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Management of acetaminophen poisoning in the US and Canada: A consensus statement

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

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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 practice to optimize care of patients with acetaminophen poisoning.

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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.

Introduction

Acetaminophen poisoning may occur as a self-harm attempt or the inadvertent consumption of repeated doses in the treatment of pain or fever. Toxic effects of acetaminophen are characterized by hepatocellular damage, which may lead to acute liver injury, acute liver failure, or death. In 2021, US poison centers received more than 80 000 cases involving an acetaminophen product.[1] The National Electronic Injury Surveillance System estimated that 78 414 emergency department (ED) visits occurred annually in the US from January 1, 2006, through December 31, 2007, for overdoses of acetaminophen-containing products.[2] In Canada, approximately 4500 hospitalizations occur each year because of acetaminophen overdose.[3]

Clinical guidelines for the management of acetaminophen poisoning are needed. The past 25 years have witnessed numerous changes in acetaminophen poisoning, such as the introduction of products that contain greater amounts of acetaminophen, extended-release preparations, and new combination drugs of acetaminophen with opioids or other ingredients. Variation in care appears to stem from differing availability of resources, new treatment modalities, staffing of poison centers (PCs) and emergency departments (EDs), as well as patient behavior and other medical specialties. Unlike other countries, the US and Canada have not developed authoritative clinical practice guidelines for acetaminophen poisoning.

We created a practice guideline for PCs and EDs in the US and Canada. The panel members were chosen by the leading clinical toxicology organizations of the US and Canada: America's Poison Centers, the American Academy of Clinical Toxicology, the American College of Medical Toxicology, and the Canadian Association of Poison Control Centers.

Methods

The process involved extensive preparation composed of accumulating and summarizing the literature and current PC guidelines. Using a modified Delphi method, the panel created a decision framework and determined the appropriate management of a patient with acetaminophen poisoning.[4] The panel identified clinical decisions and formed recommendations. We incorporated the review from several organizations (eTable 1 in Supplement 1). The project began in March 2021 and ended in March 2023. This qualitative study followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) reporting guideline.[5]

We obtained guidelines for management of acetaminophen poisoning from PCs and toxicology fellowships in the US and Canada as well as clinical decision support software (UpToDate, version 3.42.0 [Wolters Kluwer] and Poisindex, version 2.0.1 [Merative Micromedex]). The medical literature was obtained using Ovid, PubMed, Embase, and Cochrane, filtered using the terms *acetaminophen* and *overdose* and *practice guidelines*. Focused searches were performed for more specific aspects of the guidelines that required additional literature (ie, decontamination).

The 21 panel experts were trained in multiple relevant clinical specialties (eTable 2 in Supplement 1). One author (R.C.D.) served as the nonvoting panel chair and drafted the initial voting statements based on the relevant literature and guidelines. The consensus process presented statements regarding each element of patient management to the panel members in each round. A total of 20 virtual meetings were held during 12 months (February 2022 to February 2023). For each question, a panel member could vote agree, disagree, or strongly disagree. Consensus was defined as 75% of the panel voting agree with no strong disagreement votes. A single strong disagreement vote resulted in further refinement until the panel achieved consensus.

Results

Our final literature base consisted of 84 guidelines and 278 publications (eTable 3 in Supplement 1). Most of the medical literature and all the guidelines met evidence quality 5 (opinion of respected

authorities; case reports). Only 7 articles met evidence quality 1 (properly powered and conducted randomized clinical trial; systematic review with meta-analysis).

In 11 rounds, the panel defined and evaluated 14 topics and created a decision framework that followed the natural progression of a poisoned patient: clinical assessment, gastrointestinal decontamination, and immediate treatment, including antidote administration. The panel also addressed special issues: extended-release acetaminophen products, repeated ingestions, high-risk massive ingestion, pregnancy, children younger than 6 years, body weight greater than 100 kg, coingestants, transplant evaluation, and enhanced elimination techniques.

Management of Suspected Acute Ingestion of Immediate-Release Acetaminophen Products

Acute ingestion is the most common presentation of acetaminophen poisoning. The panel emphasized the role of the patient's history. Despite its importance, few reports evaluate methods for procuring an accurate history. The committee defined an unreliable or inaccurate history as one that lacks sufficient detail to establish dose and time of ingestion, that contains conflicting statements, or when the patient has symptoms, signs, or laboratory values inconsistent with the history. If in doubt, the history should be considered unreliable, and the pathway for unreliable or unknown history should be followed (**Figure 1**).

The panel discovered controversy regarding the definition of acute ingestion. Most articles and guidelines recommend use of the Rumack-Matthew nomogram to determine the need for treatment with acetylcysteine, but many used the nomogram in a manner inconsistent with the original studies[6,7] supporting its use. The nomogram applies only for acute ingestions, but various publications and PC guidelines define acute ingestion as a single ingestion that occurs for a period of 1 hour, 8 hours, or another period, depending on the source. In contrast, the source publications[8-10] for the nomogram defined acute ingestion as "history of known or suspected acute ingestion 7.5 g or more of acetaminophen within 24 hours of admission." The principal investigator of these studies confirmed that any pattern of acetaminophen ingestion was enrolled as long as the serum acetaminophen concentration was measured within 24 hours of swallowing the first tablet, capsule, or liquid (B.H.R., written communication, March 7, 2023). Therefore, acute ingestion includes any ingestion period of less than 24 hours regardless of the ingestion pattern. In contrast, a repeated supratherapeutic ingestion occurs during a period of greater than 24 hours.

The panel chose to revise the Rumack-Matthew nomogram by including only lines that guide clinical action (**Figure 2**). The blood concentration of acetaminophen is simply plotted on the nomogram, and acetylcysteine is administered to patients whose concentration is above the treatment line.

Administration of Acetylcysteine

Acetylcysteine is administered orally or intravenously (**Figure 3**). The initial dose should be administered as soon as the need for treatment becomes evident. More than 15 different regimens were identified, but the comparative effectiveness of these regimens has not been evaluated.[11] The panel recommended use of a regimen that delivers at least 300 mg/kg orally or intravenously during the first 20 to 24 hours of treatment.

The guideline codifies the practice of acetylcysteine stopping criteria. A common clinical error is to administer acetylcysteine for a period of 20 or 21 hours and then discontinue without reassessment of the patient. However, some patients require longer treatment. The recommended practice is to administer acetylcysteine until stopping criteria are met.[12,13]

High-Risk Acetaminophen Ingestion

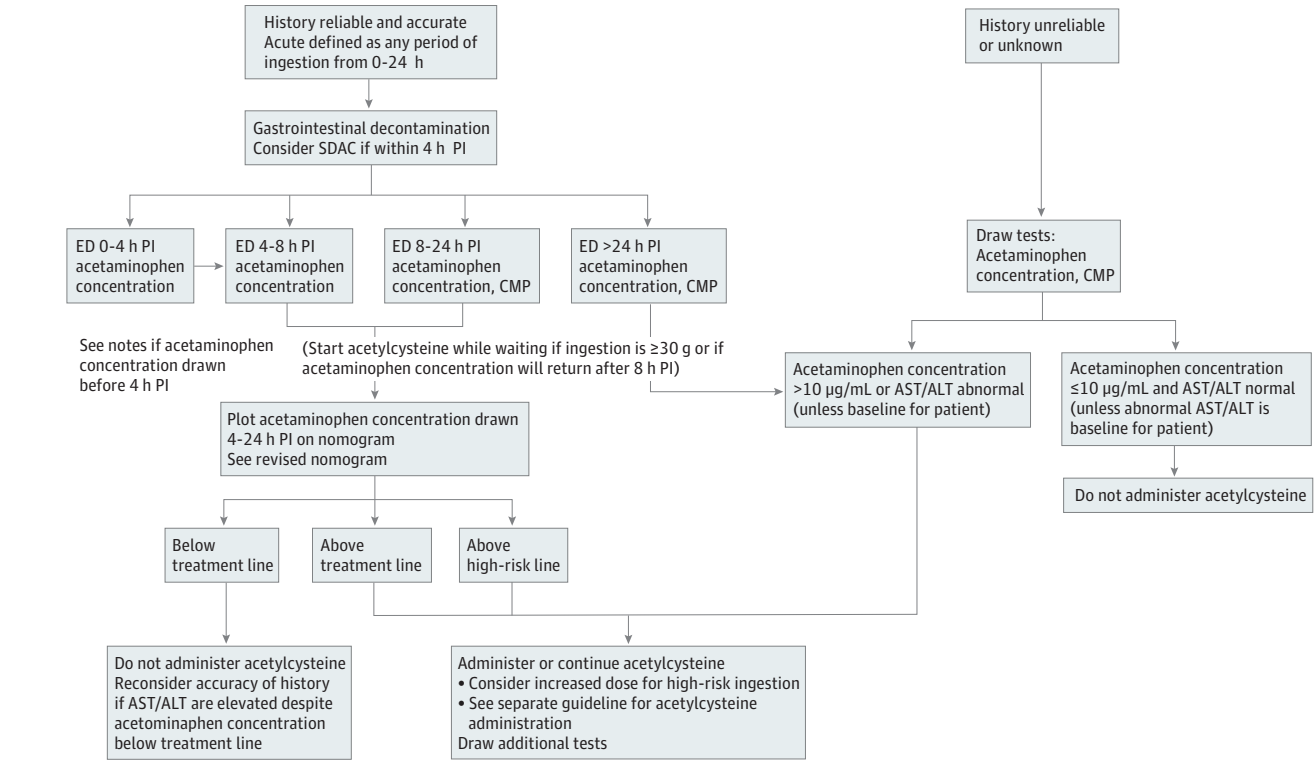
A high-risk ingestion is defined as ingestion of at least 30 g of acetaminophen or an acetaminophen concentration above the high-risk line on the nomogram (Figure 2). High-risk ingestions are managed in the same manner as other acetaminophen products with the consideration that administration of

activated charcoal may be warranted longer than 4 hours after ingestion because of prolonged absorption. Additional laboratory testing is indicated if the patient has developed signs of mitochondrial dysfunction, such as altered level of consciousness, metabolic acidosis, or hyperlactatemia. Assessment should include evaluation of other causes of altered level of consciousness. Finally, increased dosage of acetylcysteine may be warranted in consultation with a PC or clinical toxicologist.

Management of Repeated Supratherapeutic Ingestion

Repeated supratherapeutic ingestion is defined as multiple ingestions for a period greater than 24 hours. Unlike the patient with acute ingestion, management is determined by the patient's presentation (**Figure 4**). If the acetaminophen concentration is greater than 20 µg/mL (to convert to micromoles per liter, multiply by 6.614) or the aspartate aminotransferase or alanine aminotransferase level is abnormal, acetylcysteine should be administered until stopping criteria are met.

Figure 1. Management of Acetaminophen Poisoning in a Medical Facility



If the clinician determines the time of ingestion is unreliable or inaccurate, the history should be considered unreliable or unknown. The initial history should include patient age, intent, specific formulation, dose, time ingestion began, duration of ingestion, pattern of ingestion, and concomitant ingested medications. Medical history includes conditions that may affect the severity of poisoning (eg, long-term alcohol use and underlying liver disease). The physical examination should evaluate signs consistent with acetaminophen poisoning (vital signs, body weight, repeated vomiting, right upper quadrant abdominal tenderness, or mental status change). Single-dose activated charcoal (SDAC) should be considered in patients with acute ingestion of a potentially liver-toxic amount of acetaminophen unless the patient is unable to control airway or has contraindications to its use. The recommended dose is 50 to 100 g for adults and 25 to 50 g for children. An acetaminophen concentration sample drawn before 4 hours after ingestion cannot be used to risk-stratify patients on the acetaminophen nomogram. A nondetectable concentration at 2 to 4 h after ingestion typically excludes significant ingestion, but consultation with a poison center or toxicologist is recommended. Prothrombin time and international normalized ratio activity should be measured in patients with an elevated transaminase activity or clinical suspicion of liver injury. Acetylcysteine should be administered while awaiting acetaminophen concentrations if samples are drawn more than 24 hours after ingestion and the patient has signs and symptoms of toxicity. A pregnancy test result should be documented for all females of childbearing age. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CMP, complete metabolic panel; ED, emergency department; and PI, post ingestion.

Ingestion of Extended-Release Acetaminophen Products

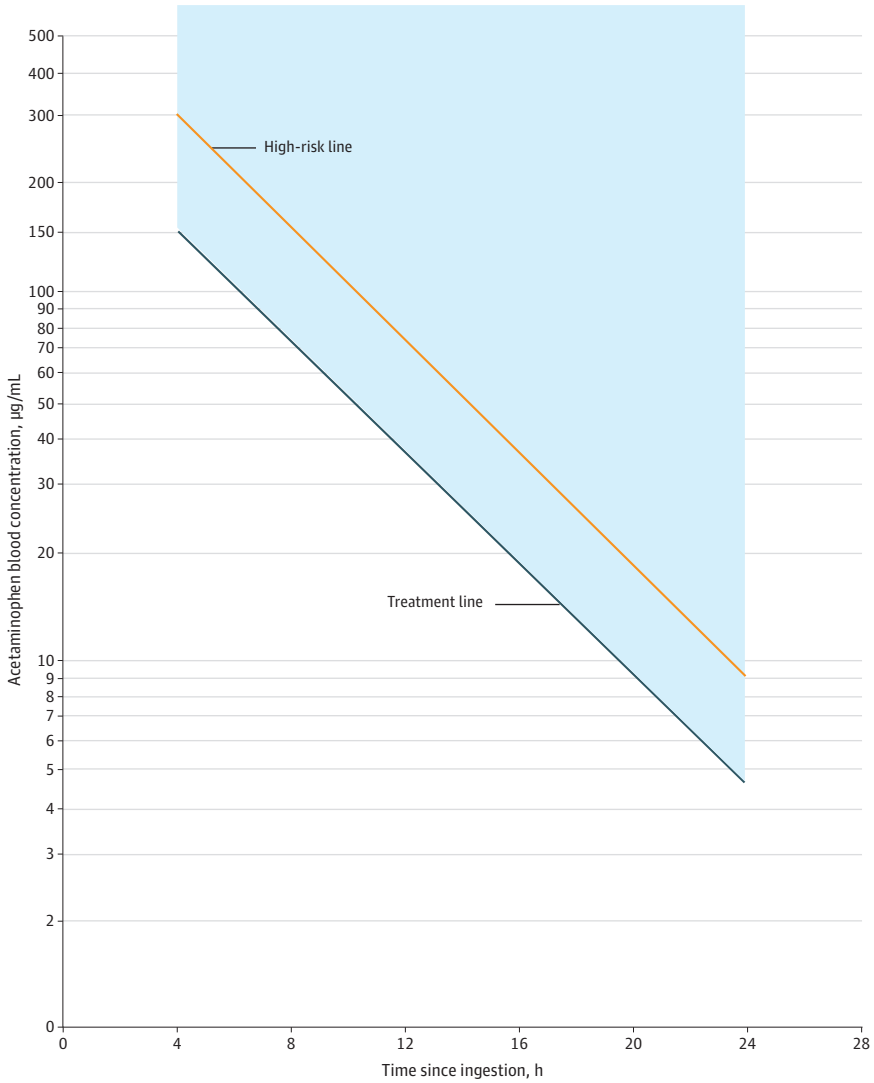
Extended release is defined as acetaminophen products available in the US or Canada and labeled for use on an 8-hour basis. Management is the same as for ingestion of other acetaminophen products except that activated charcoal may be useful longer than 4 hours after ingestion if evidence of ongoing absorption is present (eg, an increasing acetaminophen concentration).

If the acetaminophen concentration 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.

Coingestion of Acetaminophen and Anticholinergic or Opioid Agonist Medications

When acetaminophen is coingested with anticholinergic or opioid agonist medications, the clinical concern is that acetaminophen absorption may be delayed or prolonged. Management is the same as with other acetaminophen products except that if the first acetaminophen concentration measured at 4 to 24 hours after ingestion is 10 µg/mL or less, another measurement need not be taken and

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



The original Rumack-Matthew nomogram line, derived from patient data, begins at 200 µg/mL at 4 hours after ingestion.[7] The treatment line (safety line) beginning at 150 µg/mL at 4 hours was derived as 25% lower than the original nomogram line.[8] A line beginning at 300 µg/mL at 4 hours was derived as 50% greater than the original nomogram line to denote patients and increased risk of developing liver injury.[9] Acetylcysteine should be initiated if a serum or plasma acetaminophen blood concentration drawn 4 to 24 hours after ingestion falls on or above the treatment line. If the concentration falls on or above the high-risk line, many clinicians would provide an increased dose of acetylcysteine. However, the medical literature is insufficient to allow recommendation of a specific acetylcysteine dose in this circumstance.

acetylcysteine treatment is not needed. If any concentration is above the treatment line, acetylcysteine is needed.

If the acetaminophen concentration measured 4 to 24 hours after ingestion is greater than 10 µg/mL but less than the treatment line on the revised nomogram and the patient has anticholinergic or opioid clinical effects, another measurement should be taken 4 to 6 hours after the first measurement. The dose and duration of acetylcysteine treatment are the same as with other acetaminophen ingestions.

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.

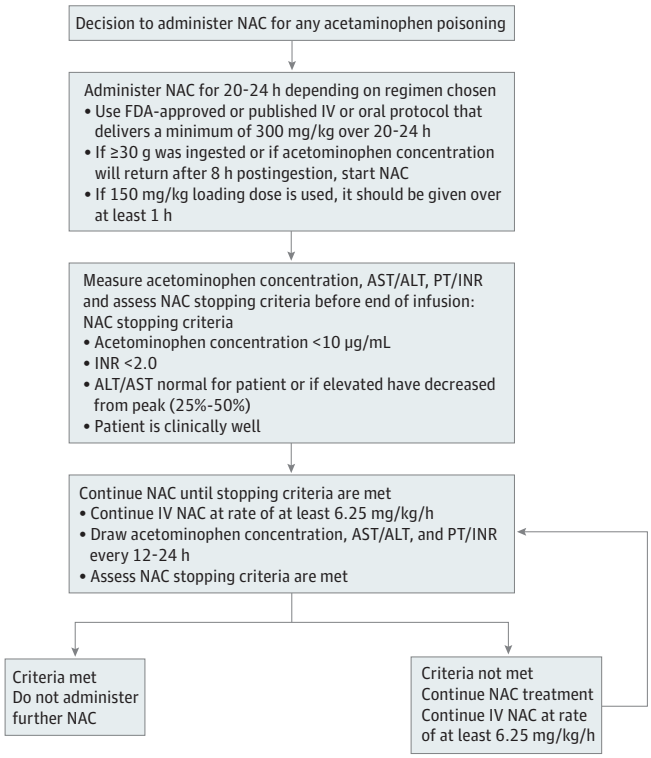
Patients Younger Than 6 Years

Management in patients younger than 6 years is the same as for older patients except that the clinician should simply contact their PC or clinical toxicologist if a child receives a single intravenous dose of acetaminophen of 90 mg/kg body weight or a cumulative dose of greater than 150 mg/kg body weight during 24 hours. With some regimens, administration of acetylcysteine requires weight-based adjustment to avoid hyponatremia for patients who weigh less than 41 kg.

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.

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



When there is 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, if waiting for testing will result in treatment starting more than 8 hours after ingestion. A prior anaphylactoid reaction is not a contraindication for administration of NAC during a subsequent overdose. If indicated, acetylcysteine should be initiated and the route or rate of administration adjusted if the patient develops adverse events, such as vomiting or an anaphylactoid reaction. When a 150-mg/kg loading dose is used, it should be infused over at least 1 hour. ALT indicates alanine transaminase; AST, aspartate transaminase; FDA, US Food and Drug Administration; IV, intravenous; INR, international normalized ratio; NAC, acetylcysteine; PT, prothrombin time.

Use of Enhanced Elimination Techniques

Enhanced elimination is recommended when a very large ingestion has occurred. The consensus panel concurred with the extracorporeal treatment of poisoning.[14] Hemodialysis is recommended in addition to treatment with acetylcysteine in a patient with an acetaminophen concentration of 900 µg/mL or greater with acidosis or altered consciousness due to acetaminophen toxic effects. If the intravenous route is used, the rate of acetylcysteine infusion should be at least 12.5 mg/kg per hour during hemodialysis. The oral acetylcysteine regimen does not require adjustment during hemodialysis.

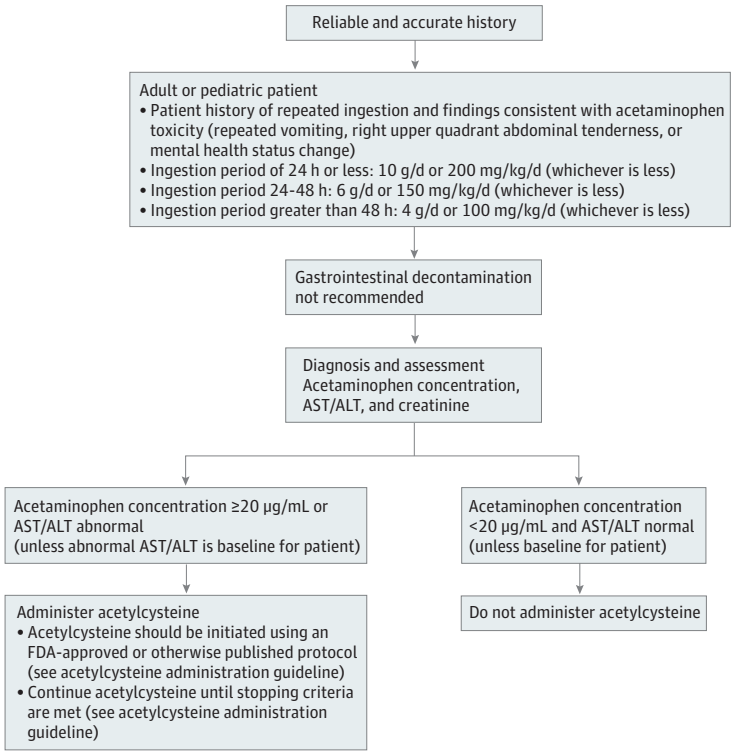
Consultation With Liver Transplant Team

Consultation with a liver transplant team for possible liver transplant should be considered in patients with progressive increases in aspartate aminotransferase or alanine aminotransferase and coagulation abnormalities. Liver transplant team consultation should also be considered in patients with encephalopathy or multisystem failure despite acetylcysteine treatment.

Discussion

The need for more standardized care of acetaminophen poisoning is pressing. Although a common toxicologic condition, an individual acute-care clinician rarely encounters a patient with serious poisoning patient. Unfamiliarity fosters suboptimal clinical management and treatment. Unlike most other poisonings, acetaminophen-induced acute liver failure is life-threatening, and the use of acetylcysteine can be lifesaving. A missed diagnosis, delay in treatment, or interruption of acetylcysteine infusion is potentially lethal. A guideline that provides management guidance could optimize patient outcomes, reduce disruption for patients and caregivers, and reduce costs by

Figure 4. Management of Repeated Supratherapeutic Ingestion of Acetaminophen



The revised nomogram should not be used for assessment of repeated ingestions that span more than 24 hours. ALT indicates alanine transaminase; AST, aspartate transaminase; FDA, US Food and Drug Administration.

shortening the length of hospitalization.[15,16] For complicated scenarios or other questions, PC or clinical toxicology consultation is strongly recommended.

The panel identified several changes in the management of acetaminophen poisoning that clinicians may find perplexing. The importance of the patient history is a neglected aspect of care and an error that PCs often encounter in assisting clinicians in patient care. An inaccurate estimate of the time of ingestion, for example, can lead to the erroneous conclusion that acetylcysteine is not needed or can be discontinued prematurely. This mistake is potentially fatal; thus, it is recommended that if there is any doubt about the history, the patient receive acetylcysteine. This approach may result in some patients receiving acetylcysteine unnecessarily, but because acetylcysteine is a relatively safe and inexpensive drug, the trade-off of overtreatment with potentially unneeded acetylcysteine is acceptable.

Numerous changes in our understanding of acetaminophen toxic effects have developed during the past 25 years. In particular, the occurrence of acute liver injury despite early acetylcysteine treatment in patients with high-risk ingestions has become apparent.[17] Today, most PCs recommend an increased dose of acetylcysteine in high-risk ingestions, but the practice varies and few data are available to guide management. The panel harmonized the guidelines currently used by PCs to define a high-risk ingestion as one involving an acute ingestion of at least 30 g or a concentration above the high-risk line on the revised nomogram to help standardize medical care.

Another concern is the lack of high-quality evidence to guide the choice of a specific acetylcysteine regimen to use. Originally, acetylcysteine was available only as an oral solution, which was administered using 1 regimen that lasted 72 hours. An intravenous formulation with a different dosage regimen was introduced to the US in 2004. Today, there are at least 15 regimens currently recommended in the medical literature. However, published data that adequately compare the effectiveness of these variable regimens are not available. Therefore, the panel decided to recommend a minimum adequate dose of acetylcysteine rather than a specific regimen.

Another potentially fatal error is premature termination of the acetylcysteine infusion. Some patients, especially those who have ingested a large amount of acetaminophen or coingested agents that delay absorption, may have dangerous amounts of acetaminophen in the blood after the initial 21-hour infusion period specified in the package insert.[18] The panel concluded that the recommended treatment duration should be decided by clinical markers (stopping criteria) and not a set duration. If this approach is followed, it will be difficult to provide inadequate dosing that would lead to mortality or prolongation of hospitalization. Another common clinical error is to continue acetylcysteine for too long, which prolongs hospitalization. Stopping criteria provide a clear ending point to reduce ongoing infusion.

The introduction of extended-release acetaminophen formulations has caused consternation because of concerns it could prolong absorption and result in high blood concentrations of acetaminophen later than expected in the course. Clinical experience has not supported this concern, although there have been case outliers. The panel concluded that management of extended-release preparations is the same as that of other acetaminophen products, with the exception of obtaining a second acetaminophen blood concentration in some cases. However, it should be ensured that the patient has not ingested modified-release acetaminophen products. Modified-release products use a different method of prolonging acetaminophen absorption. These products have been associated with markedly delayed absorption and unexpected toxicity.[19] These products are marketed in Europe and Australia but not in the US or Canada, to our knowledge.

Another change is the introduction of acetaminophen for intravenous administration in 2011.[20] Most of the reported cases have involved iatrogenic administration attributable to miscalculation of the acetaminophen dose for small children. The Rumack-Matthew nomogram has not been validated for interpretation of acetaminophen concentrations in intravenous exposures.

The addition of fomepizole to acetylcysteine in the treatment of serious acetaminophen ingestions has been proposed. The panel concluded that the data available did not support a

standard recommendation. As for any complicated or serious acetaminophen poisoning, a PC or clinical toxicologist should be consulted.

Limitations

There are several limitations to this work. The main limitation is the lack of high-quality data that address the clinical decisions needed for the management of acetaminophen poisoning. There were only a few well-controlled comparative studies, which focused on specific issues and not on patient management. For example, a prospective observational study[11] documented the efficacy and safety of a specific infusion regimen for acetylcysteine but no studies that compared regimens in a randomized clinical trial.

Conclusion

Acetaminophen poisoning may result in acute liver failure and death if not treated with acetylcysteine in a timely manner. Future work should focus on refining critical elements of history-taking in poisoned patients, comparative effectiveness and safety research on various acetylcysteine regimens, and refining the clinical roles of fomepizole and hemodialysis in acetaminophen poisoning.

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Acquisition, analysis, or interpretation of data: Dart, Mullins, Ruha, Burns, Simone, Beuhler, Heard, Mazer-Amirshahi, Stork, Varney, Funk, Cantrell, Cole, Banner, Stolbach, Hendrickson, Lucyk, Sivilotti, Nelson, Rumack, Matoushek.

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SUPPLEMENT 1.

eTable 1. Organizations That Commented on Proposed Acetaminophen Guidelines
eTable 2. Panel Participants
eTable 3. Literature Citations Utilized by the Acetaminophen Consensus Panel

SUPPLEMENT 2.

Data Sharing Statement