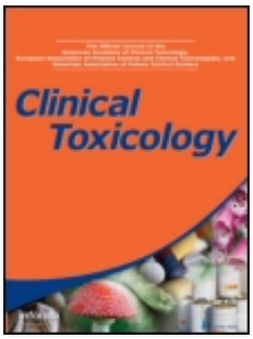

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PRACTICE GUIDELINE

Acetaminophen Poisoning: an Evidence-Based Consensus Guideline for Out-of-Hospital Management*

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The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial management of patients with suspected ingestions of acetaminophen. An evidence-based expert consensus process was used to create this guideline. This guideline applies to ingestion of acetaminophen alone and is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and the health professionals providing care. The panel's recommendations follow. These recommendations are provided in chronological order of likely clinical use. The grade of recommendation is provided in parentheses. 1) The initial history obtained by the specialist in poison information should include the patient's age and intent (Grade B), the specific formulation and dose of acetaminophen, the ingestion pattern (single or multiple), duration of ingestion (Grade B), and concomitant medications that might have been ingested (Grade D). 2) Any patient with stated or suspected self-harm or who is the recipient of a potentially malicious administration of acetaminophen should be referred to an emergency department immediately regardless of the amount ingested. This referral should be guided by local poison center procedures (Grade D). 3) Activated charcoal can be considered if local poison center policies support its prehospital use, a toxic dose of acetaminophen has been taken, and fewer than 2 hours have elapsed since the ingestion (Grade A). Gastrointestinal decontamination could be particularly important if acetylcysteine cannot be administered within 8 hours of ingestion. Acute, single, unintentional ingestion of acetaminophen: 1) Any patient with signs consistent with acetaminophen poisoning (e.g., repeated vomiting, abdominal tenderness in the right upper quadrant or mental status changes) should be referred to an emergency department for evaluation (Grade D). 2) Patients less than 6 years of age should be referred to an emergency department if the estimated acute ingestion amount is unknown or is 200 mg/kg or more. Patients can be observed at home if the dose ingested is less than 200 mg/kg (Grade B). 3) Patients 6 years of age or older should be referred to an emergency department if they have ingested at least 10 g or 200 mg/kg (whichever is lower) or when the amount ingested is unknown (Grade D). 4) Patients referred to an emergency department should arrive in time to have a stat serum acetaminophen concentration determined at 4 hours after ingestion or as soon as possible thereafter. If the time of ingestion is unknown, the patient should be referred to an emergency department immediately (Grade D). 5) If the initial contact with the poison center occurs more than 36 hours after the ingestion and the patient is well, the patient does not require further evaluation for acetaminophen toxicity (Grade D). Repeated supratherapeutic ingestion of acetaminophen (RSTI): 1) Patients under 6 years of age should be referred to an emergency department immediately if they have ingested: a) 200 mg/kg or more over a single 24-hour period, or b) 150 mg/kg or more per 24-hour period for the preceding 48 hours, or c) 100 mg/kg or more per 24-hour period for the preceding 72 hours or longer (Grade C). 2) Patients 6 years of age or older should be referred to an emergency department if they have ingested: a) at least 10 g or 200 mg/kg (whichever is less) over a single 24-hour period, or b) at least 6 g or 150 mg/kg (whichever is less) per 24-hour period for the preceding 48 hours or longer. In patients with conditions purported to increase susceptibility to acetaminophen toxicity (alcoholism, isoniazid use, prolonged fasting), the dose of acetaminophen considered as RSTI should be greater than 4 g or 100 mg/kg (whichever is less) per day (Grade D). 3) Gastrointestinal decontamination is not needed (Grade D). Other recommendations: 1) The out-of-hospital management of extended-release acetaminophen or multi-drug combination products containing acetaminophen is the same as an ingestion of acetaminophen alone (Grade D). However, the effects of other drugs might require referral to an emergency department in accordance with the poison center's normal triage criteria. 2) The use of cimetidine as an antidote is not recommended (Grade A).

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Keywords Acetaminophen/poisoning; Poison control centers/standards; Practice guidelines

INTRODUCTION

Scope of the Problem and Importance of the Guideline

Ingestion of acetaminophen is a common challenge for poison centers. In 2003, poison centers in the US were contacted regarding ingestion of acetaminophen or an acetaminophen-containing product by 127,171 patients (1). Of these, 38,989 were children under the age of 6 years. A total of 65,030 patients (51%) were evaluated in healthcare facilities and 327 died. Of these, 34 (10.4%) were designated as chronic and 46 (14.1%) were designated as "acute on chronic" in which a patient already on chronic acetaminophen therapy ingested an acute overdose (1). Published data suggest that the mortality rate for patients with repeated ingestion is higher than that of acute single ingestion of acetaminophen (2–4).

The evaluation of possible acetaminophen poisoning has medical, economic, and social costs. In 1995, Bond and Novak (5) estimated that 30,000–40,000 adolescents and adults ingest acetaminophen each year with the intent of self-harm. They calculated that about 15,000 adolescent and adult patients are hospitalized for an average of 2.7 days because of acetaminophen overdose. Approximately 250 of these patients die and another 50 receive liver transplants. At that time, they estimated that the total annual cost of intentional acetaminophen ingestion in the US was $86.9 million. In addition, there are numerous social and economic costs for families that arise from disruption of their lives as well as the direct costs associated with emergent visits to healthcare facilities.

The few data available indicate that the management of acetaminophen ingestion in the US is variable. The healthcare facility referral threshold for acetaminophen ingestion among US poison centers ranges from 120 mg/kg to 201 mg/kg of acetaminophen (6). A guideline that effectively determines the need for referral could optimize patient outcome, reduce costs, and reduce disruption for patients and caregivers.

Background

Definitions

The term out-of-hospital is defined as the period before a patient reaches a healthcare facility. An acute ingestion is defined as any number of ingestions that occur within a period of up to 8 hours. In recent years, the phenomenon of "chronic" acetaminophen toxicity has been described (7,8). Repeated supratherapeutic ingestion (RSTI) involves any pattern of multiple ingestions over a period of greater than 24 hours that results in a total dosage of more than 4 g per day.

Pathophysiology of Acetaminophen Toxicity

Acetaminophen is rapidly and completely absorbed after oral administration. It exhibits a large first-pass effect with uptake and metabolism in the liver. The toxicity of acetaminophen is related to the production of the reactive intermediate N-acetyl-p-benzoquinonimine (NAPQI) by the hepatic cytochrome P450 system. When the production of NAPQI exceeds the capacity to detoxify it, as can occur in overdose, the excess NAPQI binds to cellular components and can cause the death of hepatocytes. While more than one cytochrome is capable of producing NAPQI, the primary source in humans is cytochrome P450 isozyme 2E1 (CYP2E1) (9,10). CYP2E1 is an inducible enzyme. Chemicals that bind to CYP2E1 may increase (induce) or decrease (inhibit) the production of NAPQI.

It is well established that the time between ingestion of acetaminophen and administration of acetylcysteine affects the outcome of acetaminophen poisoning. While the precise threshold is unknown, a delay of more than 8–10 hours results in higher serum aminotransferase levels (11,12).

Intended Users of This Guideline

The intended users of this guideline are personnel in US poison centers. This guideline has been developed for the conditions prevalent in the US. While the toxicity of acetaminophen is not expected to vary in a clinically significant manner in other nations, the out-of-hospital conditions could be much different. This guideline should not be extrapolated to other settings unless it has been determined that the conditions assumed in this guideline are present.

Objective of This Guideline

The objective of this guideline is to assist poison center personnel in the appropriate out-of-hospital triage and initial management of patients with suspected ingestions of acetaminophen by 1) describing the process by which an ingestion of acetaminophen might be managed, 2) identifying the key decision elements, 3) providing clear and practical recommendations that reflect the current state of knowledge, and 4) identifying needs for research. This guideline applies to ingestion of acetaminophen alone. Co-ingestion of additional substances could require different referral and management recommendations, depending on the combined toxicities of the substances.

This guideline is based on an assessment of current scientific and clinical information. The expert consensus panel recognizes that specific patient care decisions may be at variance with this guideline and are the prerogative of the patient and health professionals providing care, considering all of the circumstances involved. This guideline does not substitute for clinical judgment.

METHODOLOGY

The methodology used for the preparation of this guideline was developed after reviewing the list of key elements of guidelines described by Shaneyfelt et al. (13). An expert consensus panel was established to oversee the guideline development process (Appendix 1). The American Association of Poison Control Centers (AAPCC), the American Academy of

Clinical Toxicology (AACT), and the American College of Medical Toxicology (ACMT) appointed members of their organizations to serve as panel members. To serve on the expert consensus panel, an individual had to have an exceptional record of accomplishment in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant US poison center experience, and be an opinion leader with broad esteem. Two Specialists in Poison Information were included as full panel members to provide the viewpoint of the end-users of the guideline.

Literature Search

The National Library of Medicine's MEDLINE database was searched (1966 to January 2003) using acetaminophen as a MeSH term with the subheadings poisoning (po) or toxicity (to), limited to humans. MEDLINE and PreMEDLINE (1966–January 2003) were searched using acetaminophen or paracetamol as textwords (title, abstract, MeSH term, CAS registry) plus either poison* or overdos*, limited to humans. This same process was repeated in International Pharmaceutical Abstracts (1970–January 2003, excluding abstracts of meeting presentations), Science Citation Index (1977–January 2003), Database of Abstracts of Reviews of Effects (accessed January 2003), Cochrane Database of Systematic Reviews (accessed January 2003), and Cochrane Central Register of Controlled Trials (accessed January 2003). A similar search was conducted in EMBASE using both acetaminophen and paracetamol as primary search terms. Index Medicus was hand-searched (1960–1965) using the term "analgesics and antipyretics" through 1964 and "acetaminophen" for 1965. Reactions (1980–January 2003), the acetaminophen poisoning management in POISINDEX (14), the Cochrane systematic review of interventions for acetaminophen overdoses (15), and the chapter bibliographies in four major toxicology textbooks (17–19) were reviewed for citations of additional articles with original human data. The bibliographies of recovered articles were reviewed to identify previously undiscovered articles.

Article Selection

The recovered citations were entered into an EndNote library and duplicate entries were eliminated. The abstracts of these articles were reviewed, looking specifically for those that dealt with 1) estimations of mg/kg or ingested doses with or without subsequent signs or symptoms, and 2) management techniques that might be suitable for out-of-hospital use (e.g., gastrointestinal decontamination). The panel agreed that acetylcysteine therapy could be considered for initiation in the prehospital setting. Articles excluded were those that did not meet either of the preceding criteria, did not add new data (e.g., some reviews and editorials), described inpatient-only procedures (e.g., dialysis), or described treatments that were unlikely to be used (e.g., methionine).

Data Extraction

All articles that were retrieved from the search were reviewed by a single abstractor. Each article was assigned a level of evidence score from 1 to 6 using the rating scheme developed by the Centre for Evidence-Based Medicine at Oxford University (Appendix 2); the complete paper was then reviewed for original human data regarding the toxic effects of acetaminophen or original human data directly relevant to the out-of-hospital management of patients with acetaminophen overdose. Articles without original human data were not evaluated. Doses of acetaminophen, resultant effects, times of onset of effects, therapeutic interventions or decontamination measures given, efficacy or results of any interventions, and overall patient outcomes were compiled into a table and a brief summary description of each article was written. The completed table of all abstracted articles was then forwarded to the guideline primary author and panel members for review and consideration in developing the guideline. This full evidence table is available at http://www.aapcc.org/discguidelines/guidelines%20tables/apap%20evidence%20table.pdf. Every attempt was made to locate significant foreign language articles and have their crucial information extracted, translated, and tabulated. In addition to the evidence table, several brief sub-tables were generated that included all of the articles and data relating to a particular topic (e.g., dose of acetaminophen in acute pediatric ingestions reported to cause toxicity). These were also forwarded to the primary author and guideline panel members. Finally, a written summary of the data was created and distributed by the abstractor. Copies of all of the articles were made available for reading by the panel members on a secure AAPCC website.

Guideline Writing and Review

A guideline draft was prepared by the primary author. The draft was submitted to the expert consensus panel for comment. Using a modified Delphi process, comments from the expert consensus panel members were collected, copied into a table of comments, and submitted to the primary author for response. The primary author responded to each comment in the table and, when appropriate, the guideline draft was modified to incorporate changes suggested by the panel. The revised guideline draft was again reviewed by the panel and, if there was no strong objection by any panelist to any of the changes made by the primary author, the draft was prepared for the external review process. External review of the second draft was conducted by distributing it electronically to AAPCC, AACT, and ACMT members and the secondary review panel. The secondary review panel consisted of representatives from the federal government, public health, emergency services, pediatrics, pharmacy practice, and consumer organizations (Appendix 3). Comments were submitted via a discussion thread on the AAPCC website or privately through e-mail communication to AAPCC staff. All submitted

comments were stripped of any information that would identify their sources, copied into a table of comments, and reviewed by the expert consensus panel and the primary author. The primary author responded to each comment in the table and his responses and subsequent changes in the guideline were reviewed and accepted by the panel. Following a meeting of the expert consensus panel, the final revision of the guideline was prepared.

KEY DECISION ELEMENTS

The panel identified patient age and intent as well as the estimated dose and timing of ingestion as critical elements needed to evaluate an ingestion of acetaminophen. This process has not been experimentally evaluated in published studies. However, there are well-known practice patterns ascribed to by essentially all US poison centers. For example, all poison centers obtain a defined information data set from each caller. The standard poison center process includes ascertainment of the history, assessment of this historical information in the context of the patient's exposure, estimation of the dose ingested, and recommendation for referral and initial out-of-hospital management.

REVIEW OF THE MEDICAL LITERATURE

Patient Age and Intent

A potentially toxic ingestion of acetaminophen may occur in an adult or a child. There are fundamental differences between patients below the age of 6 years and patients who are 6 years of age or older. Young patients are often discovered during or soon after ingestion. Older patients are more likely to attempt self-harm and to conceal the attempt. Most deaths from acetaminophen poisoning occur in adults with acute overdoses. In contrast, nearly all deaths attributed to acetaminophen reported in the medical literature regarding children under the age of 6 years have involved RSTI overdosage. There were no articles identified that directly addressed the relationship between patient age and intent (i.e., unintentional vs. intentional ingestion). The Toxic Exposure Surveillance System of the American Association of Poison Control Centers lists 14 deaths in children under the age of 6 years in the period 1990–2003. One of these deaths involved an acute exposure to acetaminophen but the child had also ingested diphenhydramine and iron (20).

Published evidence suggests that preschool children are less susceptible to the same weight-adjusted doses and serum concentrations of acetaminophen that are associated with severe toxicity in older patients (21,22). This may be due to an increased capacity to metabolize acetaminophen through nontoxic mechanisms (23). Furthermore, the liver size of a small child is larger in proportion to body weight than that of an adult (24). The amount of glutathione available to detoxify the acetaminophen metabolite may be disproportionately greater in small children; therefore, the capacity of a young child to metabolize acetaminophen in a nontoxic manner may be greater than that of an adult.

Dose and Pattern of Acetaminophen Ingestion

The evidence regarding the relationship between acetaminophen dose and toxicity is limited primarily to case reports and case series (level 4) and to cohort or case-control studies (levels 2 and 3, respectively). Studies reviewed for this guideline were categorized by age (less than 6 years of age or 6 years of age and older) and by pattern (acute ingestion, repeated ingestion). In most cases, toxicity actually meant the potential for toxicity as predicted by the Rumack-Matthew nomogram. In some articles, information on pediatric overdoses was commingled with information on adult overdoses, making information on the two groups impossible to separate. Furthermore, some articles defined pediatric patients as less than 17 years of age while others defined them as less than 7 or 12 years of age. A survey of US poison center managers found that the dose threshold triggering referral to a healthcare facility varied greatly. Triage threshold values ranged from 120 to 201 mg/kg for acute, unintentional ingestions of acetaminophen. Centers using relatively low thresholds (e.g., 150 mg/kg) referred patients to hospitals more frequently than centers using higher thresholds (e.g., 200 mg/kg) (6).

Acute Single Ingestions by Patients 6 Years of Age and Older

No randomized clinical trials involving the out-of-hospital treatment of intentional acetaminophen overdose have been reported. Several randomized controlled trials (level 1b) have reported the administration of an acute single supratherapeutic dose of acetaminophen. Doses in these studies have ranged from 4 to 7.8 g (up to 75–80 mg/kg). Serum aminotransferase levels were not reported in these studies, but all of the patients survived and none was noted to develop clinical signs of hepatotoxicity (25–30). The applicability of these studies to acetaminophen overdose is limited by the small number of subjects, the use of healthy subjects, and the lack of laboratory investigations to assess subclinical hepatic toxicity.

Only observational studies were found relating the estimated dose of acetaminophen to liver injury or potential toxicity as represented by the Rumack-Matthew nomogram. A number of case reports and case series (level 4), and various cohort or case-control studies (levels 2b and 3b) containing specific information on ingested doses and patient outcome have reported acetaminophen levels above the possible toxicity line (31–33). The smallest reported doses associated with evidence of hepatic injury have ranged from 3.25 to 10 g (2,34–46). A cohort analysis (level 2b) described several patients in whom acute doses of less than 12 g were associated with hepatotoxicity, but the exact doses were not specified (47). This same study reported deaths in patients with reported

doses as low as 15 g. In contrast, some reports have described large single ingestions with documented serum concentrations of acetaminophen above the possible or probable toxicity nomogram lines that did not result in toxicity (48).

The conflicting reports of hepatic injury following doses at or just above the therapeutic dose are likely explained by the nature of the evidence. Studies (levels 2b and 4) have documented that there is poor correlation between the reported dose and either subsequent acetaminophen serum concentration or clinical outcome (31,42,43,49–53). The correlation between reported dose and subsequent serum concentration or toxicity for children with unintentional ingestion is also poor (53–55).

The history of ingestion might be inaccurate because it is often obtained during a period of extreme emotional stress for both the patient and their family. Furthermore, there are often confounding factors such as co-ingestion of ethanol or other drugs that affect the central nervous system. In most reports available, the accuracy of the history was not addressed and the history was not confirmed by outside sources (e.g., family members) or objective evidence (e.g., empty product containers). Fortunately, accurate dose information is usually not needed for patients 6 years of age or older because treatment is guided by the serum acetaminophen concentration.

Repeated Supratherapeutic Ingestion (RSTI) by Patients 6 Years of Age and Older

The maximum daily dosage of acetaminophen recommended by a major manufacturer is 1 g every 4 hours, not to exceed 4 g a day for patients 12 years of age or older (56). Four randomized clinical trials (level 1b) were found that involved multiple ingestions of acetaminophen over a period of more than 1 day. Gelotte et al. (57) administered 4, 6, or 8 g/day in divided doses to adults for 3 days. These doses were not associated with accumulation of acetaminophen, changes in serum aminotransferase levels, or effects on other monitoring parameters. The application of this study in clinical practice is limited by its use of normal subjects and the controlled environment of a clinical research center. Other prospective studies administered 4–6 g/day to patients without adverse clinical effect, including patients with acute stroke and head and neck cancer (58–61). Level 4 reports describe ingestion of over 20 g/day for years (62) and ingestion of 25 g over 25 hours (63) without adverse effects.

The interpretation of the medical literature of repeated acetaminophen doses is complicated by the effects of conditions that are thought to lower the threshold for toxicity. These are generally categorized as either conditions that increase the production of the reactive metabolite NAPQI or that decrease the ability to detoxify NAPQI (e.g., decreased concentration of glutathione). Authors report that low daily doses of acetaminophen, ranging from minimal daily doses of 2.4–6 g in alcoholics, patients with starvation, or those on chronic antituberculous medications have been associated with elevated aminotransferase levels (40,64–66). Case reports (level 4), case series (level 4), and cohort (level 2b) or case-control (level 3b) studies have reported either greater severity of injury or a lower threshold dose for the development of hepatotoxicity after acetaminophen ingestion by patients chronically ingesting alcohol or other compounds thought to increase susceptibility to acetaminophen toxicity (e.g., isoniazid use, prolonged fasting) (2,34,36–38,40,41,46,50,65,67–72). Evidence (level 4) indicating that a patient's alcoholic state does not contribute to outcome has also been reported (12,42).

Each of these reports uses the theoretical framework of enhanced production of NAPQI and the reduction of defenses as represented by glutathione. Chronic ethanol abuse is a useful condition to study because of its prevalence and because it involves both increased production of NAPQI and reduction of glutathione (73). The primary inducers of CYP2E1 with medical relevance are ethanol, acetone, and isoniazid. It is important to understand that drugs that induce CYP2E1 must bind to the enzyme and thereby are competitive inhibitors of the enzyme. Thus, when both ethanol and acetaminophen are ingested concurrently, the metabolism by CYP2E1 and hepatotoxicity of acetaminophen are decreased (10). When ethanol is subsequently eliminated, however, the induced enzyme remains and metabolism of acetaminophen is increased for several hours (10). Therefore, concurrent ingestion of acetaminophen and ethanol is not expected to enhance injury from acetaminophen. However, acetaminophen ingestion (especially in overdose) soon after elimination of ethanol can theoretically potentiate the effect of acetaminophen overdosage.

While animal and human data support the concept that induction of CYP2E1 occurs during the use of ethanol, the clinical meaning of this effect remains unclear. For example, level 1b data indicate that the effect of ethanol is not clinically apparent at a therapeutic acetaminophen dosage. The administration of acetaminophen 4 g/day for 2 days to confirmed alcoholic patients under controlled conditions did not produce increases in serum aminotransferase levels or alterations of international normalized ratios (74). Similarly, the administration of the maximum dosage to patients with liver disease (hepatitis, cirrhosis) was also found to not affect serum aminotransferase levels (75).

A systematic review (level 1a) of publications involving alcohol and acetaminophen has documented a contrast between prospective studies and case reports. All prospective articles failed to find liver injury at therapeutic doses. In contrast, many case reports and small case series found an association of liver injury in alcoholic patients with dosages of 4 g/day or less (76). There are no data that address the issue of CYP2E1 on RSTI acetaminophen. If alcohol or other disease states enhance the toxicity of acetaminophen, the dosage at which the phenomenon develops is unknown.

Patients with acute co-ingestion of acetaminophen with alcohol or gastrointestinal antimotility agents and patients taking cimetidine chronically have been reported to be at decreased

risk of liver injury (levels 2b and 4) (31,47,50,53,77,78). Other authors have found no correlation between acute alcohol consumption and severity of toxicity (level 2b) (46). Schmidt et al. (47) reported that acute ingestion of benzodiazepines exacerbated hepatic encephalopathy after acute acetaminophen overdose but that acute use of opiates was protective against hepatotoxicity (level 2b). Schmidt et al. also reported that chronic use of opioids, benzodiazepines, and acetaminophen increased the risks of various negative outcomes after acute acetaminophen overdoses. The meaning of the conflicting results of these studies is unclear. It is likely that most differences reported are the result of an unrecognized confounder or systematic error. For example, the history of RSTI is typically taken after days of ingestion. Often the period of ingestion has included events known to impair memory such alcohol intoxication or co-ingestion of psychoactive drugs as well as difficulties imposed by an underlying illness (fever, sleep deprivation, etc.). While these results may stimulate future studies, they are too uncertain to apply to a clinical guideline.

Acute Single Ingestions by Patients Less than 6 Years of Age

No randomized clinical trials were found evaluating the acute threshold dose for the development of clinical acetaminophen toxicity (i.e., laboratory evidence of liver injury) or even potential toxicity as determined by the Rumack-Matthew nomogram in children of any age. Several observational studies investigated the potential safety and efficacy of various poison center protocols in the management of acute, accidental pediatric (less than 6 or 7 years of age) ingestions of acetaminophen (6,55,68,79,80). Most articles (levels 2b, 3b, and 4) suggest that patients with ingestions of less than 200 mg/kg could be managed at home, provided that the acetaminophen dose is known. One level 4 study created a model to predict serum concentrations after ingestion of acetaminophen (81). The authors concluded that a referral dose of 250 mg/kg was appropriate for children. This study did not include any children with serum acetaminophen concentrations above the “probable toxicity” line of the Rumack-Matthew nomogram. However, it is likely that all of these studies had insufficient power to detect the rare event of toxicity after a single dose of acetaminophen in a child under the age of 6 years. Very few cases of toxicity after acute single ingestion by a child under the age of 6 years were found in the medical literature and in the AAPCC TESS database (20). If this type of toxicity occurs, it is rare.

In contrast, case reports and case series (level 4) and various cohort (level 2b) or case-control studies (level 3b) containing information on specific ingested doses and patient outcome have reported potential toxicity or actual toxicity in children less than 6 years old with single doses thought to be in the range of 146 to 190 mg/kg (82,83).

Acute single ingestion resulting in toxicity has been reported more commonly in adolescents. The lowest dose resulting in liver injury involved a 13-year-old of unknown weight who died of hepatic failure after reportedly ingesting 2.5 g of acetaminophen (84). A 14-year-old girl developed an INR of 1.6 after an acute ingestion of 4 g acetaminophen; however, she had also received an excessive dose of acetylcysteine (40 g) intravenously prior to the measurement (85). As for adults, the few cases of toxicity associated with low doses stand in contrast to the numerous cases in which toxicity was not observed until acute doses exceed 150 mg/kg/day (48). The most likely explanation is historical inaccuracy as described above under adult overdose.

Repeated Supratherapeutic Ingestion (RSTI) by Patients Less than 6 Years of Age

No randomized clinical trials could be found that evaluated the minimum cumulative daily dose for the development of laboratory evidence of liver injury after pediatric RSTI (69, 86–90). The dosages of acetaminophen associated with elevation of aminotransferase levels in case reports (level 4), case series (level 4), and cohort analyses (level 2b) have ranged from the normal therapeutic dosage (20 mg/kg/day) to 600 mg/kg/day or more (90). Most reports indicate that dosages of 120 to 174 mg/kg/day for multiple days are needed to produce toxicity (69,82,87).

Two case series (level 4) reported toxicity associated with histories of smaller ingestions. One report identified 47 children below the age of 12 years with hepatotoxicity after acetaminophen RSTI. Toxicity developed after reported daily doses of 60–420 mg/kg/day for 1–21 days (89). A retrospective review of a liver transplant service identified four children who developed severe hepatic injury after doses of 20–71 mg/kg/day for 7 days (90). Another case series recorded doses ranging from 23 to 100 mg/kg day associated with liver injury in children (91). Perhaps due to inaccurate histories provided by patients, the data presented contain many inconsistencies. For example, the highest serum acetaminophen concentration reported among children with presumed acetaminophen toxicity was 14 mg/L after dosages ranging from 20 to 200 mg/kg/day.

In contrast, prospective and retrospective studies in children have used acetaminophen dosages up to and exceeding 90 mg/kg/day without liver injury. Lesko and Mitchell (92) found no clinical evidence of toxicity in a prospective study of 28,130 children administered up to 60 mg/kg/day (level 1b). Further, both level 1b and level 4 studies have documented the use of dosage above 90 mg/kg/day without adverse effect (93–96). Thus, the data for pediatric RSTI are conflicting and with a pattern similar to reports involving acute overdose—prospectively collected data are sparse and do not indicate potential for hepatic injury, while retrospectively collected data provide evidence of an association of relatively low dosages, even therapeutic dosages, with liver injury. Again, the cause is likely to be historical inaccuracies. Overdoses in children are subject to the same concerns as in adults but also present their own unique set of concerns as parents may over- or underestimate the actual ingested dose depending on the circumstances.

Potential Out-of-Hospital Management Techniques to Prevent or Ameliorate Acetaminophen Toxicity After Ingestion

The consensus panel identified these potential strategies for reducing acetaminophen absorption in the out-of-hospital setting: 1) reducing absorption, 2) inhibiting metabolism, or 3) detoxifying the reactive intermediate metabolite, NAPQI. Absorption can be decreased by gastrointestinal decontamination, metabolism can be inhibited by drugs such as cimetidine, and detoxification can be accomplished by the administration of acetylcysteine. The risk-benefit analysis of these techniques is difficult. The primary difficulty is that the treatment of acetaminophen toxicity with acetylcysteine is usually successful when acetylcysteine is initiated within 8–10 hours of acute ingestion (11,12). Thus, it is difficult to show an improvement in patient outcome for any out-of-hospital intervention because the administration of acetylcysteine reduces the potential benefit of the intervention to near zero. However, potential benefit could be realized in situations where acetylcysteine is not available.

There were data available in the literature for each type of intervention; however, there were no studies found that specifically addressed the out-of-hospital administration of various antidotes or treatments.

Gastrointestinal Decontamination

The potential strategies for reducing absorption after acetaminophen ingestion that could be reasonably be performed in an out-of-hospital setting include emesis with ipecac syrup or administration of activated charcoal. Only those articles that contained specific information about these measures as well as some description of their outcomes have been included.

All reports in the medical literature combined out-of-hospital and in-hospital interventions in the setting of acute ingestion. There were no articles specifically investigating the out-of-hospital use of induced emesis or activated charcoal. There were also no articles addressing the effectiveness of decontamination measures for an RSTI pattern of ingestion. Since studies of RSTI demonstrate that liver injury develops after more than 1 day of ingestion, these patients probably present for care too late for decontamination to be effective.

Two level-1 articles examined decontamination measures after acute overdose. The remaining decontamination data are limited to randomized controlled trials (level 1b) of simulated overdose in healthy volunteers given a single subtoxic, but supratherapeutic, dose of acetaminophen, and observational studies such as cohort (level 2b) or case-control (level 3b) analyses of patients who had ingested single overdoses.

A systematic review (level 1a) concluded that activated charcoal, gastric lavage, and ipecac-induced emesis are able to reduce the absorption of acetaminophen, but also concluded that their clinical benefit is unclear (15). One randomized controlled trial (level 1b) of overdose patients examined the efficacy of different decontamination procedures (ipecac-induced emesis, activated charcoal, lavage, or untreated control). However, the primary outcome measure was percent reduction of the serial serum acetaminophen concentration (first concentration compared with last), which might not be an adequate outcome indicator (97). The study found that the three decontamination methods reduced acetaminophen serum concentrations by 39–51%.

Two randomized controlled trials (level 1b) were identified that examined the efficacy of ipecac-induced emesis in simulated overdose. In one study, ipecac syrup given within 5 minutes of ingestion was effective at reducing overall acetaminophen absorption by 66%, as measured by the area under the curve (AUC) but was not effective when administered at 30 or 60 minutes after ingestion (98). In the second study, ipecac syrup given 1 hour after simulated overdose was effective at reducing the acetaminophen AUC compared with control by about 25% and its efficacy was comparable to activated charcoal (99).

Several cohort analyses (level 2b) based on retrospective reviews evaluated the efficacy of ipecac syrup after acetaminophen overdose. One found a decrease in the likelihood of developing severe hepatotoxicity or death in the cohort of patients who had emesis or gastric lavage within 6 hours of ingestion (100). The two other studies focused on children. One found that ipecac-induced emesis within 60 minutes reduced the mean 4-hour serum acetaminophen concentration by 77% based on a comparison with 4-hour concentrations predicted by a pharmacokinetic model. After 60 minutes, the mean reduction of the 4-hour concentration was about 40% (101). The second pediatric cohort investigation found that 4-hour acetaminophen concentrations were reduced by about 50%, compared with untreated controls when emesis occurred within 90 minutes of the ingestion (79).

One case-control study (level 3b) of patients with acute acetaminophen overdose found that the group that developed hepatic injury was less likely to have undergone gastric emptying by lavage or induced emesis than the group that did not develop hepatic injury; however, the difference was not statistically significant (33).

Six randomized controlled trials (level 1b) have investigated the efficacy of activated charcoal in reducing acetaminophen absorption in healthy volunteers receiving supratherapeutic, but nontoxic, doses of acetaminophen. In these studies, activated charcoal (50–60 g) reduced the serum acetaminophen AUC by 25–67% if given at 1 hour after ingestion (102–105). Another study found that activated charcoal (1 g/kg) mixed with soda and given 15 minutes after simulated overdose reduced acetaminophen absorption by 74% (30). The efficacy of activated charcoal decreased when it was administered more than 1 hour after ingestion in most studies and one study found no benefit in AUC or 4-hour serum concentration when activated charcoal was given 2–4 hours after simulated overdose (29,103). One study reported a reduction in AUC of 23% compared with control when activated charcoal was given 2 hours after ingestion (104).

Two nonrandomized but controlled studies (level 2b) using simulated overdose were identified. One found a decrease in AUC (about 60%) with immediate administration of activated charcoal, but the difference was smaller and not statistically significant when activated charcoal was given at 1 hour after ingestion (106). The other study found an AUC reduction of about 50% with both immediate and 30-minute activated charcoal administration (107).

One prospective cohort (level 2b) study of activated charcoal in adult acetaminophen overdoses found that patients who received activated charcoal plus acetylcysteine within 8 hours of their overdoses were significantly less likely to develop liver injury or hepatotoxicity when compared with those receiving acetylcysteine alone within 8 hours (108). Another cohort study (level 2b) in overdose patients found that the group that received activated charcoal within 2 hours had fewer patients who subsequently developed 4-hour serum acetaminophen concentrations in the possible or probable toxicity range compared with the group that did not receive activated charcoal. The benefit decreased after 2 hours (109).

Two studies directly compared ipecac-induced emesis to activated charcoal. One randomized controlled (level 1b) study in simulated overdose patients found no difference between the two in efficacy as measured by reduction in AUC (99). A randomized trial (level 1b) in simulated overdose patients found a slightly more rapid decline in acetaminophen serum concentrations with activated charcoal compared to ipecac-induced emesis (97). Another level-1b study looked at the difference between activated charcoal with sorbitol and activated charcoal without sorbitol but found no significant difference in efficacy as measured by AUC (102).

Two studies found activated charcoal to be ineffective in reducing acetaminophen absorption. One was a simulated overdose trial in volunteers (level 2b) that found no difference in AUC between controls and those receiving 25 g of activated charcoal 15 minutes after ingestion (110). A retrospective cohort (level 2b) study in children with actual overdoses found no difference in 4-hour serum acetaminophen concentrations between the activated charcoal and no decontamination cohorts (54).

Two articles (level 2b and level 4) reported on the use of general gastric decontamination measures but did not specify the specific method investigated (51,55).

Studies indicate that the use of decontamination measures have the potential to interfere with the effectiveness of acetylcysteine. For example, ipecac syrup induces vomiting that can interfere with the administration of oral acetylcysteine. Activated charcoal binds acetylcysteine (111) and reduces its bioavailability (112), although the clinical importance of these findings is unknown (113).

Body Position

One randomized, controlled trial (level 1b) of simulated overdose found that the acetaminophen AUC was significantly less with left lateral decubitus and supine positions compared to prone, sitting, or right lateral decubitus (26).

Limitations of Published Decontamination Data

Simulated overdose studies in volunteers might be a poor representation of what occurs in real acetaminophen overdoses, in which larger doses are ingested, patients are not fasting, and co-ingestants that affect gastrointestinal motility might be involved. Volunteer studies might underestimate the efficacy of decontamination if gastric emptying is delayed in overdoses or they might overestimate efficacy if the decontamination measures become less effective with massive acetaminophen doses (by stoichiometry), tablet bezoar formation, or because of activated charcoal binding to food or other co-ingestants rather than acetaminophen.

There are also challenges in the interpretation of cohort and case-control studies. There could be other differences between the cases and controls other than the variable being tested (e.g., ingested doses, times to treatment might differ, and use of acetylcysteine might differ). They also tend to rely on retrospective data-gathering, a process that produces its own unique disadvantages (e.g., decisions on treatment could have been based on some piece of history that was not recorded or recorded inaccurately in the medical record).

Inhibition of Acetaminophen Metabolism

Cimetidine has been proposed as an antidote for acetaminophen poisoning (78,114–116). It has the advantage of being available as an over-the-counter (OTC) medication. One prospective (level 1b) trial in overdose patients presenting more than 8 hours after ingestion found no added benefit (as measured by liver function tests) from cimetidine when it was added to acetylcysteine treatment (116). One nonrandomized, controlled trial in healthy adults with simulated overdoses found that cimetidine, given orally for 2 days prior to acetaminophen, decreased the overall clearance of acetaminophen, implying some benefit to its administration in overdoses (78). Three case reports (level 4) of its use had inconclusive outcomes (70,115,117).

Detoxification of Acetaminophen Metabolite (NAPQI)

The pharmaceutical formulation of acetylcysteine (but not the OTC tablet formulation) has been tested and found to reduce or prevent liver injury following acetaminophen ingestion (17,118). There were no randomized controlled (level 1b) trials evaluating the efficacy of acetylcysteine in the out-of-hospital setting. Many observational studies reported the use of acetylcysteine in the out-of-hospital setting but did not explicitly give information on its effectiveness and so they are not specifically addressed here (3,44,51,53,54,67,72,119,120). In addition, multiple case reports and case series (level 4) were reported in which the efficacy of acetylcysteine could not be assessed.

Retrospective cohort (level 2b), prospective cohort (level 2b), and case-control (level 3b) analyses have reported that acetylcysteine, either in its usual oral or intravenous dosage, or as an unspecified dosage or route of administration, is effective at reducing mortality or at reducing the subsequent incidence and severity of liver injury after acetaminophen overdose (2,12,33,38,42,43,46,50,52,82,83,108,121).

The degree of acetylcysteine efficacy also appears to depend on the time after overdose at which it is given. Read et al. (50) found that patients with serum acetaminophen concentrations above the treatment line receiving acetylcysteine within 16 hours (dose and route not specified) had a survival rate of 94% (18 of 19) compared to 0% (none of seven) in an untreated cohort (level 2b). Prescott et al. reported that intravenous infusion of acetylcysteine more than 10 hours after acetaminophen ingestion in 15 patients was associated with more severe liver damage than was associated with earlier administration (level 4) (16,122). Smilkstein et al. (17) found that the 72-hour oral acetylcysteine regimen was most effective if given within 8 hours of ingestion. It was still effective, albeit less so, if administered up to 24 hours after ingestion (level 4). Bray et al. (123) reported that survival in a cohort treated with acetylcysteine within 24 hours of ingestion was 65% vs. 38% for an untreated cohort (level 2b). In another level-2b study, Bray et al. (38) noted that survival was 67% in patients treated within 8–12 hours compared to 7% in untreated controls. In a level-2b study, Makin et al. (42) showed that survival was better in patients treated with intravenous acetylcysteine within 24 hours (80%) and that patients treated after 24 hours were still more likely (78%) to survive than untreated controls (48%).

Other studies have supported the concept that an increase in the interval between acetaminophen ingestion and acetylcysteine administration is associated with a higher rate of liver injury (2,33,46,52,82,83,121). In a large cohort analysis (level 2b), Schmidt et al. (47) found that mortality after acute acetaminophen overdose depended on time to acetylcysteine treatment, with mortality rates for the 0–12, 12–24, 24–48, and more than 48 hour groups of 0.4%, 6%, 13%, and 19%, respectively. One study (level 2b) found no difference in survival between small treated and untreated cohorts (43).

Few studies have examined the efficacy of acetylcysteine in patients with RSTI. Makin et al. (42) included 45 patients with RSTI; however, the study did not specifically address the efficacy of acetylcysteine in this subgroup (level 2b). Several case reports (level 4) of its use in patients with RSTI were located, but no assessment of benefit from acetylcysteine could be gleaned from them (63,64,86–88,124). No studies were found that directly compared different routes or dosages of acetylcysteine. Spiller et al. (108) found that activated charcoal did not interfere with acetylcysteine efficacy as measured by liver function abnormalities (level 2b).

The acetylcysteine data suffer from the same limits as cohort and case-control studies for decontamination. However, the volume of information available about acetylcysteine and the loss of efficacy as time to administration increases indicate that acetylcysteine is effective.

Role of Different Acetaminophen Formulations

Acetaminophen is available in extended-release formulations that contain more acetaminophen (650 mg/tablet), are released over a longer period than the usual “extra strength” formulations, and are intended for use three times per day. Case reports and case series (level 4) indicate that a patient’s serum acetaminophen concentration might cross the Rumack-Matthew nomogram lines at times much later than anticipated.

Six articles addressing extended-release acetaminophen overdose were identified (27,28,125–128). Two studies were randomized, controlled (level 1b) pharmacokinetic comparisons with regular extra-strength acetaminophen in healthy volunteers taking simulated overdoses. In one study, both the peak serum acetaminophen concentration and the AUC were significantly lower for extended-release formulation compared with similar doses of the extra-strength formulation. Time-to-peak concentration was not significantly longer (27). In the second study, peak acetaminophen concentrations were significantly lower for the extended-release product, but AUC and time to peak were not different from the typical extra-strength product (28).

The other articles were case reports or case series (level 4) of overdoses with extended-release acetaminophen in which several patients were noted to have serum acetaminophen concentrations that crossed the nomogram line despite initially nontoxic serum concentrations (126–128). Hepatotoxicity developed in one patient who ingested a handful of extended-release acetaminophen and did not present to an emergency department until 19 hours after the ingestion where she was treated with acetylcysteine (125).

Acetaminophen is also available in a formulation containing diphenhydramine. In overdose, diphenhydramine could theoretically decrease gastrointestinal motility and slow absorption of acetaminophen. One case report (level 4) described a patient who had acutely ingested 46 g of acetaminophen plus 2.3 g diphenhydramine and developed a serum acetaminophen concentration that crossed the nomogram line for possible toxicity at 10.5 hours despite earlier measurements that were below the line (129). The patient developed mild liver function abnormalities.

Although unusual, some exposures to acetaminophen occur by rectal suppositories. The panel concluded that the out-of-hospital management of patients with rectal exposure should be assessed in the same manner as those who have ingested acetaminophen.

Poison Center Referral of Patients to Healthcare Facilities

The acetaminophen nomogram is used by plotting a serum acetaminophen concentration at the time after ingestion that it was drawn. The blood sample should be drawn at 4 hours after ingestion or as soon as possible thereafter. For many children,

the ingestions are discovered soon after they occur, raising the issue of when patients should be referred to healthcare facilities for further evaluation. If patients are referred immediately, they could arrive more than 3 hours before their blood sample is to be drawn. This could allow for the administration of a decontamination method such as ipecac syrup or activated charcoal, but could also produce long waiting times and consume emergency department resources.

Time of Referral

The data in human volunteers indicate that ipecac-induced emesis and activated charcoal are both effective in reducing the serum concentration of acetaminophen (130). However, several factors discourage use of these treatments in children. First, the incidence of serious toxicity from the acute ingestion of acetaminophen by children is very low (3). Second, the effectiveness of either ipecac syrup or activated charcoal is reduced as time elapses (130). Finally, an effective antidote (acetylcysteine) is widely available. However, one study (level 2b) indicated that early activated charcoal administration might reduce the number of patients that require acetylcysteine treatment (109). The panel determined that if activated charcoal could be administered within 2 hours of a significant acetaminophen ingestion, it would be appropriate to do so.

The panel concluded that in the case of a single unintentional ingestion by a child without suspicious circumstances, the child should be referred to arrive in time to have a stat serum acetaminophen concentration determined at 4 hours after ingestion. Thus, the specialist in poison information will need to ascertain the travel time for the patient and the potential delay at the receiving facility.

Type of Healthcare Facility

There were no studies found that addressed the issue of the type of healthcare facility that would be suitable for managing an acetaminophen overdose. The panel concluded that patients should be referred to emergency departments that have the ability to measure serum concentrations of acetaminophen and either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in a timely manner.

Follow-Up

There were no studies that addressed the frequency or type of out-of-hospital follow-up for any type of ingestion.

CONCLUSIONS

Key Decision Elements

The panel identified the patient's age, intent, the pattern of ingestion, as well as the dose and formulation of the acetaminophen product ingested as critical information that would be needed in order to make a sound triage decision. In addition, specific information about conditions that might increase acetaminophen toxicity (alcoholism, isoniazid use, prolonged fasting) should be obtained.

Patient Age and Intent

All patients in whom suicidal or malicious intent (e.g., child abuse or neglect) is known or suspected should be referred to emergency departments for medical evaluation. Adults with definite unintentional ingestion or children less than 6 years of age in whom neither self-harm nor abuse are suspected can be considered for out-of-hospital management.

Dose and Pattern of Acetaminophen Ingestion

Acetaminophen may be ingested over a short period (acute ingestion) or a longer period (RSTI). Most adult patients with single acute ingestions of acetaminophen have attempted self-harm. Patients 6 years of age or older with demonstrated unintentional acetaminophen ingestion of at least 10 g or 200 mg/kg (whichever is lower) over a period of less than 8 hours warrant prompt medical evaluation in an emergency department. For patients under the age of 6 years, an acute single ingestion (ingestion period of less than 8 hours) of 200 mg/kg or more of acetaminophen warrants evaluation in an emergency department.

Liver toxicity following acetaminophen RSTI is likely to be related to both dose and duration of exposure. Therefore, concern for liver injury increases as the dosage increases and as the duration of ingestion exceeds 24 hours. For patients 6 years of age and older, the panel concluded that referral to an emergency department is warranted for those, who ingest at least 10 g or 200 mg/kg/day (whichever is less) over a single 24-hour period, or at least 6 g or 150 mg/kg/day (whichever is less) per 24-hour period for 48 hours or longer. For children less than 6 years of age, the following referral thresholds for repeated ingestion were created: 200 mg/kg or more over a period of 8–24 hours, 150 mg/kg or more per 24-hour period for the preceding 48 hours, and 100 mg/kg or more per 24-hour period for the preceding 72 hours or longer.

Although the data are uncertain, pregnant patients and those with histories of prolonged fasting, chronic ethanol ingestion, or chronic isoniazid ingestion should probably be evaluated if more than 4 g/day or 100 mg/kg/day (whichever is less) of acetaminophen are consumed, particularly if signs consistent with acetaminophen hepatotoxicity are present (e.g., repeated vomiting, marked anorexia, jaundice).

Potential Out-of-Hospital Management Techniques to Prevent or Ameliorate Acetaminophen Toxicity After Ingestion

Activated Charcoal

The consensus panel concluded that activated charcoal administration reduced acetaminophen absorption but the potential risks and overall benefits could not be determined.

Therefore, the use of decontamination cannot be routinely advocated. However, the panel recognized that the use of activated charcoal should be guided by the individual poison center's assessment of the circumstances, the local policies for prehospital care in their service area, and potential benefit-to-risk analysis in their service area. Exceptions should be made on a case-by-case basis. For example, activated charcoal administration could be appropriate for patients who might have ingested large doses of acetaminophen and who are located several hours from an emergency department.

Inhibition of Acetaminophen Metabolism

The panel concluded that the available literature indicates that cimetidine inhibits the metabolism of acetaminophen. However, the literature does not convincingly demonstrate that it improves outcome.

Detoxification of Acetaminophen Metabolite (NAPQI)

The panel agreed that acetylcysteine is an effective treatment for acetaminophen poisoning, but that there are no published data regarding the out-of-hospital use of acetylcysteine. The panel concluded that acetylcysteine therapy could potentially be initiated in the prehospital environment, especially in situations in which the emergency department is far away. The dietary supplement tablet form of acetylcysteine has not been tested as an antidote for acetaminophen toxicity and, therefore, only the pharmaceutical product should be used.

Role of Unusual Formulations of Acetaminophen

The panel concluded that knowledge of the extended-release nature of a product would not affect the out-of-hospital management of a patient. Concomitant ingestion of other substances should be investigated in all patients so that an additional poisoning does not go unrecognized.

Time of Emergency Department Referral

Patients in whom suicidal, homicidal, or abuse intent is suspected should be referred to an emergency department immediately regardless of the dose ingested or the time since ingestion. When the time of ingestion is known accurately and suicidal, homicidal, or abuse intent is not involved, the patient with acetaminophen ingestion alone should be instructed to arrive at the emergency department in time to have their stat serum acetaminophen concentration drawn at 4 hours after ingestion. Based on the available evidence, a serum acetaminophen concentration before 4 hours cannot be recommended.

Other Issues

The panel concluded that poison centers should follow local procedures for follow-up frequencies. The panel chose not to form conclusions on several issues due to the lack of information available. These included the mode of transportation to emergency departments, the effects of circadian rhythm on toxicity, the role of patient gender, and the body position for transport. The use of an acetaminophen serum concentration to determine the need for acetylcysteine therapy was not addressed by the panel because it is not applied in the out-of-hospital environment.

RECOMMENDATIONS

These recommendations are provided in chronological order of likely clinical use. The grade of recommendation is provided in parentheses.

1. The initial history obtained by the specialist in poison information should include the patient's age and intent (Grade B), the specific formulation and dose of acetaminophen, the ingestion pattern (single or multiple), duration of ingestion (Grade B), and concomitant medications that might have been ingested (Grade D).
2. Any patient with stated or suspected self-harm or who is the recipient of a potentially malicious administration of acetaminophen should be referred to an emergency department immediately regardless of the amount ingested. This referral should be guided by local poison center procedures (Grade D).
3. Activated charcoal can be considered if local poison center policies support its prehospital use, a toxic dose of acetaminophen has been taken, and fewer than 2 hours have elapsed since the ingestion (Grade A). Gastrointestinal decontamination could be particularly important if acetylcysteine cannot be administered within 8 hours of ingestion.

Acute, Single, Unintentional Ingestion of Acetaminophen

1. Any patient with signs consistent with acetaminophen poisoning (e.g., repeated vomiting, abdominal tenderness in the right upper quadrant or mental status changes) should be referred to an emergency department for evaluation (Grade D).
2. Patients less than 6 years of age should be referred to an emergency department if the estimated acute ingestion amount is unknown or is 200 mg/kg or more. Patients can be observed at home if the dose ingested is less than 200 mg/kg (Grade B).
3. Patients 6 years of age or older should be referred to an emergency department if they have ingested at least 10 g or 200 mg/kg (whichever is lower) or when the amount ingested is unknown (Grade D).
4. Patients referred to an emergency department should arrive in time to have a stat serum acetaminophen concentration determined at 4 hours after ingestion or as soon as possible thereafter. If the time of ingestion is

unknown, the patient should be referred to an emergency department immediately (Grade D).
5. If the initial contact with the poison center occurs more than 36 hours after the ingestion and the patient is well, the patient does not require further evaluation for acetaminophen toxicity (Grade D).

Repeated Supratherapeutic Ingestion of Acetaminophen (RSTI)

1. Patients under 6 years of age should be referred to an emergency department immediately if they have ingested:
   - 200 mg/kg or more over a single 24-hour period, or
   - 150 mg/kg or more per 24-hour period for the preceding 48 hours, or
   - 100 mg/kg or more per 24-hour period for the preceding 72 hours or longer (Grade C).
2. Patients 6 years of age or older should be referred to an emergency department if they have ingested:
   - at least 10 g or 200 mg/kg (whichever is less) over a single 24-hour period, or
   - at least 6 g or 150 mg/kg (whichever is less) per 24-hour period for the preceding 48 hours or longer.
3. In patients with conditions purported to increase susceptibility to acetaminophen toxicity (alcoholism, isoniazid use, prolonged fasting), the dose of acetaminophen considered as RSTI should be greater than 4 g or 100 mg/kg (whichever is less) per day (Grade D).
4. Gastrointestinal decontamination is not needed (Grade D).

Other Recommendations

1. The out-of-hospital management of extended-release acetaminophen or multi-drug combination products containing acetaminophen is the same as an ingestion of acetaminophen alone (Grade D). However, the effects of other drugs might require referral to an emergency department in accordance with the poison center's normal triage criteria.
2. The use of cimetidine as an antidote is not recommended (Grade A).
3. These recommendations are summarized in Appendices 4 and 5.

IMPLICATIONS FOR RESEARCH

The panel identified several topics for which additional research or analysis of existing data would be useful.

1. Further information is needed to determine the single or repeated dosages of acetaminophen that produce liver damage in children.
2. Further information regarding the effect of a child's age and the relation to intent is needed.
3. Further investigation is needed to determine whether any subgroup of adult or pediatric patients has increased susceptibility to acetaminophen. If this effect exists, it is crucial to determine the threshold dose for liver injury in these special populations.
4. Research is needed about out-of-hospital management of acetaminophen ingestions in pregnant patients.
5. The feasibility, effectiveness, and safety of the out-of-hospital use of acetylcysteine should be investigated (including the use of OTC products).
6. The feasibility, effectiveness, and safety of the out-of-hospital use of activated charcoal for acetaminophen poisoning should be investigated.
7. Although the phenomenon of RSTI is increasingly recognized, there is little information available concerning it. Research into its pathophysiology and management is needed.

DISCLOSURE

Dr. Dart is employed by Denver Health, which provides professional services to many pharmaceutical companies, including McNeil Consumer and Specialty Pharmaceuticals. There are no other potential conflicts of interest reported by the expert consensus panel or project staff regarding this guideline.

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APPENDIX 1

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APPENDIX 2

Grades of Recommendation and Levels of Evidence

Grade of Recommendation	Level of Evidence	Description of Study Design
A	1a	Systematic review (with homogeneity) of randomized clinical trials
	1b	Individual randomized clinical trials (with narrow confidence interval)
	1c	All or none (all patients died before the drug became available, but some now survive on it; or when some patients died before the drug became available, but none now die on it.)
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality randomized clinical trial)
	2c	"Outcomes" research
	3a	Systemic review (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case series, single case reports (and poor quality cohort and case control studies)
D	5	Expert opinion without explicit critical appraisal or based on physiol or bench research
Z	6	Abstracts

APPENDIX 3

Secondary Review Panel Organizations

Ambulatory Pediatric Association
American Academy of Breastfeeding Medicine
American Academy of Emergency Medicine
American Academy of Pediatrics
American Association for Health Education
American College of Clinical Pharmacy
American College of Emergency Physicians
American College of Occupational and Environmental Medicine
American Public Health Association
American Society of Health-System Pharmacists
Association of Maternal and Child Health Programs
Association of Occupational and Environmental Clinics
Association of State and Territorial Health Officials
Canadian Association of Poison Control Centres
Centers for Disease Control and Prevention—National Center for Injury Prevention and Control
Consumer Federation of America
Consumer Product Safety Commission
Department of Transportation
Emergency Medical Services for Children
Emergency Nurses Association
Environmental Protection Agency
European Association of Poisons Control Centres and Clinical Toxicologists
Food and Drug Administration
National Association of Children's Hospitals and Related Institutions
National Association of Emergency Medical Services Physicians
National Association of Emergency Medical Technicians
National Association of School Nurses
National Association of State Emergency Medical Services Directors
National Safe Kids Campaign
Teratology Society
World Health Organization International Programme on Chemical Safety

APPENDIX 4

Algorithm for Out-of-Hospital Management of Acute Acetaminophen Ingestions

Is self-harm, suicidal, or malicious intent suspected? YES→ Refer to emergency department.

NO ↓

Does patient have signs of liver failure (e.g., repeatedvomiting, jaundice, right upper abdomen tenderness, mental changes)? YES→ Refer to emergency department.

NO ↓

Have more than 36 hours passed since the ingestion? YES → Toxicity unlikely to occur. No referral or treatment is needed.

NO ↓

Has the patient ingested a potentially toxic dose of acetaminophen (i.e., ≥200 mg/kg for patients <6 yr of age; ≥10 g or ≥200 mg/kg, whichever is less, for patients ≥6 yr of age)?* YES→ Refer to emergency department to have stat serum acetaminophen concentration determined at 4 hrafter ingestion.

NO ↓

No referral or treatment is needed.

* Activated charcoal should be considered if local poison center policies support its prehospital use, if a toxic dose of acetaminophen has been taken and fewer than 2 hours have elapsed since the ingestion, or if acetylcysteine cannot be initiated within 8 hours after the ingestion.

APPENDIX 5

Algorithm for Out-of-Hospital Management of Repeated Supratherapeutic Acetaminophen Ingestions (RSTI)

Is self-harm, suicidal, or malicious intent suspected? YES → Refer to emergency department.

NO ↓

Has the patient ingested a potentially toxic dose of acetaminophen? YES → Refer to emergency department.

For patients <6 yr of age:
≥200 mg/kg over 8–24 hours
≥150 mg/kg/day for 2 days
≥100 mg/kg/day for 3 days or longer
For patients ≥6 yr of age:*
≥10 g or 200 mg/kg (whichever is less) over a single 24-hour period
≥6 g or 150 mg/kg (whichever is less) per 24-hour period for 48 hours or longer

NO ↓

No referral or treatment is needed.

*A referral dose of 4 g/day or 100 mg/kg/day (whichever is less) should be considered for patients with suspected risk factors(e.g., alcoholism, isoniazid therapy, prolonged fasting).