Complete Summary

GUIDELINE TITLE

Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management.

BIBLIOGRAPHIC SOURCE(S)

Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, Chyka PA, Caravati EM, Wax PM, Keyes DC, Woolf AD, Scharman EJ, Booze LL, Troutman WG, American Association of Poison Control Centers. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2006;44(1):1-18. PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Acetaminophen poisoning

Note: This guideline applies to ingestion of acetaminophen alone. Co-ingestion of additional substances could require different referral and management recommendation depending on the combined toxicities of the substances.

GUIDELINE CATEGORY

Evaluation
Management
Risk Assessment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Internal Medicine
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Emergency Medical Technicians/Paramedics
Nurses
Pharmacists
Physicians

GUIDELINE OBJECTIVE(S)

To assist U.S. poison center personnel in the appropriate out-of-hospital triage and initial management of patients with suspected ingestions of acetaminophen by:

- Describing the process by which an ingestion of acetaminophen might be managed
- Identifying the key decision elements
- Providing clear and practical recommendations that reflect the current state of knowledge
- Identifying needs for research

TARGET POPULATION

Children under 6 years of age and older children and adults with acute and repeated ingestion of acetaminophen

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Assessment of key decision elements for triage
    - Patient intent
    - Patient's age
    - Pattern of ingestion (single or multiple)
    - Dose and formulation of the acetaminophen product ingested
    - Duration of ingestion
    - Conditions that might increase acetaminophen toxicity (alcoholism, isoniazid use, prolonged fasting) and co-ingestants
2. Serum acetaminophen concentration measurements

Management

1. Referral to an emergency department
2. Activated charcoal when appropriate
3. Detoxification with acetylcysteine if the emergency department is far away

   Note: The dietary supplement tablet form of acetylcysteine has not been tested as an antidote for acetaminophen toxicity, therefore only the pharmaceutical product should be used.

4. Home observation
5. Cimetidine as an antidote (considered, but not recommended)

MAJOR OUTCOMES CONSIDERED

- Mortality
- The threshold dose for the development of toxicity after acute and repeated acetaminophen ingestion
- Signs and symptoms of toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search

The National Library of Medicine's MEDLINE database was searched (1966 to January 2003) using acetaminophen as a Medical Subject Heading (MeSH) term with the subheadings poisoning (po) or toxicity (to), limited to humans. MEDLINE and PreMEDLINE (1966 to 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 to January 2003, excluding abstracts of meeting presentations), Science Citation Index (1977 to January 2003), Database of Abstracts of Reviews of Effects (accessed Jan 2003), Cochrane Database of Systematic Reviews (accessed Jan 2003), and Cochrane Central Register of Controlled Trials (accessed Jan 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 to January 2003), the acetaminophen poisoning management in POISINDEX, the Cochrane systematic review of interventions for acetaminophen overdoses, and the chapter bibliographies in four major toxicology textbooks 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).

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Articles were assigned level-of-evidence scores based on the Grades of Recommendation table developed by the Centre for Evidence-Based Medicine at Oxford University. Single case reports were classified along with case series as level 4.

Levels of Evidence	Description of Study Design
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)
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
4	Case series, single case reports (and poor quality cohort and case control studies)
5	Expert opinion without explicit critical appraisal or based on physiology or bench research
6	Abstracts

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

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 (see the "Rating Scheme for the Strength of the Evidence" field); 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 American Association of Poison Control Centers (AAPCC) Web site.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

An expert consensus panel was established to oversee the guideline development process (see Appendix 1 of the original guideline document). 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 track record in clinical care and scientific research in toxicology, board certification as a clinical or medical toxicologist, significant U.S. 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.

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.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The rating scheme for the strength of the recommendation (A-D, Z) is directly tied to the level of evidence supporting the recommendation.

Grades of Recommendation	Levels of Evidence
A	1a
	1b
	1c
B	2a
	2b
	2c
	3a
	3b
C	4
D	5
Z	6

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External review of the second draft was conducted by distributing it electronically to American Association of Poison Control Centers (AAPCC), American Academy of Clinical Toxicology (AACT), and American College of Medical Toxicology (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 (see Appendix 3 of the original guideline). Comments were submitted via a discussion thread on the AAPCC Web site 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.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Grades of recommendation (A-D, Z) and levels of evidence (1a-6) are defined at the end of the "Major Recommendations" field.

Note: 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.

    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)**.

Definitions:

Grades of Recommendation and Levels of Evidence

Grades of Recommendation	Levels 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

Grades of Recommendation	Levels of Evidence	Description of Study Design
	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 physiology or bench research
Z	6	Abstracts

CLINICAL ALGORITHM(S)

Algorithms are provided in Appendices 4 and 5 of the original guideline document for out-of-hospital management of acute acetaminophen ingestion and out-of-hospital management of repeated supratherapeutic acetaminophen ingestion.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate out-of-hospital triage and initial management of patients with suspected ingestions of acetaminophen
- Optimized patient outcome
- Reduced costs
- Reduced disruption for patient and caregivers

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline has been developed for the conditions prevalent in the U.S. 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.

- 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.
- 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).
- 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.

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).

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Dart RC, Erdman AR, Olson KR, Christianson G, Manoguerra AS, Chyka PA, Caravati EM, Wax PM, Keyes DC, Woolf AD, Scharman EJ, Booze LL, Troutman WG, American Association of Poison Control Centers. Acetaminophen poisoning: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 2006;44(1):1-18. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005

GUIDELINE DEVELOPER(S)

American Association of Poison Control Centers - Professional Association

SOURCE(S) OF FUNDING

Maternal and Child Health Bureau, Health Resources and Services Administration, U.S. Department of Health and Human Services

GUIDELINE COMMITTEE

Not stated

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Poison Control Centers Web site.

Print copies: Available from the American Association of Poison Control Centers, 3201 New Mexico Avenue NW, Suite 330, Washington, DC 20016

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on October 31, 2005. The information was verified by the guideline developer on November 28, 2005.

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