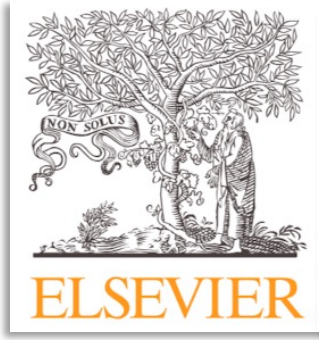
MJA 212 (4) • 2 March 2020

7 Standard acetylcysteine regimen

Standard two-bag regimen*†

- Initial infusion
  - acetylcysteine 200 mg/kg (maximum 22 g) in glucose 5% 500 mL (child, 7 mL/kg up to 500 mL) or sodium chloride 0.9% 500 mL (child, 7 mL/kg up to 500 mL) intravenously, over 4 hours
- Second acetylcysteine infusion
  - acetylcysteine 100 mg/kg (maximum 11 g) in glucose 5% 1000 mL (child, 14 mL/kg up to 1000 mL) or sodium chloride 0.9% 1000 mL (child, 14 mL/kg up to 1000 mL) intravenously, over 16 hours†‡
- If ongoing acetylcysteine is required, continue at the rate of the second infusion (eg, 100 mg/kg over 16 h). Higher ongoing infusion rates (eg, 200 mg/kg over 16 h) may be required for massive paracetamol ingestions and a clinical toxicologist should be consulted

* Acetylcysteine is also compatible with 0.45% saline + 5% dextrose. † For adults (aged ≥ 14 years), dosing should be based on actual body weight rounded up to the nearest 10 kg, with a ceiling weight of 110 kg. For children (aged < 14 years), use actual body weight. ‡ If the initial paracetamol concentration was more than double the nomogram line following an acute ingestion, increase acetylcysteine dose to 200 mg/kg (maximum 22 g) in glucose 5% 1000 mL (child, 14 mL/kg up to 1000 mL) or sodium chloride 0.9% 1000 mL (child, 14 mL/kg up to 1000 mL) intravenously, over 16 hours. Monitoring with pulse oximetry for the first 2 hours of the infusion is recommended. ◆



Research Paper

Efficacy of a two bag acetylcysteine regimen to treat paracetamol overdose (2NAC study)

Anselm Wong[a,b,c,*], Geoff Isbister[d,e], Richard McNulty[f,g], Katherine Isoardi[h,i], Keith Harris[j,k], Angela Chiew[l,m], Shaun Greene[a,b,n,o], Naren Gunja[g,p,q], Nicholas Buckley[r,s], Colin Page[j,k], Andis Graudins[c,t]

EClinicalMedicine 20 (2020) 100288

two- bag regimen resulted in **3** episodes of **severe non-allergic anaphylactic reactions**

three-bag regimen resulted in **15** episodes of **severe non-allergic anaphylactic reaction**

No statistical analysis evidence

Significantly **less** **cutaneous and systemic non-allergic anaphylactic reactions**

two-bag and **three-bag regimen** (1.3% [n = 17] and 7.1% [n = 65]

RiskDifference: **5.8%**, 95%CI 7.6 to 4.0, p < 0.0001

Significantly less **gastrointestinal reactions (nausea and/or vomiting)**

two-bag and **three-bag** regimen (19% [n = 245] vs 31% [n = 279], p < 0.0001

Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial

D Nicholas Bateman, James W Dear, H K Ruben Thanacoody, Simon H L Thomas, Michael Eddleston, Euan A Sandilands, Judy Coyle, Jamie G Cooper, Aryelly Rodriguez, Isabella Butcher, Steff C Lewis, A D Bastiaan Vliegenthart, Aravindan Veiraiah, David J Webb, Alasdair Gray

Lancet 2014; 383: 697–704

Published Online
November 28, 2013
http://dx.doi.org/10.1016/S0140-6736(13)62062-0

Panel 1: Acetylcysteine regimens used in the study

UK standard schedule (duration 20·25 h)[16]

- 150 mg/kg in 200 mL, over 15 min
- 50 mg/kg in 0·5 L, over 4 h
- 100 mg/kg in 1 L, over 16 h

Modified (shorter) protocol (duration 12 h)

- 100 mg/kg in 200 mL, over 2 h
- 200 mg/kg in 1 L, over 10 h
- 0·5 L of 5% dextrose, to 20·25 h

Acetylcysteine is administered in 5% dextrose.

Outline

1. Management of Suspected Acute Ingestion of Immediate-Release Acetaminophen Products
2. Administration of Acetylcysteine
3. **Special conditions**

Management of Repeated Supratherapeutic Ingestion

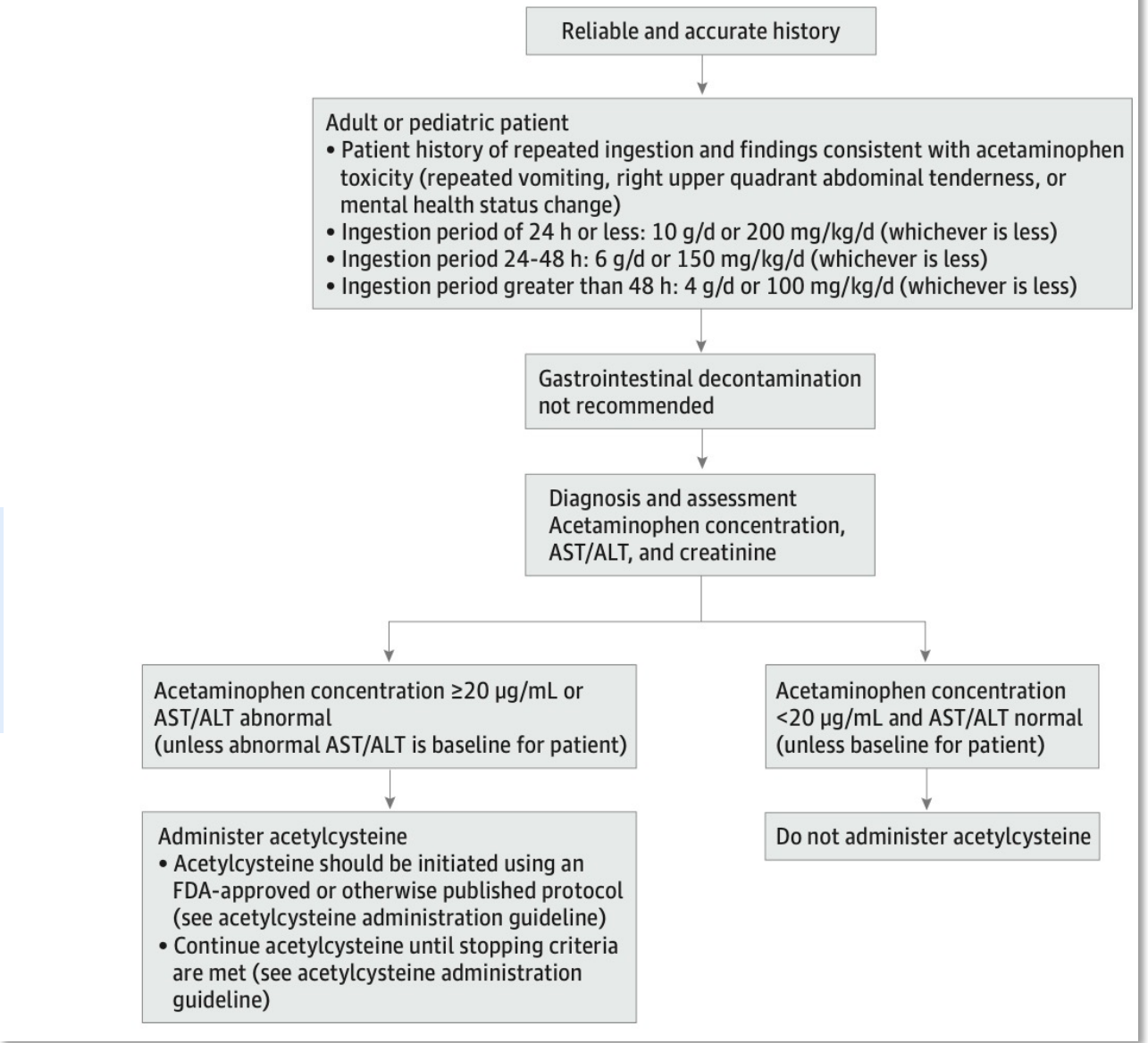
Repeated Supratherapeutic Ingestion

Defined as **multiple ingestions** for a period **>24 hours**

Acetylcysteine(NAC) should be administered if

- Acetaminophen concentration **>20 µg/mL**
- Or the aspartate aminotransferase(AST) or alanine aminotransferase(ALT) level is **abnormal**

Figure 4. Management of Repeated Supratherapeutic Ingestion of Acetaminophen



Ingestion of Extended-Release Acetaminophen Products

Extended-Release Acetaminophen Products

- Defined as acetaminophen products labeled for use on **an 8-hour basis**

The **same management** as ingestion of other acetaminophen products

- **Except** that **activated charcoal may be useful** **longer than 4 hours after ingestion** if evidence of **ongoing absorption** is present (e.g. an increasing acetaminophen concentration).

Acetaminophen concentration **at 4 to 12 hours** after ingestion

- If **below the treatment line** but **>10 µg/mL**, it should be **measured again 4 to 6 hours** after the first measurement

Coingestion of Acetaminophen and Anticholinergic or Opioid Agonist Medications

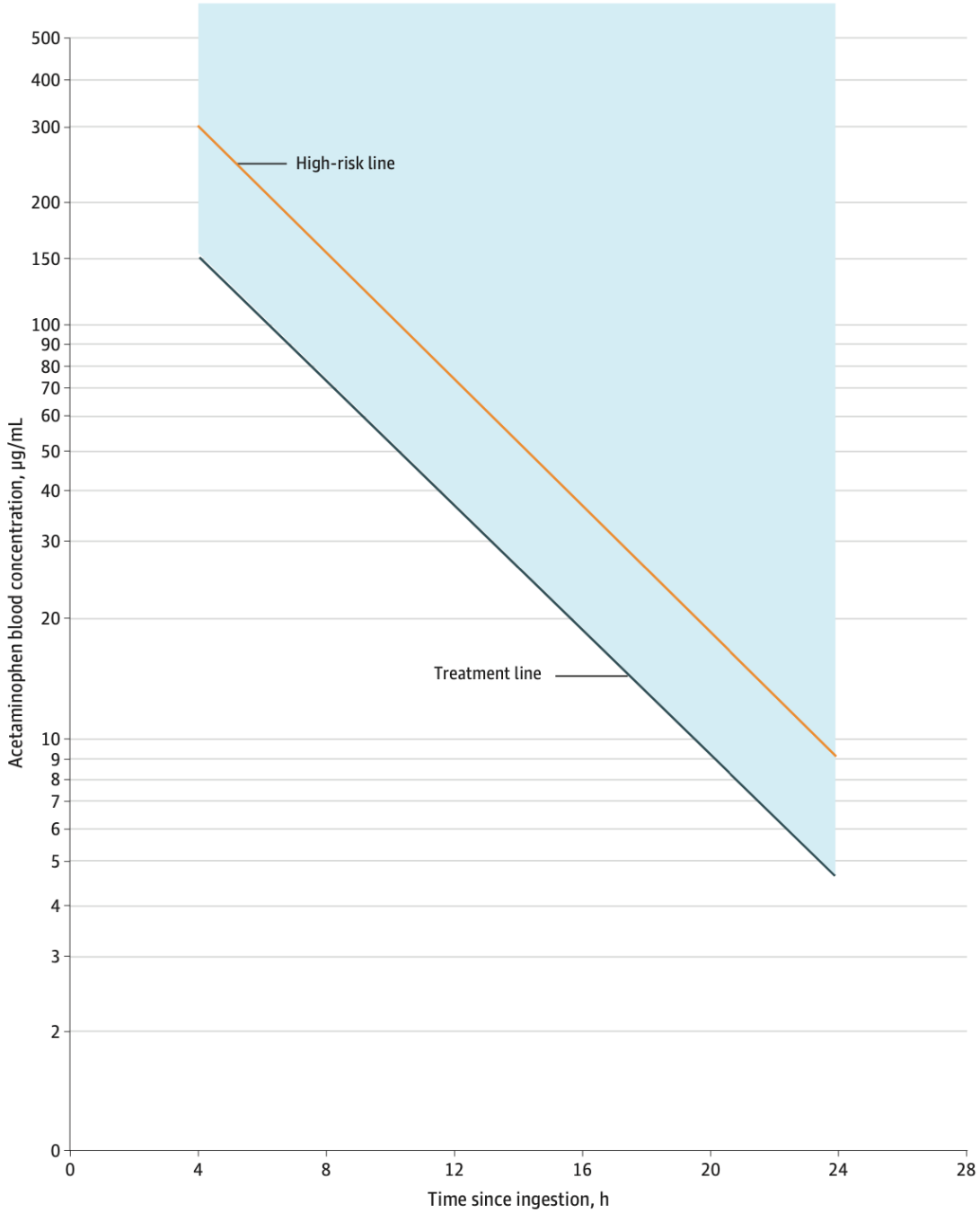
Acetaminophen absorption may be **delayed** or **prolonged**

The **same management** as ingestion of other acetaminophen products

Acetaminophen concentration **at 4 to 24 hours** after ingestion

- If **below the treatment line** but **>10 µg/mL**, it should be **measured again 4 to 6 hours** after the first measurement
- If **<10 µg/mL**, another measurement need **not** be taken and acetylcysteine treatment is **not** needed

Figure 2. Revised Rumack-Matthew Nomogram for the Acute Ingestion of Acetaminophen



Acute Ingestion of Immediate-Release Acetaminophen

- 4h after ingestion
- If unknown time of ingestion → **Measured immediately**

Repeated Supratherapeutic Ingestion

- If the acetaminophen concentration **>20 µg/mL** → **Tx NAC**

Ingestion of Extended-Release Acetaminophen Products

If the concentration **4 to 12 hours** after ingestion

- below treatment line but **>10 µg/mL**: **measured again 4 to 6 hours** after the first measurement

Co-ingestion of Acetaminophen and Anticholinergic or Opioid Agonist Medications

If the concentration **4 to 24 hours** after ingestion

- below treatment line but **>10 µg/mL**: **measured again 4 to 6 hours** after the first measurement
- **<10 µg/mL: no need** for another measurement and acetylcysteine treatment.

Patients Younger Than 6 Years

- PC or clinical toxicologist if
  1. a **cumulative dose** of **>150 mg/kg** body weight during 24 hours
  2. a **single intravenous dose** of acetaminophen of **90 mg/kg** body weight

- Management in patients <6 years is the **same** as for older patients

- Administration of acetylcysteine requires **weight-based adjustment** to avoid hyponatremia for patients who weigh less than 41 kg.

Patients Younger Than 6 Years

Acetadote.com Available dose calculator and detailed pediatric dilution directions for IV acetylcysteine

IV Acetadote Dosage Calculator

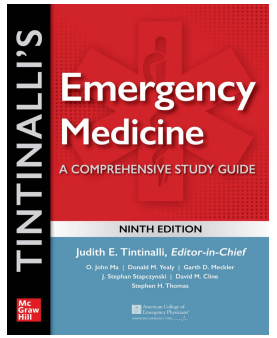
Use the Acetadote dosage calculator to calculate the accurate dose of Acetadote for your patients.

Enter your patient's weight below and click "Calculate."

Enter patient weight: 20 ○Pounds ◉Kilograms Calculate Reset

Weight: 20 Kilograms

Loading Dose:	15	mL Acetadote	OR	3000	mg Acetadote in	60	mL of diluent, infused over 60 minutes
Second Dose:	5	mL Acetadote	OR	1000	mg Acetadote in	140	mL of diluent, infused over 4 hours
Third Dose:	10	mL Acetadote	OR	2000	mg Acetadote in	280	mL of diluent, infused over 16 hours



Pregnancy

- The standard evaluation and management of acetaminophen poisoning are the **same** in the pregnant patient

- **Except** that some clinicians prefer the intravenous route for acetylcysteine administration. However, **no data are available** to demonstrate that the oral route is less effective in the pregnant patient.

Use of Enhanced Elimination Techniques

Hemodialysis is recommended in addition to treatment with acetylcysteine

- Acetaminophen concentration of **900 µg/mL or greater**
- **Acidosis** or **Altered consciousness** due to **acetaminophen toxic effects**

Acetylcysteine during hemodialysis

- If the **intravenous** route is used, the **rate** of acetylcysteine infusion should be **at least 12.5 mg/kg/hour**.
- If the **oral** acetylcysteine regimen is used, it does **not** require adjustment.

Consultation With Liver Transplant Team

Consider consultation with a liver transplant team if

- **Progressive increases** in AST or ALT and **coagulation abnormalities**
- With **encephalopathy** or **multisystem failure** despite acetylcysteine treatment.

King's College criteria for selection of ALF patients for liver transplantation

- **King's College (original)**

Table 1
King's College criteria for selection of ALF patients for liver transplantation (according to Ref. [6])

Paracetamol-induced ALF
Arterial blood pH < 7.30 (irrespective of grade of encephalopathy)
OR all of the following
- Prothrombin time >100 s (INR >6.5)
- Serum creatinine >300 μmol/L
- Grade III or IV hepatic encephalopathy

Non-Paracetamol induced ALF
Prothrombin time >100 s (INR > 6.5) (irrespective of grade of encephalopathy)
OR any 3 of the following (irrespective of grade of encephalopathy)
- Age <10 or >40 years
- Etiology: non-A/non-B hepatitis, drug-induced
- Duration of jaundice to encephalopathy >7 days
- Prothrombin time >50 (INR > 3.5)
- Serum bilirubin >300 μmol/L

- **King's College + Lactate***

*as predictors of poor prognosis without transplant

Acetaminophen	Non-acetaminophen
• Lactate >3.5	• INR > 6.5 with HE
or	or
• pH < 7.3 or lactate >3	• Any 3 of 5 with HE
or	– Age <10 or >40 yrs
• Grade III or IV HE and	– Bili > 300
– INR > 6.5	– Coag: INR > 3.5
– Creatinine > 300	– Duration jaundice to HE > 7 days
	– Etiology: Non A-E, other drug

King's College Criteria remain the most clinically useful with sensitivity of 68-69% and specificity of 82-92%

Lee WM, et al. AASLD Practice Guidelines. Hepatology 2011

- **Lactate**
  - >3.5 mmol/L after early resuscitation
  - or >3.0 mmol/L after full resuscitation

NAC Adverse reaction management

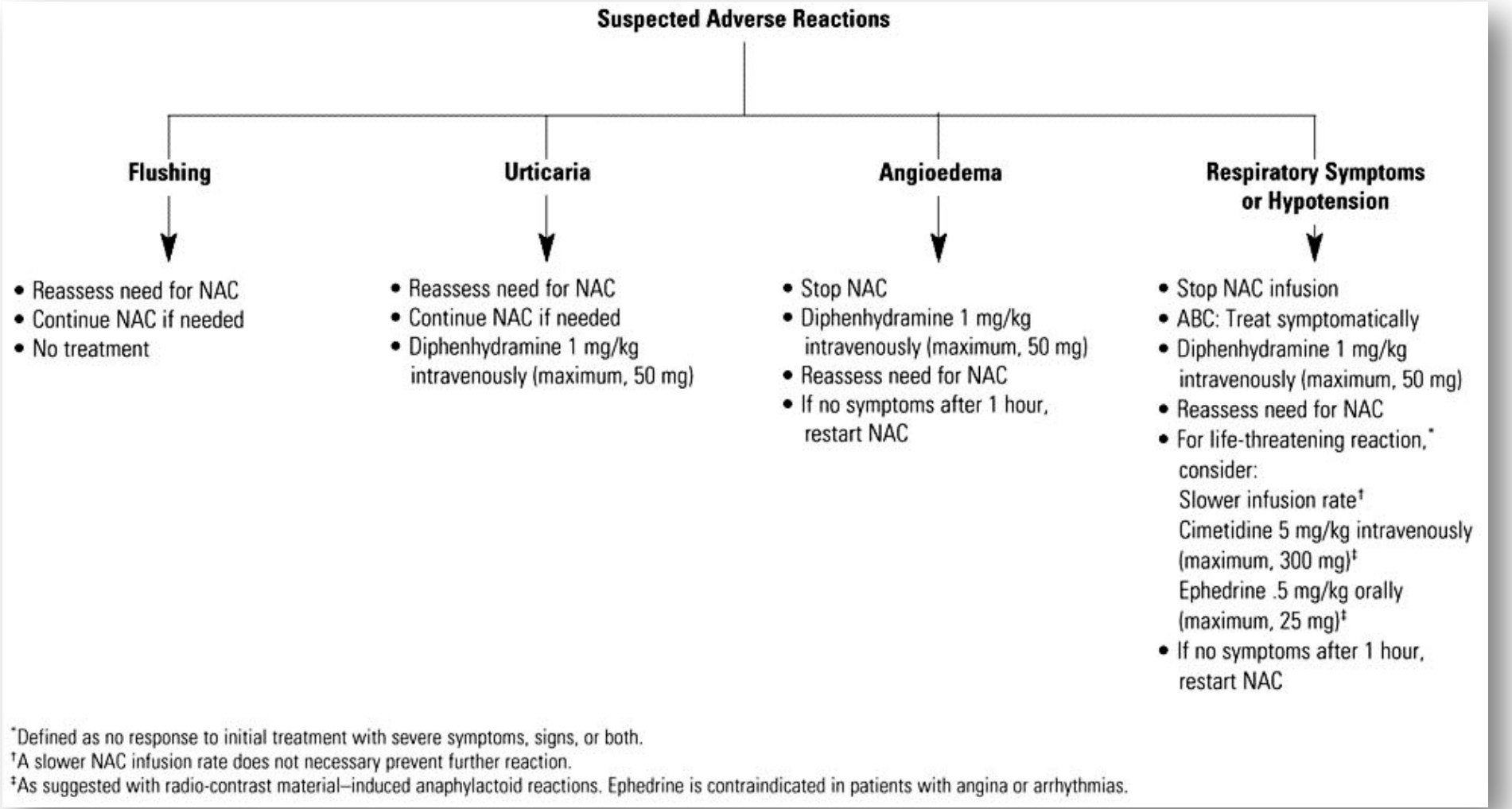
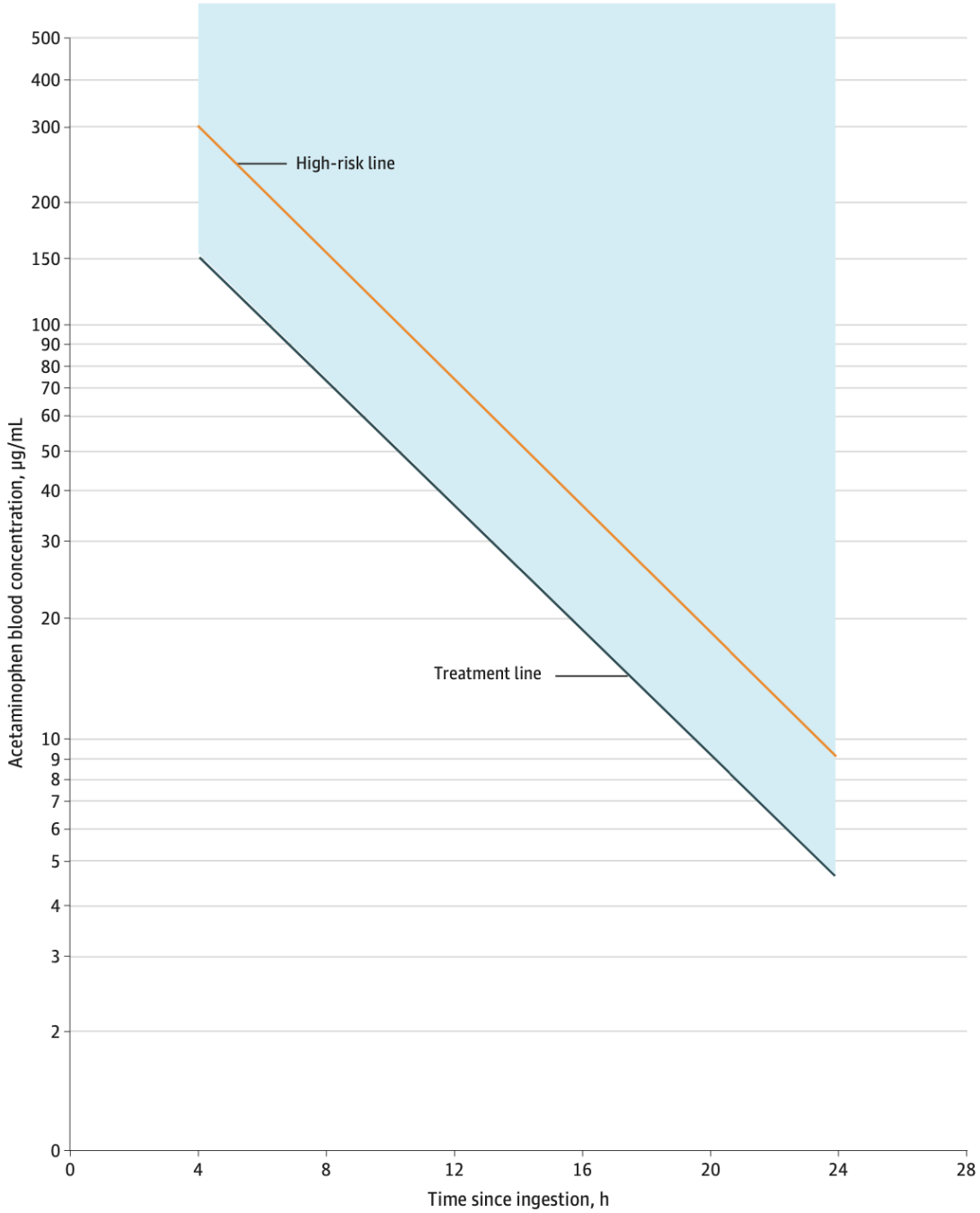


Figure 2. Revised Rumack-Matthew Nomogram for the Acute Ingestion of Acetaminophen



Take Home Message

Acute Ingestion of Immediate-Release Acetaminophen

- 4h after ingestion
- If unknown time of ingestion → **Measured immediately**

Repeated Supratherapeutic Ingestion

- If the acetaminophen concentration **>20 µg/mL** → **Tx NAC**

Ingestion of Extended-Release Acetaminophen Products

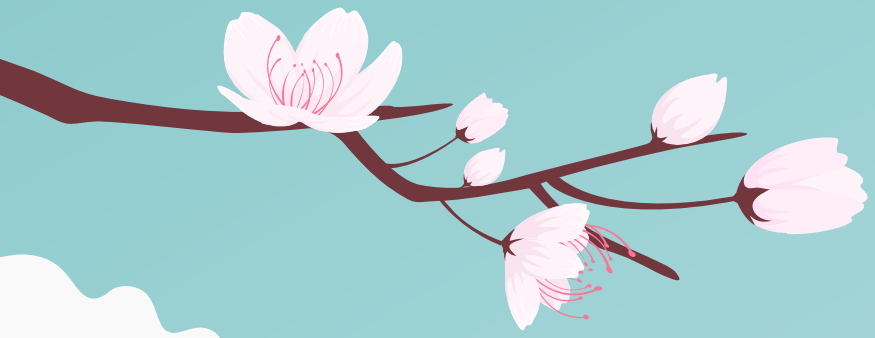
If the concentration **4 to 12 hours** after ingestion

- below treatment line but **>10 µg/mL**: **measured again 4 to 6 hours** after the first measurement

Co-ingestion of Acetaminophen and Anticholinergic or Opioid Agonist Medications

If the concentration **4 to 24 hours** after ingestion

- below treatment line but **>10 µg/mL**: **measured again 4 to 6 hours** after the first measurement
- **<10 µg/mL: no need** for another measurement and acetylcysteine treatment.



Thank You