Common Toxicological Exposures in the PICU

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Objectives

- Discuss common PICU toxicological emergencies
- Evaluation
- Treatment

Circulation

AHA FOCUSED UPDATE

2023 American Heart Association Focused Update on the Management of Patients With Cardiac Arrest or Life-Threatening Toxicity Due to Poisoning: An Update to the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Endorsed by the American Academy of Pediatrics

Eric J. Lavonas, MD, MS, Chair; Peter D. Akpunonu, MD; Ann M. Arens, MD; Kavita M. Babu, MD; Dazhe Cao, MD; Robert S. Hoffman, MD; Christopher O. Hoyte, MD, MBA; Maryann E. Mazer-Amirshahi, PharmD, MD, MPH, PhD; Andrew Stolbach, MD, MPH; Maude St-Onge, MD, PhD; Trevonne M. Thompson, MD; George Sam Wang, MD; Amber V. Hoover, RN, MSN; Ian R. Drennan, ACP, PhD, Vice Chair; on behalf of the American Heart Association

ABSTRACT: In this focused update, the American Heart Association provides updated guidance for resuscitation of patients with cardiac arrest, respiratory arrest, and refractory shock due to poisoning. Based on structured evidence reviews, guidelines are provided for the treatment of critical poisoning from benzodiazepines, β-adrenergic receptor antagonists (also known as β-blockers), L-type calcium channel antagonists (commonly called calcium channel blockers), cocaine, cyanide, digoxin and related cardiac glycosides, local anesthetics, methemoglobinemia, opioids, organophosphates and carbamates, sodium channel antagonists (also called sodium channel blockers), and sympathomimetics. Recommendations are also provided for the use of venoarterial extracorporeal membrane oxygenation. These guidelines discuss the role of atropine, benzodiazepines, calcium, digoxin-specific immune antibody fragments, electrical pacing, flumazenil, glucagon, hemodialysis, hydroxocobalamin, hyperbaric oxygen, insulin, intravenous lipid emulsion, lidocaine, methylene blue, naloxone, pralidoxime, sodium bicarbonate, sodium nitrite, sodium thiosulfate, vasodilators, and vasopressors for the management of specific critical poisonings.

Key Words: AHA Scientific Statements ■ advanced cardiac life support ■ American Heart Association ■ antidotes ■ drug overdose ■ heart arrest ■ poisoning ■ resuscitation

TOP 10 TAKE-HOME MESSAGES FOR MANAGEMENT OF PATIENTS WITH CARDIAC ARREST OR LIFE-THREATENING TOXICITY DUE TO POISONING

1. Treatment of cardiac arrest and life-threatening toxicity due to poisoning often requires special-
extracorporeal membrane oxygenation, in addition to effective basic and advanced life support. Timely consultation with a medical toxicologist, clinical toxicologist, or regional poison center facilitates rapid and effective therapy.
2. Opioid overdose remains the leading cause of cardiac arrest due to poisoning in North America.

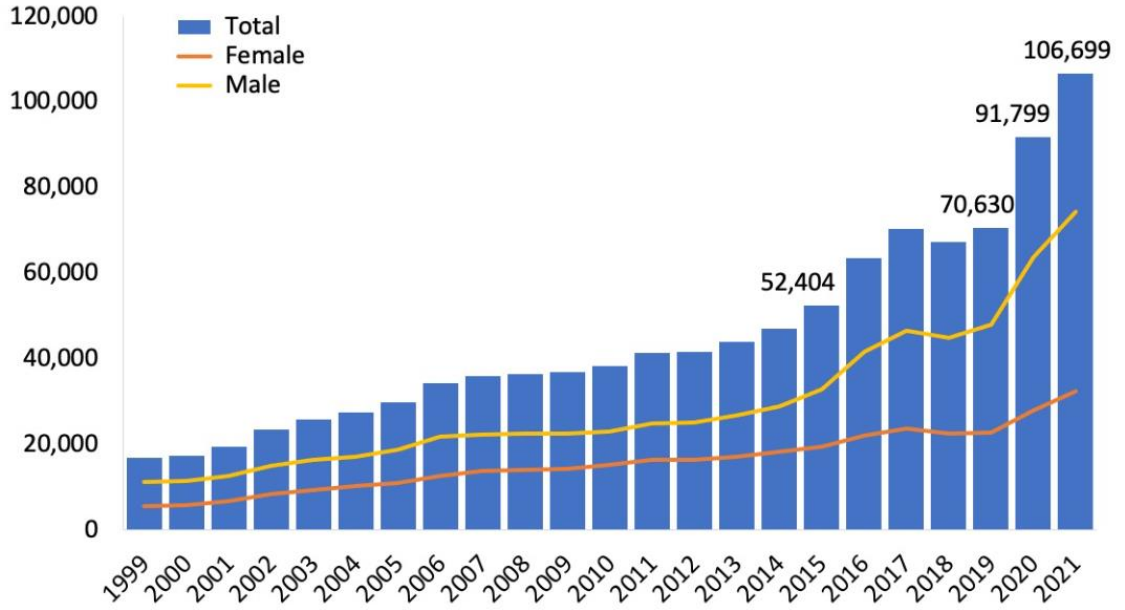
Illicitly Manufactured Fentanyl (IMF)

Drug Overdose Deaths in US

- In 2019, 70,630 drug overdose deaths
  - 21.6 per 100,000 standard population
- The rate in 2018 (20.7) was significantly lower than 2017 (21.7)
- The rate in 2019 (21.6) was significantly higher than 2018 and similar to the rate in 2017.

- ***In 2020: 91,799 drug overdose deaths***
  - ***27.9 per 100,000 population***
  - ***70,029 involved opioids***
- ***In 2021: 107,622 deaths***
  - ***80,816 involved opioids***

Figure 1. National Drug-Involved Overdose Deaths*, Number Among All Ages, by Gender, 1999-2021



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

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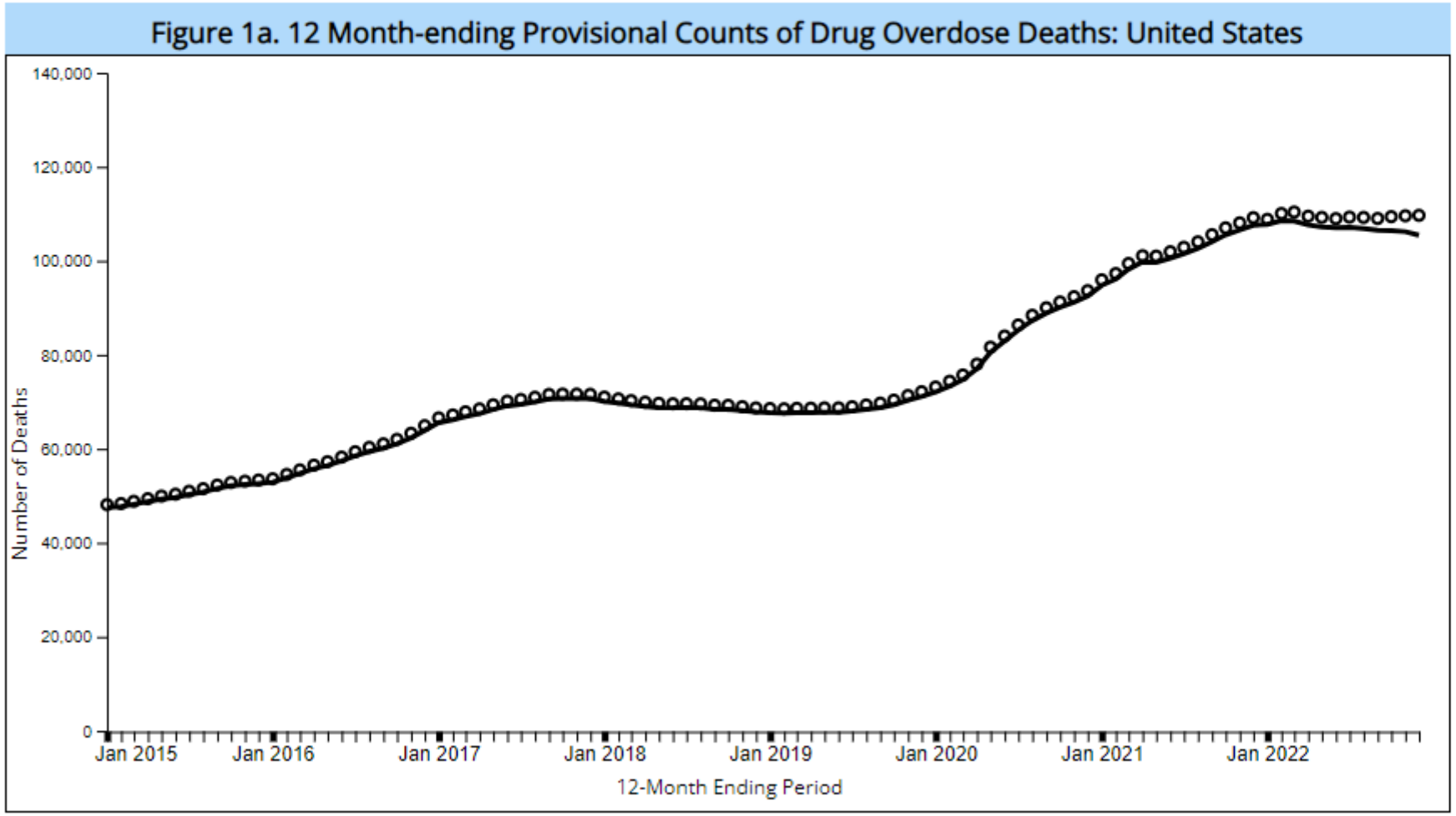
https://www.cdc.gov/nchs/fastats/drug-overdoses.htm
https://www.cdc.gov/nchs/data/databriefs/db394-H.pdf
https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

12 Month-ending Provisional Number and Percent Change of Drug Overdose Deaths

Based on data available for analysis on: May 7, 2023



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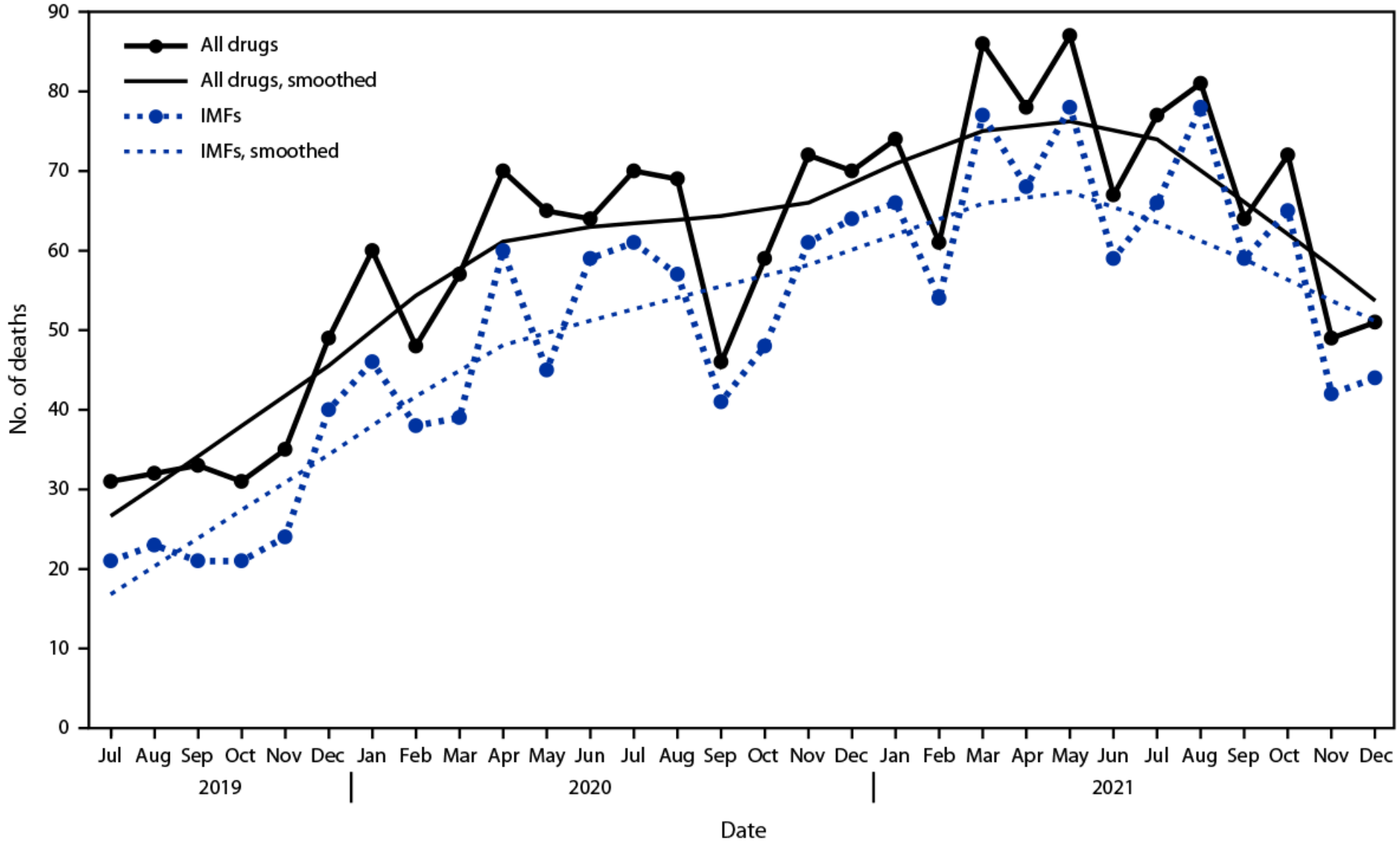
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

- July–December 2019 to July–December 2021, median monthly overdose deaths increased 109%, and deaths involving IMFs increased 182%
- 90% of overdose deaths involved opioids, and 83.9% involved IMFs
  - Only 35% of decedents had documented opioid use history.
- Counterfeit pill evidence was present in 24.5% of overdose deaths
  - 40.9% of decedents had evidence of mental health conditions or treatment.

Tanz PMID 36520659

FIGURE 1. Number of drug overdose deaths and deaths involving* illicitly manufactured fentanyls† among persons aged 10–19 years (N = 1,808), by month — State Unintentional Drug Overdose Reporting System, 32 jurisdictions,§ July 2019–December 2021¶



Abbreviations: IMF = illicitly manufactured fentanyl; SUDORS = State Unintentional Drug Overdose Reporting System.

(CDC, 2022)

Characteristics of Fatal Poisonings Among Infants and Young Children in the United States

Christopher E. Gaw, MD, MBE, Allison E. Curry, PhD, MPH, Kevin C. Osterhoudt, MD, MSCE, Joanne N. Wood, MD, MSHP, Daniel J. Corwin, MD, MSCE

(doi: 10.1542/peds.2022-059016)

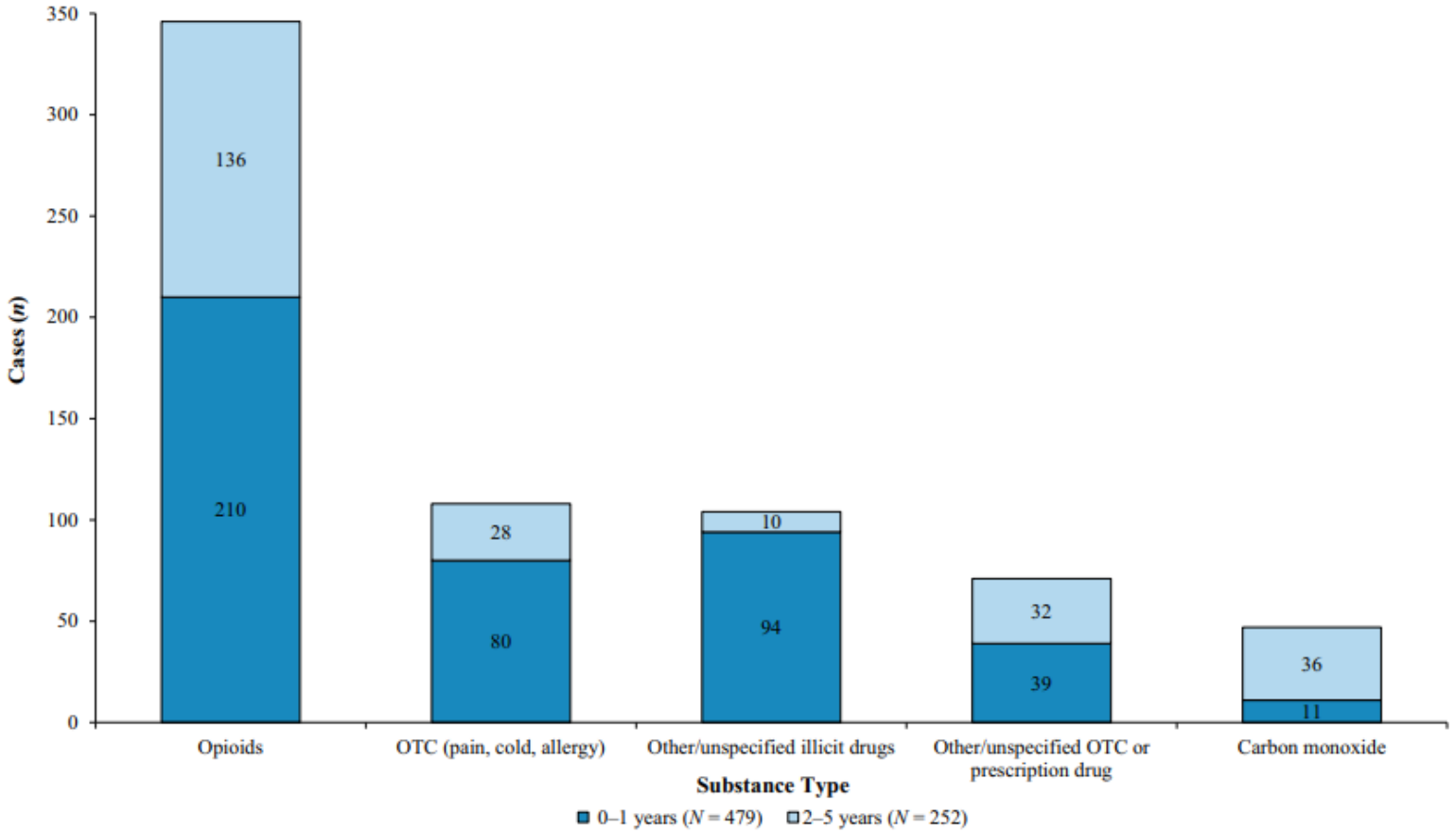


FIGURE 1
Fatal pediatric poisonings by age and selected contributing substances, NFR-CRS, 2005–2018. *CDR committees may identify >1 substance as contributing to death in a single case.

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Gaw et al 2023

Characteristics of Fatal Poisonings Among Infants and Young Children in the United States

Christopher E. Gaw, MD, MBE, Allison E. Curry, PhD, MPH, Kevin C. Osterhoudt, MD, MSCE, Joanne N. Wood, MD, MSHP, Daniel J. Corwin, MD, MSCE

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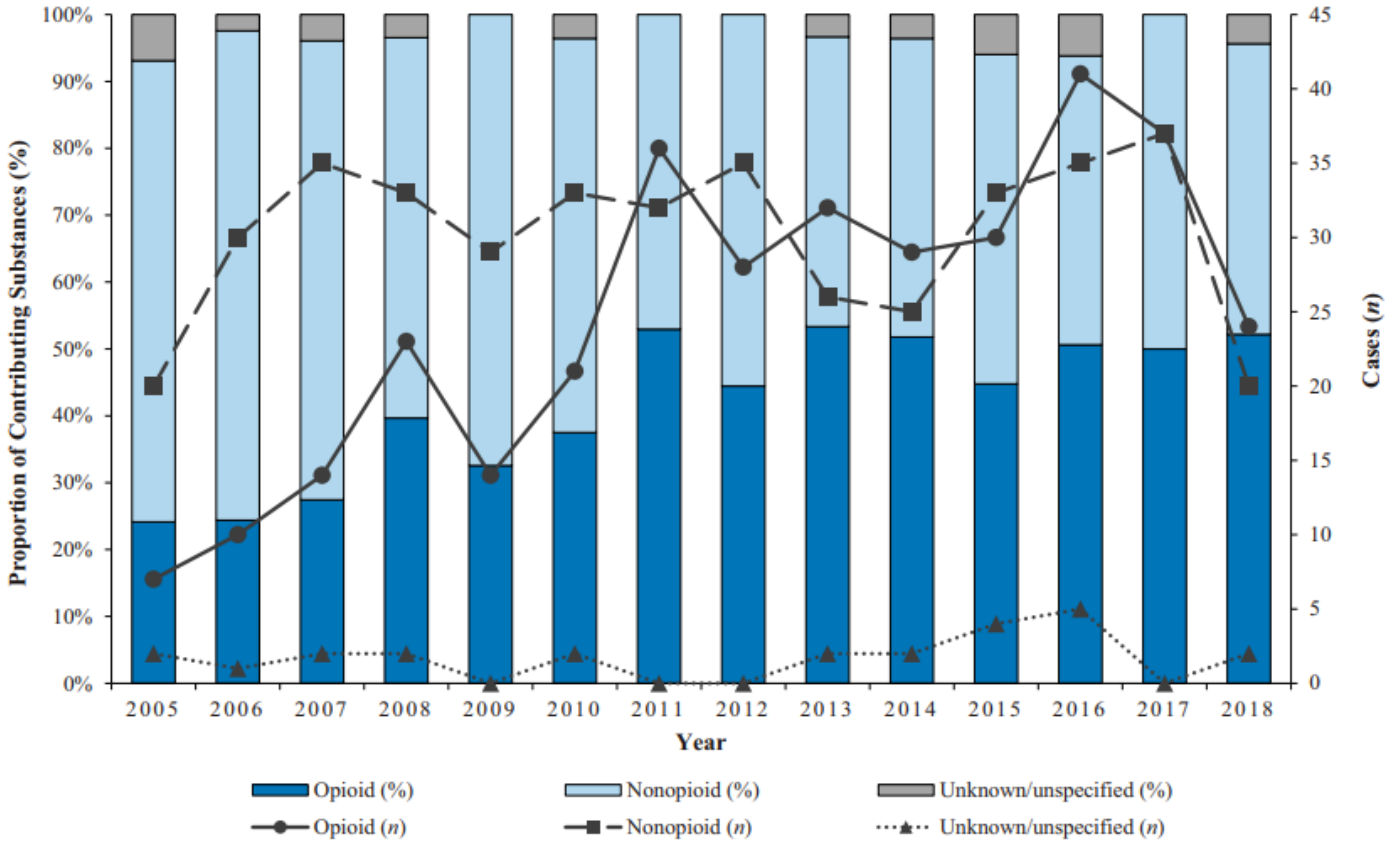

FIGURE 2

Number and proportion of opioid and nonopioid substances contributing to death by year, NFR-CRS, 2005–2018. *CDR committees may identify both an opioid and nonopioid substance as contributing to death in a single case.

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Gaw et al 2023

July 2016: influx of counterfeit pills resembling oxycodone, Xanax, and Norco

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https://emergency.cdc.gov/han/han00395.asp

July 2018: Fentanyl analogs being mixed with heroin or sold as heroin

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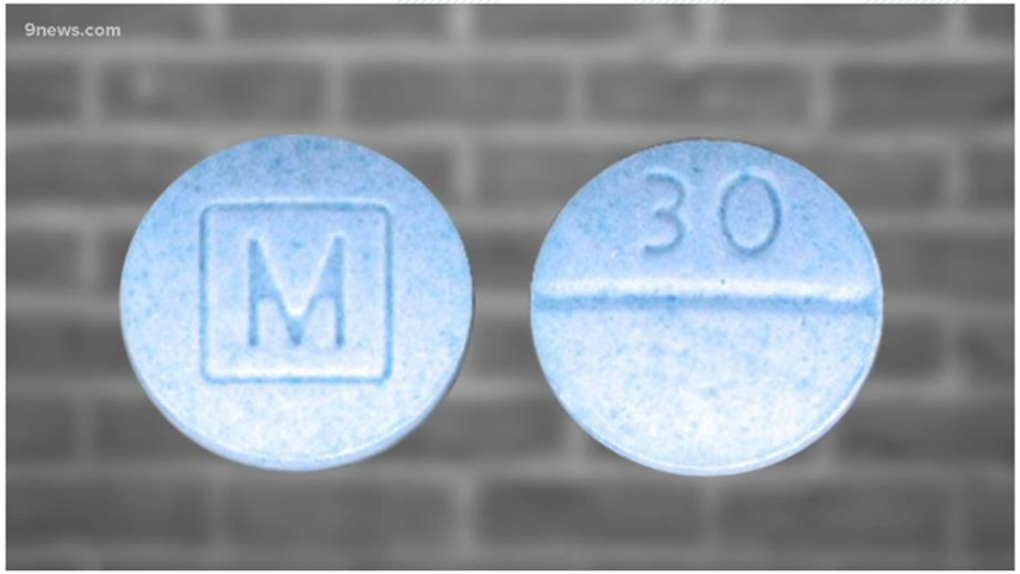
https://emergency.cdc.gov/han/han00413.asp

Contaminated with Fentanyl

- Illicitly manufactured pharmaceuticals
  - Benzodiazepines (Alprazolam/Xanax)
  - Oxycodone
- Recreational drugs
  - Methamphetamine
  - Heroin
  - Cocaine

Fentanyl overdose deaths spike, Denver Police seize 3x more this year

"When you're selling fentanyl, you're selling a time bomb. It's only a matter of time before it goes off in that person's life."



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https://www.9news.com/video/news/health/fentanyl-overdose-deaths-spike/73-a2bf0915-0cdc-4a37-8808-dd492db2cb5e

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journal homepage: www.elsevier.com/locate/ajem

Fentanyl contaminated "M30" pill overdoses in pediatric patients

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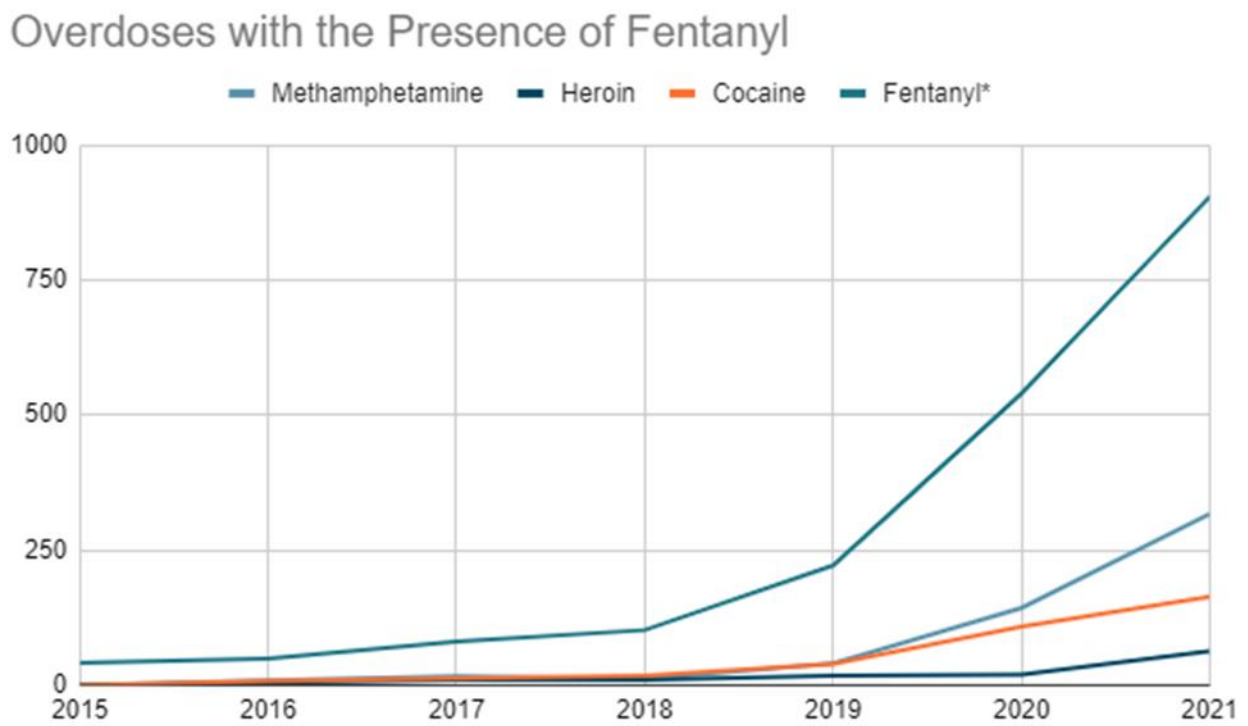
Joynt PMID 34030905

	Methamphetamine	Heroin	Cocaine	Fentanyl*
2015	0	0	0	41
2016	9	5	8	49
2017	17	10	13	81
2018	12	10	18	102
2019	40	18	39	222
2020	143	20	108	540
2021	317	63	164	905



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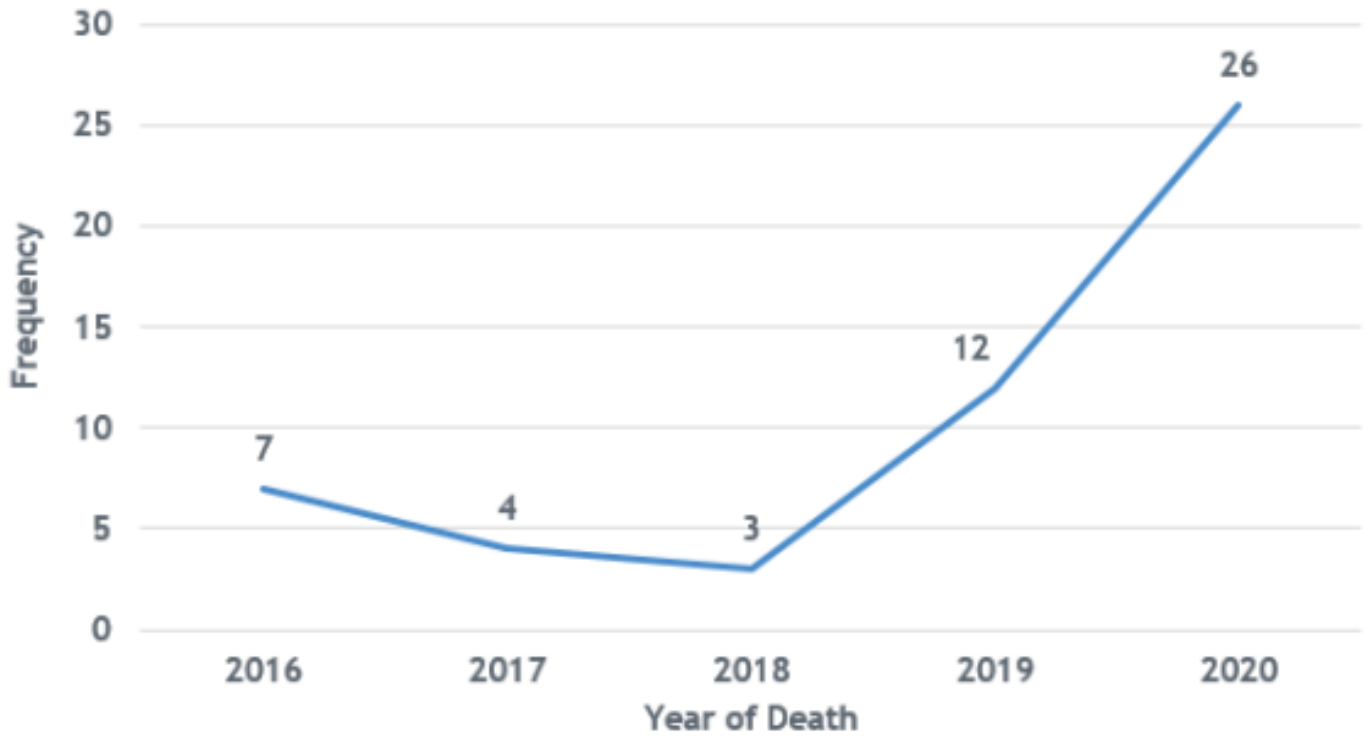
Source: Vital Statistics Program, Colorado Department of Public Health and Environment.

Colorado Child Fatality Prevention System

Figure 1. Poisoning and overdose deaths occurring among those under age 18 in Colorado by year, 2016-2020 (n=52)



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Isotonitazene

Report on a novel emerging class of highly potent benzimidazole NPS opioids: Chemical and in vitro functional characterization of isotonitazene

Peter Blanckaert[1†] | Annelies Cannaert[2†] | Katleen Van Uytfanghe[2] | Fabian Hulpia[3] | Eric Deconinck[4] | Serge Van Calenbergh[3] | Christophe Stove[2]

- Benzimidazole Derivatives
- Etonitazene
- Clonitazene
- Nitazene

- Highly potent synthetic opioid

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Notes from the Field: Nitazene-Related Deaths — Tennessee, 2019–2021

Weekly / September 16, 2022 / 71(37);1196–1197

Allison Roberts, PhD[1]; Jessica Korona-Bailey, MPH[1]; Sutapa Mukhopadhyay, PhD[1] (VIEW AUTHOR AFFILIATIONS)

Roberts PMID 36107790

J Med Toxicol. 2020 Jan;16(1):41-48. doi: 10.1007/s13181-019-00735-w. Epub 2019 Aug 30.

Naloxone Dosing After Opioid Overdose in the Era of Illicitly Manufactured Fentanyl

Joseph Carpenter [1 2], Brian Patrick Murray [3], Sukhshant Atti [3], Tim P Moran [4], Arthur Yancey [4], Brent Morgan [3 4]

Affiliations + expand

PMID: 31471760 PMCID: PMC6942078 DOI: 10.1007/s13181-019-00735-w

- Retrospective ED/EMS review of patients receiving naloxone AND had + opiates, fentanyl or both on UDS
- 121 included, median age 38 years
- In the naloxone dose analysis: no significant difference in dosing
  - fentanyl-only (median 0.8 mg, IQR 0.4-1.6; p = 0.68)
  - fentanyl + opiate (median 0.8 mg, IQR 0.4-1.2; p = 0.56)
  - opiate-only group (median 0.58 mg, IQR 0.4-1.6).

Pharmaceuticals

- 14 yo F, handfuls of OTC analgesic, began vomiting 1-2 hours after and told POC. No other meds missing. No PHMX. POC brought in 6 hrs post time of likely ingestion.

- VS 37.5, HR 100, RR 20, BP 115/60, 100% RA
- Mild epigastric TTP, otherwise exam normal
- Na 140, K 3.5, Cl 105, Bicarb 21, BUN 20, Cr 0.7, Glu 100

Acetaminophen

- Analgesic and antipyretic
- Inhibition of prostaglandin synthesis and cyclooxygenases

- Acute Toxicity
  - 200 mg/kg
  - 7.5 grams

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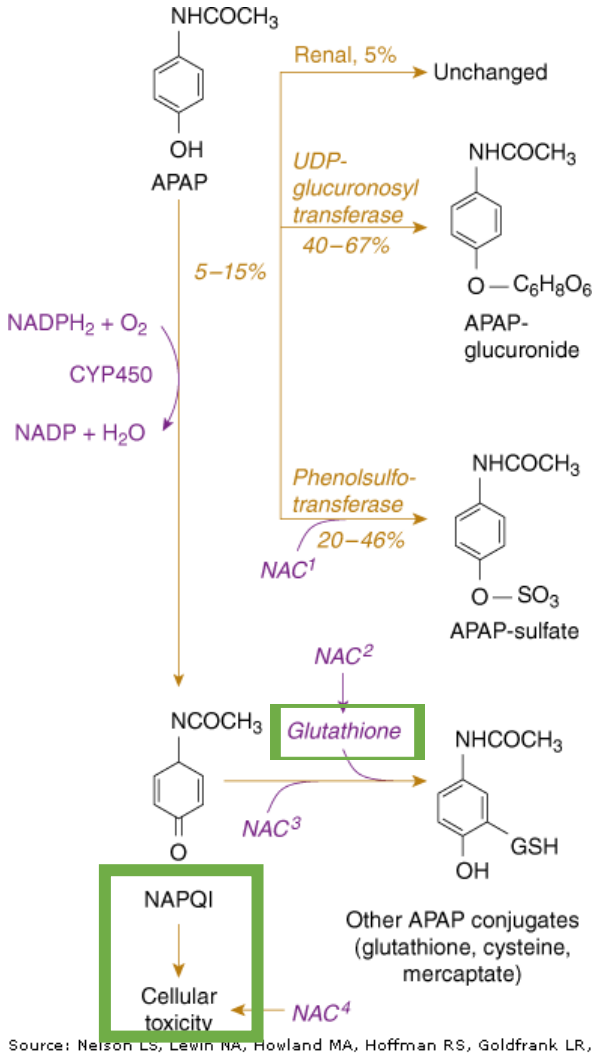


Source: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE: *Goldfrank's Toxicologic Emergencies, 9th Edition*: http://www.accessemergencymedicine.com

Treatment/Risk Stratification

- Categories of Ingestion
  - Acute
  - RSTI/Unknown
- NAC – 2 bag method
- Adverse Events: N/V/D, anaphylactoid (rate related, usually initial bolus infusion), flushing
  - Less with 2 bag method
- *PICU admission criteria: INR > 2, or > 1.5 with encephalopathy*
  - Liver consult

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

Abstract

IMPORTANCE The US and Canada currently have no formal published nationwide guidelines for specialists in poison information or emergency departments 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.

EVIDENCE REVIEW Four clinical toxicology societies (America's Poison Centers, American Academy of Clinical Toxicology, American College of Medical Toxicology, and Canadian Association of Poison Control Centers) selected participants (n = 21). Led by a nonvoting chairperson using a modified Delphi method, the panel created a decision framework and determined the appropriate clinical management of a patient with acetaminophen poisoning. Unique to this effort was the collection of guidelines from most poison centers in addition to systematic collection and review of the medical literature. Comments from review by external organizations were incorporated before the guideline was finalized. The project began in March 2021 and ended in March 2023.

FINDINGS The search retrieved 84 guidelines and 278 publications. The panel developed guidelines for emergency department management of single or repeated ingestion of acetaminophen. In addition, the panel addressed extended-release formulation, high-risk ingestion, coingestion of anticholinergics or opioids, age younger than 6 years, pregnancy, weight greater than 100 kg, and intravenous acetaminophen use. Differences from current US practice include defining acute ingestion as an ingestion presentation from 4 to 24 hours after overdose was initiated. A revised form of the Rumack-Matthew nomogram was developed. The term *massive ingestion* was replaced with the term *high-risk ingestion* and denoted by a specific nomogram line. Other recommendations include specific criteria for emergency department triage, laboratory evaluation and monitoring parameters, defining the role of gastrointestinal decontamination, detailed management of acetylcysteine treatment, associated adverse effects, and stopping criteria for acetylcysteine treatment, as well as criteria for consultation with a clinical toxicologist. Finally, specific treatment considerations, including acetylcysteine dosing, fomepizole administration, and considerations for extracorporeal elimination and transplant evaluation, were addressed.

CONCLUSIONS AND RELEVANCE This qualitative study provides a consensus statement on consistent evidence-based recommendations for medical, pharmacy, and nursing education and

Key Points

Question What is the appropriate management of acetaminophen poisoning after acute or repeated ingestion?

Findings This qualitative study used an expert-derived consensus according to a modified Delphi process to provide explicit clinical guidance on the assessment, management, and treatment of acetaminophen poisoning.

Meaning These recommendations provide a rationale for current approaches to the management of acetaminophen poisoning.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

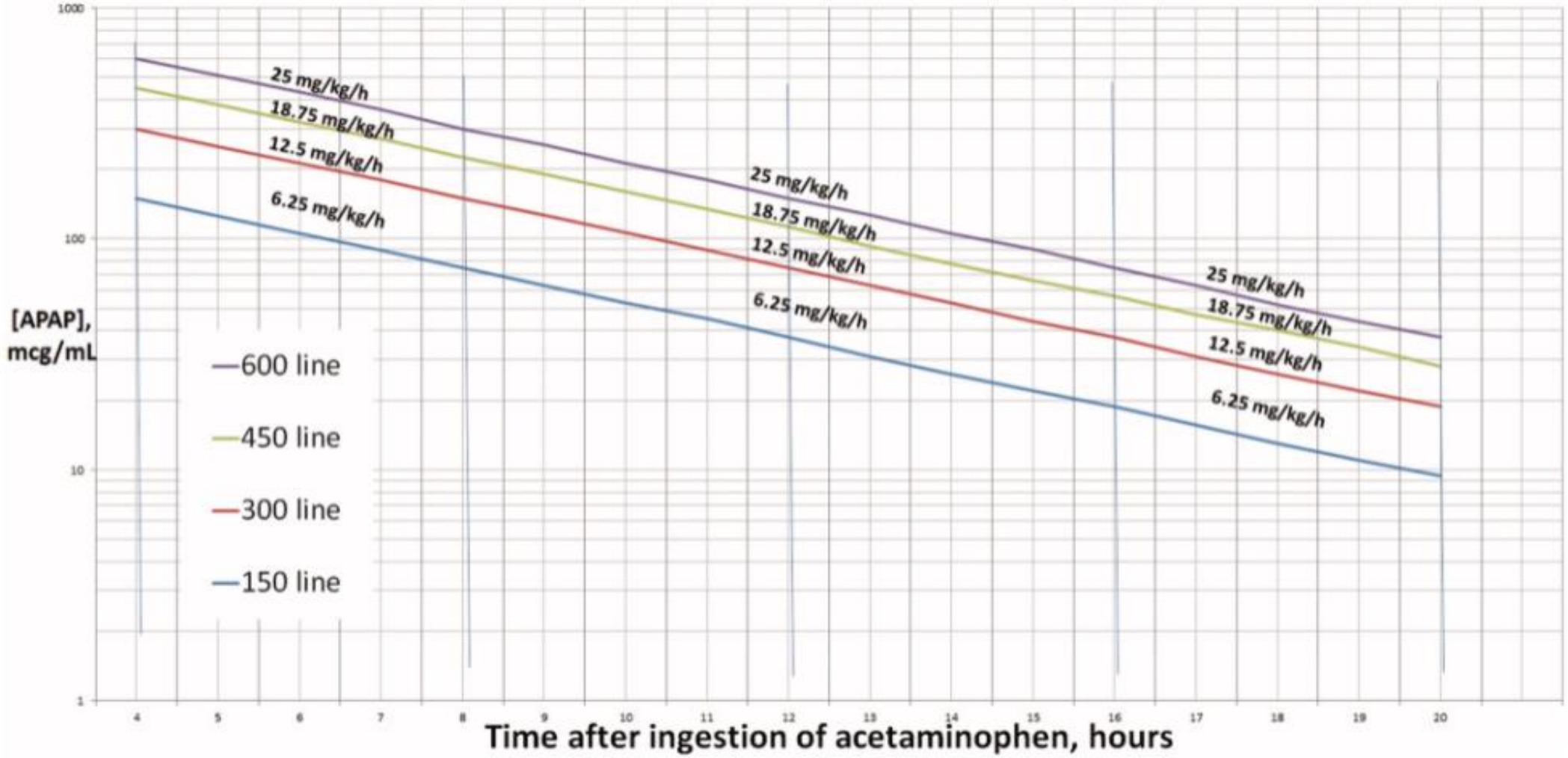
Review > Clin Toxicol (Phila). 2019 Aug;57(8):686-691. doi: 10.1080/15563650.2019.1579914.
Epub 2019 Feb 19.

What is the most appropriate dose of *N*–acetylcysteine after massive acetaminophen overdose?

Robert G Hendrickson [1]

Affiliations + expand

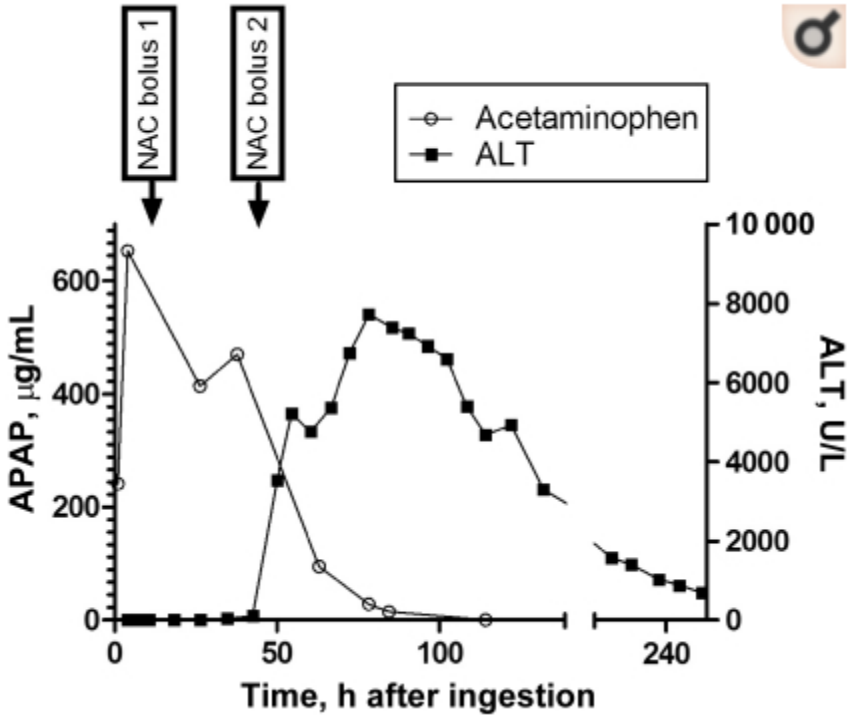
PMID: 30777470 DOI: 10.1080/15563650.2019.1579914


1000
100
10
1
[APAP], mcg/mL
25 mg/kg/h
18.75 mg/kg/h
12.5 mg/kg/h
6.25 mg/kg/h
25 mg/kg/h
18.75 mg/kg/h
12.5 mg/kg/h
6.25 mg/kg/h
25 mg/kg/h
18.75 mg/kg/h
12.5 mg/kg/h
6.25 mg/kg/h
600 line
450 line
300 line
150 line
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Time after ingestion of acetaminophen, hours

Pediatrics. 2011 Apr;127(4):e1077-80. doi: 10.1542/peds.2010-2521. Epub 2011 Mar 14.

Hepatic failure despite early acetylcysteine following large acetaminophen-diphenhydramine overdose.

Wang GS[1], Monte A, Bagdure D, Heard K.



Others:
Opioids
Extended Release Preps

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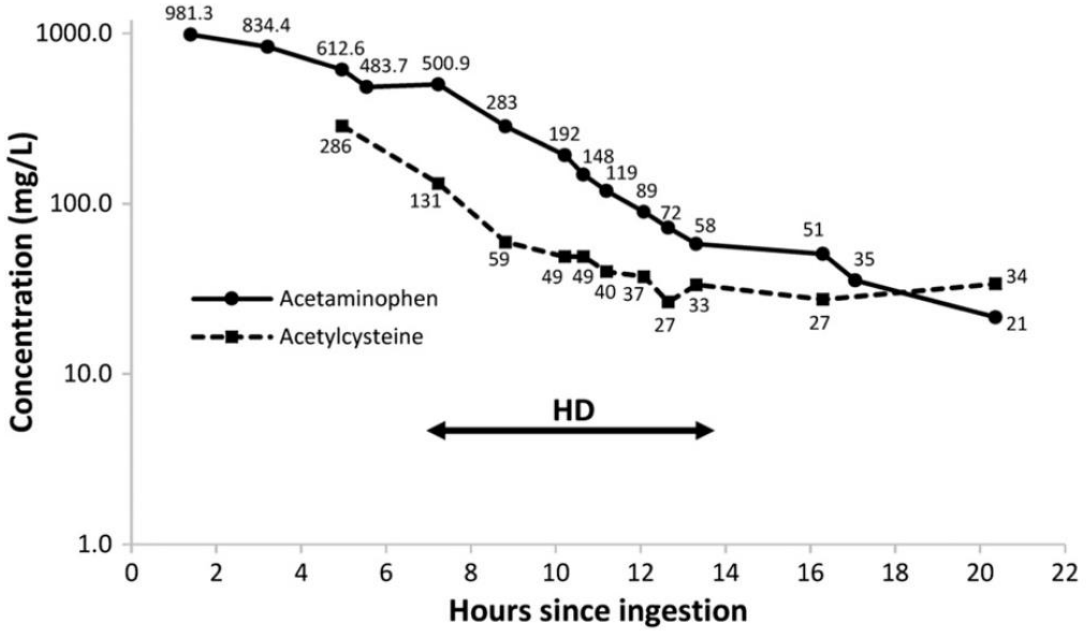
Clin Toxicol (Phila). 2016 Jul;54(6):519-22. doi: 10.1080/15563650.2016.1175006. Epub 2016 Apr 27.

Massive acetaminophen overdose: effect of hemodialysis on acetaminophen and acetylcysteine kinetics.

Ghannoum M[1], Kazim S[2], Grunbaum AM[3], Villeneuve E[4], Gosselin S[2,5].



-transformed acetaminophen and acetylcysteine concentrations versus time.

- APAP elimination half-life was 5.2 hours prior to hemodialysis, 1.9-hours during hemodialysis and 3.6 hours post hemodialysis.
- Hemodialysis removed a total of 20.6 g of APAP and 17.9 g of acetylcysteine.

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Prognostic Factors

- The most commonly used indicator for the need for immediate transplantation in adults with APAP toxicity is the King's College Criteria (KCC).
- Survival rate of adult patients who meet KCC and do not receive organ transplant is < 20%.

pH < 7.30 after fluid resuscitation

OR

Combination of:

- **Cr > 3.4 mg/ml**
- **PT > 100 s (INR > 6.5)**
- **Grade III or IV encephalopathy**

- Other scores used for need for transplantation include APACHE II score > 15, APACHE III score > 60, or combination of hypoglycemia, coagulopathy and lactic acidosis.

Br J Clin Pharmacol. 2021 Aug;87(8):3332-3343. doi: 10.1111/bcp.14755. Epub 2021 Feb 23.

Predicting mortality from acetaminophen poisoning shortly after hospital presentation

Mark C Yarema [1 2 3 4 5 6], David W Johnson [1 2 7 4], Marco L A Sivilotti [8 9], Alberto Nettel-Aguirre [7 10 11], Chris DeWitt [12 13], Sophie Gosselin [14 15 16], Nancy Murphy [16 17], Charlemagne Victorino [10], Benoit Bailey [18], Kathryn Dong [5], Elizabeth Haney [19], Roy Purssell [12 13], Margaret Thompson [9 20], Jason A Lord [6], Daniel A Spyker [21], Barry H Rumack [22]

Affiliations + expand

PMID: 33507553 DOI: 10.1111/bcp.14755

BOX 1 Description of each prognostic criterion

Criterion	Definition
King's College criteria	• Serum pH <7.30 after appropriate fluid resuscitation • Or *all* of the following: ◦ Prothrombin time (PT) >100 seconds (INR >6.5) ◦ Creatinine >3.3 mg/dL (300 μmol/L) ◦ Grade 3 or 4 encephalopathy
Model for End Stage Liver Disease (MELD)	Calculated as $9.57 \times \log_e$ (creatinine in mg/dL) + $3.78 \times \log_e$ (total bilirubin in mg/dL) + $11.2 \times \log_e$ (INR) + 6.43. A score ≥33 after onset of acute liver failure may be indicative of poor prognosis
Lactate	≥3.5 mmol/L at any time
Phosphate	≥1.2 mmol/L at least 48 h after the earliest reported time of ingestion
KCH or lactate	Meeting either KCH or lactate criteria
KCH or phosphate	Meeting either KCH or phosphate criteria

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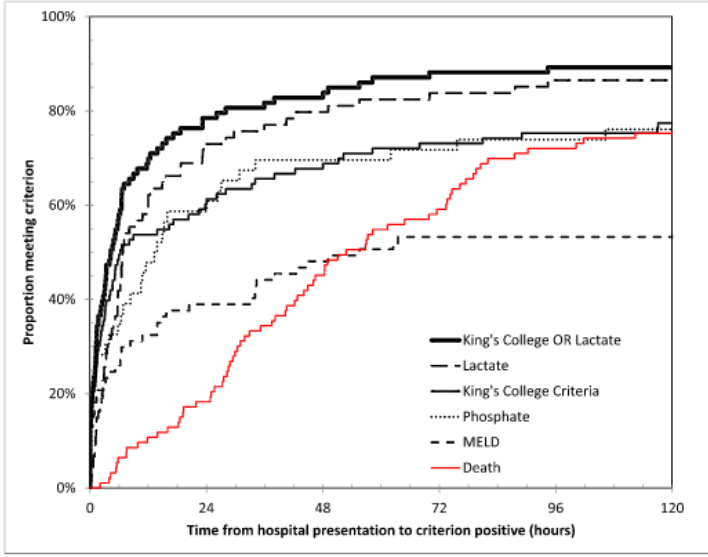
Yarema et al, Predicting Mortality

TABLE 3 Sensitivity of prognostic indicators for deaths attributed to acetaminophen toxicity (n = 93)

Prognostic indicator	All criteria data available (n)	Prognostic indicator positive (n)	Sensitivity (95% CI)	Time interval from hospital presentation until indicator positive (all cases), hours median [IQR]	Time interval from hospital presentation until indicator positive (positive cases only), hours median [IQR]
KCH criteria	93	79	0.85 (0.76, 0.92)	6.1 [1.2, 85]	4.6 [1.0, 31]
MELD ≥33	77	42	0.55 (0.43, 0.66)	52 [4.4, ∞]	6.3 [0.6, 34]
Lactate ≥3.5 mmol/L	74	64	0.86 (0.77, 0.93)	6.8 [2.9, 29]	6.3 [2.7, 15]
Phosphate ≥1.2 mmol/L at 48+ h post ingestion start	46	38	0.83 (0.69, 0.92)	13.2 [0.9, 91]	9.4 [0.7, 26]
KCH or lactate	93	87	0.94 (0.86, 0.98)	4.2 [1.0, 16]	3.3 [0.9, 12]
KCH or phosphate	93	82	0.88 (0.80, 0.94)	5.2 [0.5, 45]	3.1 [0.3, 24]



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Review > Toxicol Lett. 2022 Feb 1;355:47-61. doi: 10.1016/j.toxlet.2021.11.005. Epub 2021 Nov 14.

Use of fomepizole (4-methylpyrazole) for acetaminophen poisoning: A scoping review

Ali Mohammad Pourbagher-Shahri [1], Jonathan Schimmel [2], Farshad M Shirazi [3], Samaneh Nakhaee [1], Omid Mehrpour [4]

- In vitro, animal studies
- Human case reports

- Fomepizole inhibits CYP2E1

- Fomepizole binds the adenosine triphosphate (ATP) binding site of JNK

- 19 yo F, c/o tinnitus and decreased hearing. Discharged home, presented next day with continued vomiting, increased fatigue and diaphoresis.
- VS 37.0, HR 129, RR 40, BP 112/89, 100% RA
  - Kussmaul breathing, tachypnea, diaphoretic.
  - Awake and alert, but fatigued, SOB
- VBG: 7.2/35/-/12/8.2
- Na 132, K 3.3, Cl 104, Bicarb 11, BUN 24, Cr. 1.55

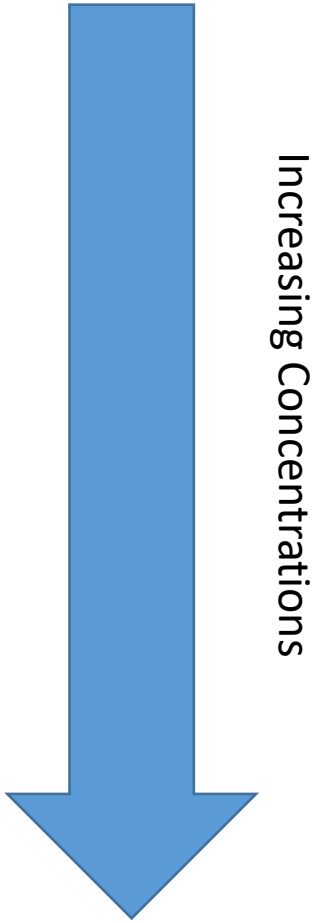
Aspirin

- Antipyretic, analgesic, anti-inflammatory
- Uncouples Oxidative Phosphorylation

- Bismuth Subsalicylate (Pepto Bismol)
  - 1ml = 8.7 mg of salicylic acid
- Oil of wintergreen (methyl salicylate)
  - 1 ml of 98% - 1.4 grams

Toxicity

- Ototoxicity
- Vomiting
- Respiratory alkalosis
- Metabolic acidosis
- ALI
- Seizures
- Cerebral Edema
- Death



Br Med J (Clin Res Ed). 1982 Nov 13;285(6352):1383-6. doi: 10.1136/bmj.285.6352.1383.

Diuresis or urinary alkalinisation for salicylate poisoning?

L F Prescott, M Balali-Mood, J A Critchley, A F Johnstone, A T Proudfoot

PMID: 6291695 PMCID: PMC1500395 DOI: 10.1136/bmj.285.6352.1383

Free PMC article

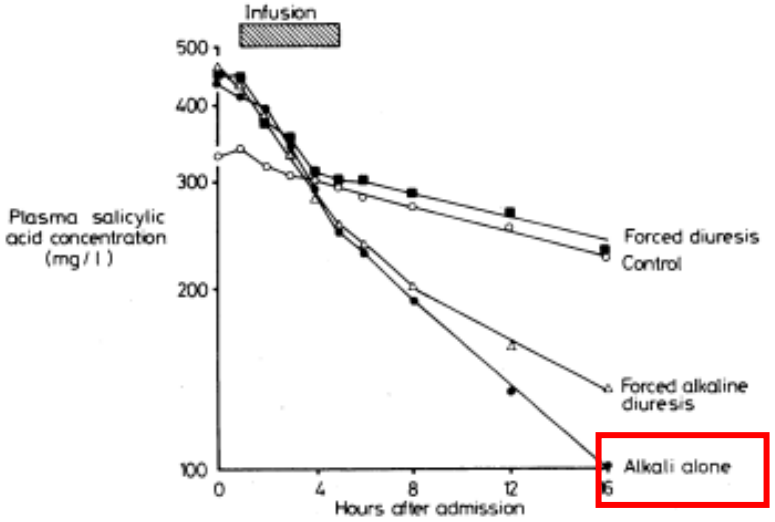


FIG 1—Mean plasma concentrations of salicylic acid in patients with aspirin overdosage receiving different treatment regimens of fluid and alkali.

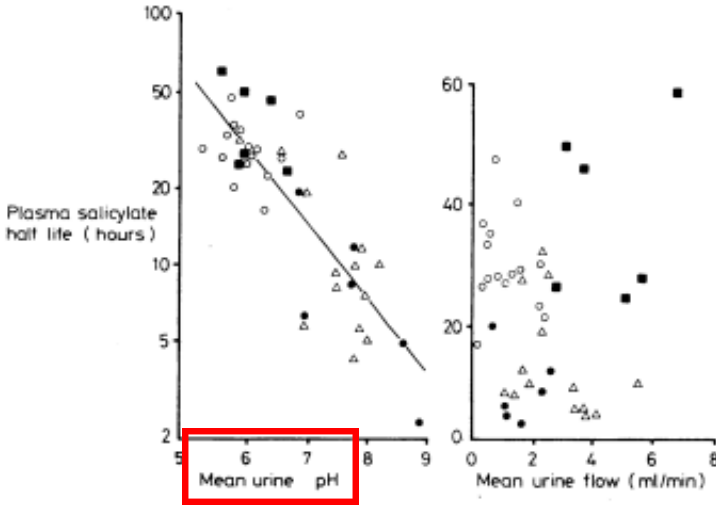


FIG 2—Correlation between log plasma salicylate half life and urine pH from four to 16 hours and lack of correlation between salicylate half life and urine flow over same period.
○ Control. △ Forced alkaline diuresis. ■ Forced diuresis. ● Alkali alone.

TABLE IV—*Urine pH, flow rate, and renal clearance of salicylic acid over the period zero time to 16 hours (mean values ± SD)*

Treatment	Urine pH	Urine flow rate (ml/min)	Renal salicylate clearance (ml/min)
Control	6·1 ± 0·4	1·4 ± 0·8	1·4 ± 1·4
Forced alkaline diuresis	7·3 ± 0·4*	5·1 ± 1·2*	17·5 ± 10·1*
Forced diuresis	6·5 ± 0·3	5·8 ± 1·9*	4·4 ± 1·8*†
Alkali alone	8·1 ± 0·5*†	2·6 ± 0·7*†	23·5 ± 13·7*

*Significantly different from control ($p < 0·05$).
†Significantly different from forced alkaline diuresis ($p < 0·05$).

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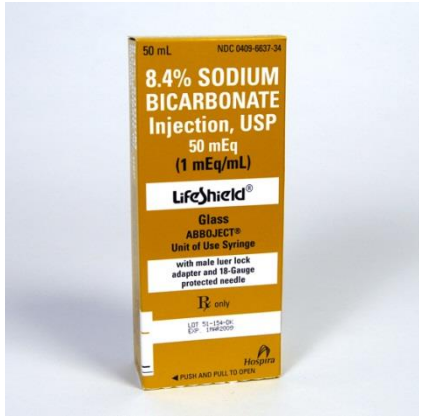
Sodium Bicarbonate



- Indications: ASA level > 30 mg/dl
- Dose: D5W + 3 amps of Sodium bicarb @ 1.5 MIVF, with KCL
- Goal: urine pH 7.5-8, or serum pH 7.55, declining ASA concentrations
- Follow BMP, VBG, ASA q 1-2 hr, initially, space as tolerates
- Activated Charcoal

Indications for Hemodialysis

- CNS changes: AMS, seizures, coma
- Renal failure
- Rising level despite adequate alkalization
- CHF
- Severe acid/base abnormality of electrolyte disturbance
- Coagulopathy
- ASA > 100 mg/dl

EXTRIP

In Poisoning Workgroup

Blood P… …he Evidence and Providing Recommendations

- ACETAMINOPHEN (PARACETAMOL)
- AMATOXINS
- BACLOFEN
- BARBITURATES
- ß-ADRENERGIC ANTAGONISTS
- CALCIUM CHANNEL BLOCKERS
- CARBAMAZEPINE
- DIGOXIN
- ETHYLENE GLYCOL
- GABAPENTIN / PREGABALIN
- ISONIAZID
- LITHIUM
- METFORMIN
- METHANOL
- METHOTREXATE
- PHENYTOIN
- QUININE / CHLOROQUINE
- SALICYLATES
- THALLIUM
- THEOPHYLLINE
- TRICYCLIC ANTIDEPRESSANTS
- VALPROIC ACID

Newsflash: New EX… …hed!

202…

2021: Baclofen, Isoniazid, ß-adre…

2020: Calcium Chann… … / Pregabalin

Pending: Dabiga…

Tweets by @ExtripWorkgroup

EXTRIP
@ExtripWorkgroup

Should we dialyze a patient who is toxic from high-dose or oral methotrexate? The jury is now out: cjasn.asnjournals.org/content/early/…

Or on our website: extrip-workgroup.org

- 17 yo F overdosed on her mood stabilizer. Within 1 hour of ingestion had a brief GTC seizure at home. EMS called and BIBA and had another 2 min GTC witness in ED. Received 4 mg Ativan. NO sedated, tremulous.
- VS Temp 37.8, HR 140, BP 140/80, RR 25, 94% on RA
- Mydriasis, nystagmus, extremity tremor, tachycardia, hyperreflexia

Bupropion

- Monocyclic aminoketone – cathinone (amphetamine-like)
  - Active metabolite hydroxybupropion
- Therapeutic MOA - Inhibits reuptake of dopamine and NE, minimal effects on MAO or serotonin
- Seizures, coma – can be delayed 10-24 hours (SR prep)
- Hallucinations
- Hypotension
- QRS/QTc interval widening, dysrhythmias
  - Gap junction blockade

Toxicity of **Bupropion** Overdose Compared With Selective Serotonin Reuptake Inhibitors.

Overberg A, Morton S, Wagner E, Froberg B.

Pediatrics. 2019 Aug;144(2):e20183295. doi: 10.1542/peds.2018-3295. Epub 2019 Jul 5.

PMID: 31278211

- 30,026 cases: 60% sertraline and fluoxetine, 11.7% buproprion
- Bupropion exposure was significantly associated with death (0.23% vs 0%; P < .001) or serious outcome (58.1% vs 19%; P < .001)
- Seizures (27.0% vs 8.5%; P < .001) and hallucinations (28.6% vs 4.3%; P < .001)
- Bupropion exposure was significantly associated with the need for
  - Cardiopulmonary resuscitation (0.51% vs 0.01%; P < .001)
  - Intubation (4.9% vs 0.3%; P < .001)
  - Vasopressors (1.1% vs 0.2%; P < .001)
  - Benzodiazepines (34.2% vs 5.5%; P < .001).

Clinical and electrocardiographic factors associated with adverse cardiovascular events in **bupropion** exposures.

Simpson M, Troger A, Feng C, Whitledge JD, Monuteaux M, Burns MM.
Clin Toxicol (Phila). 2023 Jul;61(7):529-535. doi: 10.1080/15563650.2023.2227997. Epub 2023 Jul 7.
PMID: 37417311

- 4,640 patients included in the final analysis
- 68 (1.47%) experienced an adverse cardiovascular event.
- Age (odds ratio 1.03; 95% confidence intervals 1.02-1.05)
- Single seizure (odds ratio 9.18; 95% confidence intervals 4.24-19.9)
- Complicated seizures (odds ratio 38.9; 95% confidence intervals 19.3-78.1)
- QRS widening (odds ratio 3.01; 95% confidence intervals 1.62-5.59)
- QTc prolongation (odds ratio 1.76; 95% confidence intervals 1.00-3.10)

Sodium bicarbonate treatment for QRS widening in **bupropion** overdoses.

Simpson M, Johnson L, Goldfine C.

Clin Toxicol (Phila). 2023 Jun;61(6):436-444. doi: 10.1080/15563650.2023.2218029. Epub 2023 Jun 15.

PMID: 37318051

- Retrospective cohort study of bupropion overdoses from 10 hospitals
  - January 2010 and June 2022
- Patients with documented administration of sodium bicarbonate and QRS duration > 100 ms on pre-bicarbonate electrocardiogram were included.
- 13 patients were included for final analysis.
- Six patients developed seizures; one developed ventricular tachycardia, and four received vasopressors.
- Median QRS and QTc pre-bicarbonate were 116 and 495 ms, respectively. The median change in QRS duration was -2.0 ms, which was not statistically significant (P = 0.42).
- Did not identify an association between QRS change and bicarbonate dosing (P = 0.9, R-squared = 0.001).

- 2 yo got into older brother's ADHD meds, now sleepy and difficult to arouse.
- HR 50's, BP 80/40, 90% RA, RR14
  - Miosis
  - Somnolent
  - Bradycardic

Clonidine and Imidazolines

- Used for hypertension and ADHD, ocular and nasal vasoconstrictors
  Guanfacine, tizanidine, oxymetolazine, tetrahydrozoaline
- Central Alpha 2 receptor
  - Decreases sympathetic release
- Imidazoline receptors (3)
  - I-2: opioid like effects through release of beta endorphin (stimulates opioid receptors)
- Symptoms
  - CNS depression, hypotension, bradycardia, mild hypothermia, respiratory depression, miosis
  - Wake with minimal stimulation

› Clin Toxicol (Phila). 2018 Oct;56(10):873-879. doi: 10.1080/15563650.2018.1450986. Epub 2018 Mar 16.

Naloxone reversal of clonidine toxicity: dose, dose, dose

	Awakened *n* = 40 (78.4%)	No CNS response *n* = 11 (21.6%)
Female	25 (62.5%)	8 (72.7%)
Age		
Median, years (IQR)	2.5 (2–6.5)	3 (2–6)
Dose (estimated)		
Median, mg (IQR)	0.50 (0.2–2.9)	0.55 (0.2–1.5)
Acute-on-chronic	10 (25.0%)	1 (9.1%)
Coingestant	5 (14.3%)	6 (54.5%)
Cardiovascular effects		
Bradycardia (Pre-N)	35 (87.5%)	8 (72.7%)
Bradycardia resolved	17 (48.6%) (*n* = 35)	0 (0%) (*n* = 8)
Hypotension (Pre-N)	7 (17.5%)	3 (27.3%)
Hypotension resolved	6 (85.7%) (*n* = 7)	0 (0%) (*n* = 3)
Hospital admission		
LOS, median (IQR)	1 (1–1)	1 (1–1)
Intubated	6 (15.0%)	4 (36.4%)
Naloxone administration		
Dose, median (IQR)	5.5 (3.5–10)	10 (5–10)
Dose, 10 mg	13 (32.5%)	7 (63.6%)
Maintenance drip	32 (80.0%)	2 (18.2%)
Adverse reaction	0 (0%)	0 (0%)

Pre-N: prior to naloxone administration; IQR: interquartile range.

Xylazine

- Veterinary tranquilizer
- Similar to alpha-2 agonists

- Primary misuse
- Adulterant in illicit opioids

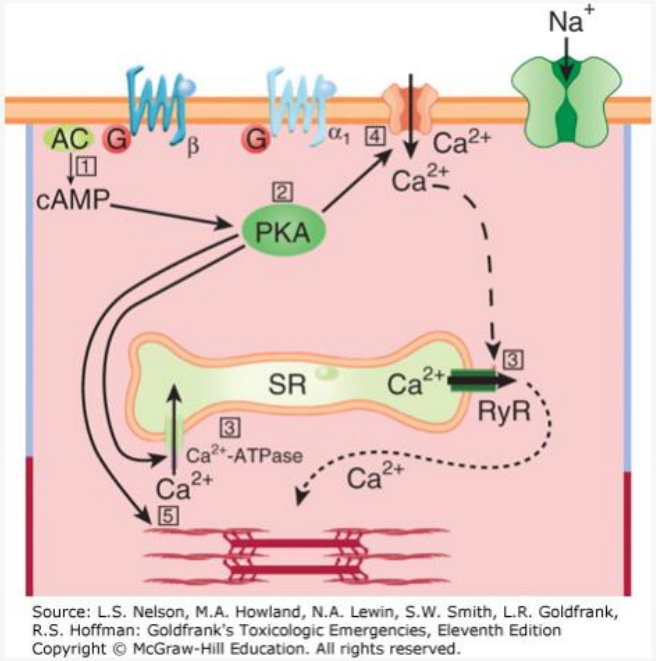
TABLE. Characteristics of drug overdose decedents with xylazine detected on postmortem toxicology (xylazine-positive) or listed as a cause of death (xylazine-involved) — State Unintentional Drug Overdose Reporting System, 38 states and the District of Columbia,* 2019

Characteristic	Classification of deaths, no. (%)	
	Xylazine-positive† (n = 826)	Xylazine-involved§ (n = 531)
Sex		
Male	602 (72.9)	388 (73.1)
Female	224 (27.1)	143 (26.9)
Race¶		
White, non-Hispanic	604 (74.8)	396 (75.4)
Black, non-Hispanic	106 (13.1)	68 (13.0)
Hispanic	90 (11.1)	—**
Other	11 (1.4)	—**
Age group, yrs		
15–24	60 (7.3)	41 (7.7)
25–34	265 (32.1)	181 (34.1)
35–44	227 (27.5)	138 (26.1)
45–54	147 (17.8)	91 (17.1)
55–64	109 (13.2)	—**
≥65	18 (2.2)	—**
U.S. Census region††		
Northeast	568 (68.8)	356 (67.0)
Midwest	144 (17.4)	91 (17.1)
South	104 (12.6)	—**
West	10 (1.2)	—**
Co-occurring drugs listed as a cause of death§§,¶¶		
Any fentanyl (including analogs)	815 (98.7)	526 (99.1)
Heroin***	215 (26.0)	151 (28.4)
Benzodiazepines	141 (17.1)	105 (19.8)
Prescription opioids†††	94 (11.4)	71 (13.4)
Cocaine	265 (32.1)	157 (29.6)
Alcohol	98 (11.9)	67 (12.6)
Methamphetamine	102 (12.4)	62 (11.7)

Kariisa PMID 34529640

β Blockers

- β1, β2, α 1
  - β1: acebutolol, atenolol, esmolol, metoprolol
  - Nonselective: Nadolol, propranolol,
  - β and α : cavedilol, labetalol

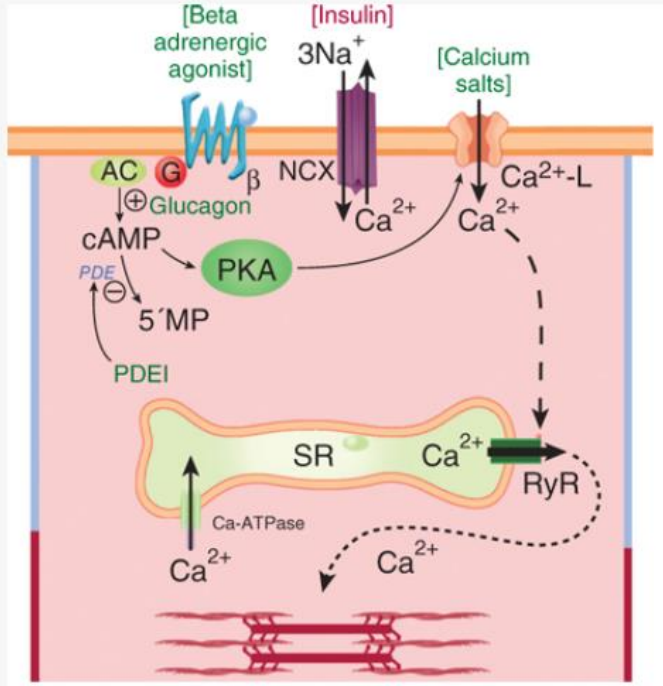


- Membrane stabilizing: acebutolol, propranolol, carvedolol

- Mostly hepatic metabolism
  - Renal: atenolol, nadolol, sotalol

Calcium Channel Blockers

- Dihydropyridine
  - Nifedipine, amlodipine, nicardipine
- Non-dihydropyridine
  - Verapamil (Phenylalkylamine)
  - Diltiazem (Benzothiazepine)
- CYP3A4
  - Also inhibit p-glycoprotein (lead to elevation of cyclosporine, digoxin)
- Norverapamil: active metabolite



Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank, R.S. Hoffman: Goldfrank's Toxicologic Emergencies, Eleventh Edition

Symptoms

- Cardiovascular: vasodilation/hypotension, reduced cardiac contractility, AV node slowing, heart block, bradycardia

- Ca Channel Blockers: *hyperglycemia (decrease in insulin release)*
- Beta Blockers: hypoglycemia (poor response, or young), hyperkalemia

Hyperglycemia

- CCBs inhibit calcium-mediated insulin secretion from the β-islet cells in the pancreas
- CCB-poisoned myocardium also becomes insulin resistant
- The combination of inhibition of insulin secretion and impaired glucose utilization may explain why severe CCB toxicity often produces significant hyperglycemia and may be a marker for the severity of poisoning

Treatment for β/Ca Blockers

- IVF
  - Aggressive resuscitation
- Atropine
- Ca repletion
  - Calcium: 5 -7 mg/kg bolus
  - 0.6 ml/kg CaGluc
  - 0.2 ml/kg CaCl
- Glucagon (β blockers)
  - 3-5 mg, 50 ug/kg, 2-5 mg/hr
  - Vomiting, tachyphylaxis
- Vasopressors
  - EPI, NE, Milrinone
  - ? Dobutamine
- Pacing
- HIE
- IL/Fat Emulsion
- ECMO

High Does Insulin Euglycemic Therapy

Proposed MOA

- Improved FFA utilization
- “forces” myocardium to be more carbohydrate dependent
- Improved glucose uptake
- *Improves inotropy*
- *Insulin leads to vasodilation* of the systemic, coronary and pulmonary microvasculature

High Does Insulin Euglycemic Therapy

- 0.5-1 unit/kg with 0.5 g/kg dextrose
- 0.5-1 unit/kg/hr and titrate if no improvement every 30 min (delay in response may be 15-60 min)
- Dextrose infusion (0.5 g/kg/hr)
- Glucose q 30 min for first 4 hrs
- Treat it like a pressor, when HDMS, wean vasopressor first
- Targeting improving in cardiac function and CO

High dose insulin for beta-**blocker** and **calcium channel-blocker** poisoning.

Cole JB, Arens AM, Laes JR, Klein LR, Bangh SA, Olives TD.
Am J Emerg Med. 2018 Oct;36(10):1817-1824. doi: 10.1016/j.ajem.2018.02.004. Epub 2018 Feb 6.
PMID: 29452919

- Median insulin bolus was 1U/kg (range, 0.5-10)
- Median starting insulin infusion was 1U/kg/h (range 0.22-10)
- Median peak infusion was 8U/kg/h (range 0.5-18)
- Adverse Effects
  - Hypokalemia occurred in 29% of patients
  - Hypoglycemia occurred in 31% of patients
  - 50% experienced hypoglycemia when dextrose infusion concentration ≤10%
  - 30% experienced hypoglycemia when dextrose infusion concentration ≥20%.

Critical care management of verapamil and diltiazem overdose with a focus on vasopressors: a 25-year experience at a single center.

Levine M, Curry SC, Padilla-Jones A, Ruha AM.

Ann Emerg Med. 2013 Sep;62(3):252-8. doi: 10.1016/j.annemergmed.2013.03.018. Epub 2013 May 1.

PMID: 23642908

Table 2. Doses of vasopressors, insulin, and glucagon in the primary group (N=33).

Drug	Number of Patients	Median (IQR) Infusion Rate	Maximal Infusion Rate
Norepinephrine	25	15 (8.4–24.5) μg/min	100 μg/min
Dopamine	19	19 (12–20) μg/kg per min	100 μg/kg per min
Epinephrine	13	20 (10–26) μg/min	150 μg/min
Isoproterenol	13	11 (5–25) μg/min	60 μg/min
Dobutamine	7	10 (7–15) μg/kg per min	245 μg/kg per min
Phenylephrine	3	100 (100–175) μg/min	250 μg/min
Insulin	3	1 (0.9–1) units/kg per h	2 unit/kg per h
Glucagon*	26	16 (5–46) mg	390 mg

*Listed as total dose, not infusion rate, because many patients had received intermittent boluses with or without a continuous infusion.

Methylene Blue

- Inhibits NO directly and NO production
- Roll in primary vasodilatory shock from dihydropyridines?

Methylene Blue

- Porcine model – MB not superior to NE in 15 animals poisoned with amlodipine (32495116)
- Rat model – MB significantly higher MAP, but did not change mortality risk (25441767)
- Case reports of successful improvements in BP (PMID: 27196698, 26310944, 21546119)
- Retrospective review, HDI vs VP for CCB.
  - 18 poisoned with amlodipine, 15 with non-DHPs (verapamil n = 10, diltiazem n = 5).
  - Median maximum concomitant vasopressors in the amlodipine group was 3 (IQR: 2-5; range 0-6) and 2 in the non-DHP group (IQR: 1-3; range 0-5; p = 0.04).
  - Median maximum epinephrine dosing was higher in the amlodipine group (0.31 mcg/kg/min) compared to non-DHPs (0.09 mcg/kg/min; p = 0.03).
  - Use of rescue methylene blue was more common in the amlodipine group (7/18 [39%]) than in the non-DHP group (0; p = 0.009).

Household Products

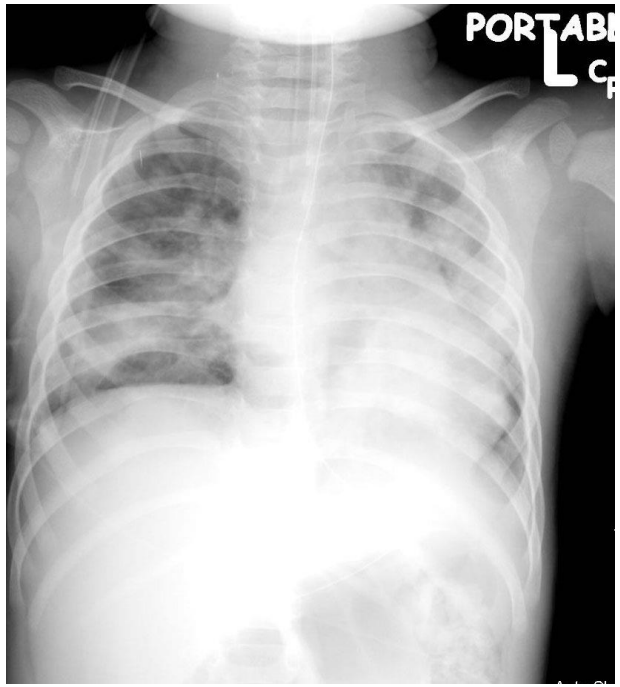
- 3 yo found outside in the shed holding a beverage container, coughing and vomiting, becoming somnolent.
- 37.9, 140's, 110/70, 88% RA, 40
  - Coughing, tachypenic
  - Tired appearing
  - Smells like fuel

Hydrocarbons

- Aliphatic
  - gasoline
- Aromatic
  - Essential oils
- Systemic toxicity
- Pneumonitis
  - Inflammatory cascade
  - Disrupt surfactant
- Properties
  - Volatility
  - Viscosity
  - Surface Tension

Management/Treatment

- CXR, 6 hr observation
- ? Steroids and antibiotics
- Surfactant



Artificial **surfactant** for therapy in **hydrocarbon**-induced lung injury in **sheep**.

Widner LR, Goodwin SR, Berman LS, Banner MJ, Freid EB, McKee TW.
Crit Care Med. 1996 Sep;24(9):1524-9. doi: 10.1097/00003246-199609000-00016.
PMID: 8797626

- Increased rate of change of arterial oxygen saturation
- Mixed venous oxygen saturation and PO2
- Differences in mortality

	Mortality (n)	
	Saline (n = 8)	Surfactant (n = 16)
Bolus		
Survived	1	8*
Died	3	0*
Aerosol		
Survived	1	8*
Died	3	0*
Total		
Survived	2	16*
Died	6	0*

*$p < .001$ compared with saline.

- The rate of change in systemic vascular resistance between 15 mins and 6 hrs also differed noticeably but not significantly (p = .053)
- Static respiratory system compliance at each of the five test pressures and static respiratory system compliance slopes did not differ at either 3 or 6 hrs

Surfactant

- Early administration (Richards)
- Worsening illness (Sommer, Mastropietro)
- On ECMO (here in PICU)

- Proposed criteria
  - Oxygenation index (OI) >7
  - ARDS criteria
  - Various PEEP, PIP, MAP thresholds

Richards PMID: 25285387
Sommer PMID: 30236893
Mastropietro PMID: 21624880

- 3 yo found in garage with an automotive product. Vomiting, ataxic and altered.
- VS T37, HR 140, RR 20, BP 90/50, 95% RA
- Intoxicated, vomiting, lungs CTA, RRR with normal perfusion, abd soft, ataxia noted.

Alcohols/Glycols

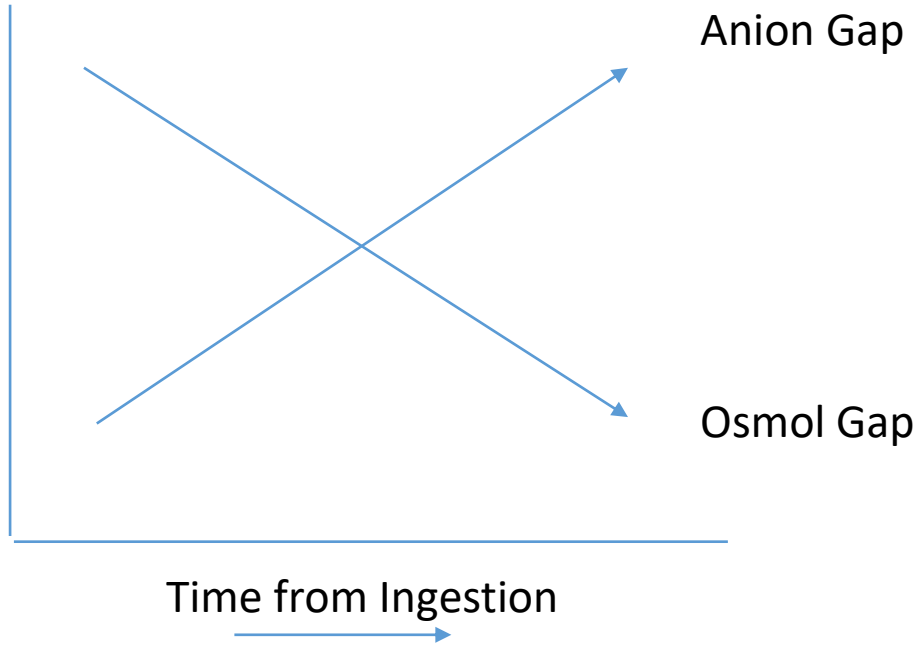
- Methanol
  - Windshield wiper fluid, fuels for stoves, paint removers
- Absorption in 30-90 minutes
- Metabolism slow
  - 8-24 hours
  - CNS depression, anion gap metabolic acidosis (formate)
  - Optic and renal toxicity

Alcohols/Glycols

- Ethylene Glycol
  - Antifreeze
- Absorption in 1-4 hours
- Rapid metabolism, toxicity appears rapidly (half life 3 hours)
- Alcohol-like intoxication without odor of alcohol
  - CNS depression (odorless alcohol like intoxication), anion gap metabolic acidosis (glycolic and oxalic acids)
  - Renal toxicity

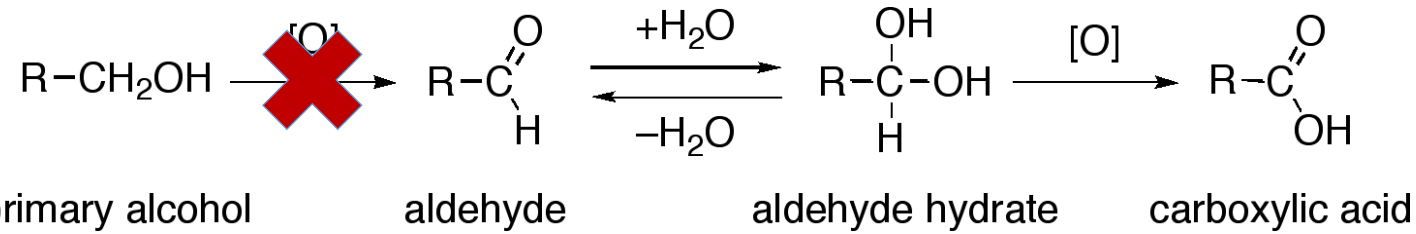
Alcohols/Glycols

- Intoxication
- Initial Osmolar Gap -> AGMA



Fomepizole

- Competitive inhibitor of alcohol dehydrogenase (the first enzyme in the metabolism of alcohols)



- Indications: ethylene glycol, methanol, severe acidosis
  - Dosing 15 mg/kg IV bolus, 10 mg/kg IV BID x 48 hours, then 15 mg/kg
  - Adverse Effect: check a BAL!!!
- Dialysis for acidosis, end organ failure

Fomepizole for ethylene glycol and **methanol poisoning**.

Brent J.

N Engl J Med. 2009 May 21;360(21):2216-23. doi: 10.1056/NEJMct0806112.

PMID: 19458366 Review. No abstract available.

- 2 Clinical trials
- Fomepizole for EG
  - Decreased toxic metabolite concentrations
  - Resolution of acidosis
  - Decreased renal injury
- Fomepizole for Methanol
  - Decreased toxic metabolite concentrations
  - Resolution of acidosis
  - No residual blindness

- Questions?
- George.wang@childrenscolorado.org
- Rocky Mountain Poison and Drug Safety: 1-800-222-1222