

# A Prospective Evaluation of Shortened Course Oral *N*-Acetylcysteine for the Treatment of Acute Acetaminophen Poisoning

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**Study objective:** Treatment with a shortened duration of oral *N*-acetylcysteine (20 to 48 hours) after acute acetaminophen poisoning is effective in the prevention of subsequent hepatic failure and death when administered to individuals meeting appropriate laboratory criteria.

**Methods:** Individuals with a potentially toxic acetaminophen ingestion according to serum acetaminophen levels were identified prospectively using a large statewide poison control system database throughout a 12-month period. *N*-acetylcysteine was administered for a minimum of 6 doses (20 hours), after which laboratory studies were obtained. Discontinuation of *N*-acetylcysteine was recommended by the poison center when 2 criteria were met: serum acetaminophen was undetectable ( $<10 \mu\text{g/mL}$ ) and liver test results were normal (serum aminotransferase, international normalized ratio). A follow-up questionnaire was administered to individuals treated with *N*-acetylcysteine for 48 hours or less to ascertain the presence of symptoms consistent with progressive hepatotoxicity.

**Results:** Of 205 acutely poisoned individuals treated with *N*-acetylcysteine for 48 hours or less, 195 were successfully contacted after discharge, and 187 of 195 (95.9%) reported no symptoms consistent with hepatic failure. Eight individuals (4.1%) reported abdominal pain or vomiting; however, none received further *N*-acetylcysteine treatment or additional hospitalization.

**Conclusion:** A shortened duration of treatment with *N*-acetylcysteine (20 to 48 hours) may be an effective treatment option in individuals considered to be at no further risk of developing liver toxicity according to the fulfillment of appropriate laboratory criteria before *N*-acetylcysteine discontinuation. [Ann Emerg Med. 2007;50:272-279.]

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## INTRODUCTION

### Background

Acetaminophen misuse is responsible for more hospitalizations after overdose than any other common pharmaceutical agent.<sup>1</sup> Although possessing an outstanding safety profile at therapeutic doses, with large ingestions and the absence of early treatment, a rapid course of progressive hepatic failure leading to death may occur. Since the initial reports of its effectiveness in the treatment of acetaminophen poisonings in

the late 1970s, *N*-acetylcysteine administration has dramatically reduced the overall mortality rate associated with acetaminophen poisonings.<sup>2-5</sup>

*N*-Acetylcysteine is believed to prevent acetaminophen-induced hepatocyte damage by replenishing glutathione stores, enhancing nontoxic routes of metabolism, acting as a free-radical scavenger, and improving hepatic microcirculatory flow.<sup>6-8</sup> When given within 8 hours of acetaminophen ingestion, *N*-acetylcysteine is nearly uniformly effective in the prevention of significant hepatotoxicity and death.<sup>4</sup> *N*-Acetylcysteine is administered either orally or intravenously

**Editor's Capsule Summary***What is already known on this topic*

Acute acetaminophen overdose is treated with *N*-acetylcysteine. The standard duration of oral acetylcysteine treatment of acute acetaminophen overdose is 72 hours. The effect of shortening the duration of therapy is unknown.

*What question this study addressed*

The authors recommended shortened treatment (20 to 48 hours) with oral acetylcysteine when their poison center was consulted for acute acetaminophen overdose, if the patient's liver tests were normal and serum acetaminophen undetectable.

*What this study adds to our knowledge*

None of the 205 poisoned patients treated with a shortened course of *N*-acetylcysteine developed signs of liver injury or liver failure.

*How this might change clinical practice*

Shortened acetylcysteine therapy appears reasonable in selected patients; however, widespread application awaits further clinical experience.

for the treatment of acute acetaminophen poisoning. Oral *N*-acetylcysteine is approved for use as a 72-hour regimen, with a loading dose of 140 mg/kg, followed by 70 mg/kg every 4 hours, for an additional 17 doses. Intravenous *N*-acetylcysteine has been used extensively throughout Europe, Australia, Canada, and portions of the United States for more than 2 decades, with success demonstrated with administration of various durations (20 to 48 hours).<sup>9-12</sup> In 2004, the US Food and Drug Administration approved a 20-hour intravenous *N*-acetylcysteine protocol for patients treated within 8 to 10 hours after an acute acetaminophen ingestion.

**Importance**

The effectiveness of oral *N*-acetylcysteine administered as a 72-hour course of treatment has been clearly demonstrated by Smilkstein et al<sup>4</sup> in a large multicentered trial. A shortened duration of oral *N*-acetylcysteine treatment in a low-risk subset of acetaminophen-poisoned patients has been proposed by several authors as an alternative treatment option.<sup>13-15</sup> Identifying those acetaminophen-poisoned individuals considered at no further risk of developing hepatotoxicity, for whom *N*-acetylcysteine may be discontinued before completion of a full 72 hours of treatment, would be of potential benefit to patients and health care providers.

**Goals of This Investigation**

The study hypothesis was that treatment with a shortened duration of oral *N*-acetylcysteine (20 to 48 hours) after acute

acetaminophen poisoning is effective in the prevention of subsequent hepatic failure and death when administered to individuals meeting appropriate laboratory criteria.

**MATERIALS AND METHODS****Study Design and Setting**

A prospective observational study was performed from July 1, 2004, to June 30, 2005, by conducting daily searches of a statewide poison control system computerized database for all cases involving acetaminophen as an ingested substance. As per our standard poison center guidelines, recommendations for treatment with a shortened oral *N*-acetylcysteine protocol were given for patients identified as having a potentially toxic serum acetaminophen concentration after an acute ingestion, defined as greater than 150  $\mu\text{g/mL}$  at 4 hours or the extrapolated equivalent up to 24 hours from the time of ingestion, assuming a 50% decrease every 4 hours, as plotted on a modified Rumack-Matthew nomogram. This shortened *N*-acetylcysteine treatment protocol included a loading dose of 140 mg/kg, followed by additional 70 mg/kg doses every 4 hours for a minimum of 20 to 36 hours. Differences in recommended shortest treatment duration exist according to variations in recommendations among the 4 separate divisions (according to geographic location) that make up the statewide poison control system. A minimum of 20 hours (6 total doses) was the typical recommendation given by 2 of the 4 divisions, and 36 hours (10 total doses) was most commonly recommended by the other 2 poison center divisions.

After the loading dose and at least 5 maintenance doses of *N*-acetylcysteine, laboratory studies were requested from the patient's health care provider. If the serum acetaminophen concentration was undetectable or less than 10  $\mu\text{g/mL}$  and the international normalized ratio (INR) and the serum aminoaspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) were at normal or near-normal levels (INR  $\leq 1.3$  and AST/ALT  $\leq 60$  IU/L), *N*-acetylcysteine discontinuation was recommended by the poison center. If the acetaminophen concentration remained detectable or the INR or transaminase levels were abnormal, continued treatment with *N*-acetylcysteine was recommended until these criteria were met. The decision to discontinue *N*-acetylcysteine therapy remained at the discretion of the primary treating physician. The study design was approved by our human research protection program in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects.

**Selection of Participants**

Patients were included if their ingestion was "acute" (ingested during less than 1 hour), the time of ingestion was known, an acetaminophen level taken a minimum of 4 hours and maximum of 24 hours from ingestion was above the treatment line when placed on the Rumack-Matthew nomogram, and *N*-acetylcysteine was initiated within 24 hours from ingestion. Patients were excluded if their ingestion was

acute-on-chronic (other acetaminophen-containing products ingested within the previous 24 hours), if their ingestion occurred at an unknown time or during an unknown duration, if intravenous *N*-acetylcysteine treatment was administered at any time, and if individuals were unable or unwilling to provide follow-up information. Patients initially enrolled who subsequently failed to meet laboratory criteria for early *N*-acetylcysteine discontinuation were excluded from the study. Patients providing a history of liver disease and those demonstrating liver function or coagulation abnormalities before *N*-acetylcysteine administration (although not uniformly recommended or obtained) were also excluded. For eligible subjects, we requested from the treating medical team or the patient a telephone number for follow-up after discharge. Discussion concerning follow-up telephone calls was made with parents if the patient was younger than 18 years.

### Data Collection and Processing

Follow-up information about patient status and laboratory data while hospitalized was collected by telephone calls made at the poison specialist's discretion, with a minimum of 1 call per day, until a final disposition was determined. After hospital discharge, study investigators reviewed data collected by poison specialists to estimate the maximum total duration of *N*-acetylcysteine treatment that may have been given. *N*-Acetylcysteine was assumed to have been administered at the time recommended by poison specialists unless otherwise recorded. If oral *N*-acetylcysteine was vomited within 1 hour from administration, a repeated dose was recommended; however, the time of the initial treatment was recorded as the time of treatment initiation. If a precise time of *N*-acetylcysteine discontinuation was not known, the time at which a telephone call by the poison specialist verified that *N*-acetylcysteine was no longer being given or the time of hospital discharge (whichever time was earlier) was recorded as the time of *N*-acetylcysteine discontinuation. Patients reported as being discharged or having *N*-acetylcysteine discontinued "yesterday" by poison specialists were arbitrarily determined to have had *N*-acetylcysteine discontinued the day previously at 10 PM. Patients discharged without having complete laboratory data recorded by the poison specialists were assumed to have had laboratory studies meeting the criteria for early *N*-acetylcysteine discontinuation.

A standard telephone questionnaire was administered to all subjects or their guardians a minimum of 3 days after hospital discharge to evaluate for signs or symptoms consistent with hepatic failure. Individuals who were transferred to inpatient psychiatric care were assessed by speaking to nursing staff. Repeated attempts were made to contact subjects until telephone contact was made, the telephone number was found to be disconnected or incorrect, or a minimum of 5 unsuccessful attempts was made. A search of the Scientific Registry of Transplant Recipients, which contains detailed information on all patients in the United States who are registered for organ transplants, was performed to determine whether individuals treated with shortened duration *N*-acetylcysteine later developed

hepatic failure and were considered for liver transplant within a 30-day period after overdose. The California State Death Index, which maintains a list of all individuals throughout the state who have died in California, was queried for individuals who were unable to be contacted after discharge for a 30-day period after overdose to determine whether these individuals had died.

### Outcome Measures

Standardized follow-up questions included (1) Are you having persistent vomiting or abdominal pain? (2) Do you have any signs of jaundice or skin discoloration? (3) Are you having any persistent sleepiness or lethargy? (4) Have you required rehospitalization? (5) Did you take any *N*-acetylcysteine after being discharged from the hospital? If any of the first 3 questions were answered yes, recommendations were made to seek immediate medical attention. A later follow-up telephone call was then made to this subset to inquire about further hospitalization or whether additional *N*-acetylcysteine treatment had been given. Outcome measures were defined as a positive response to the questionnaire pertaining to the presence or absence of the defined signs or symptoms of hepatic failure or administration of further *N*-acetylcysteine treatment.

Patients were divided into 2 risk groups on the basis of the modified Rumack-Matthew nomogram: "possible" and "probable" toxicity. Patients with acetaminophen levels between 150 and 200  $\mu\text{g/mL}$ , or the extrapolated equivalent out to 24 hours, were in the "possible" risk group. Individuals with levels of 200  $\mu\text{g/mL}$  or greater at 4 hours, or the extrapolated equivalent out to 24 hours, were in the "probable" risk group. In the case in which multiple acetaminophen levels were obtained in the first 24 hours after ingestion, the level the greatest distance from the "possible" toxicity line was used to determine in which risk group they would be. These 2 groups were also divided into treatment groups on the basis of the time from ingestion when the first dose of oral *N*-acetylcysteine was administered.

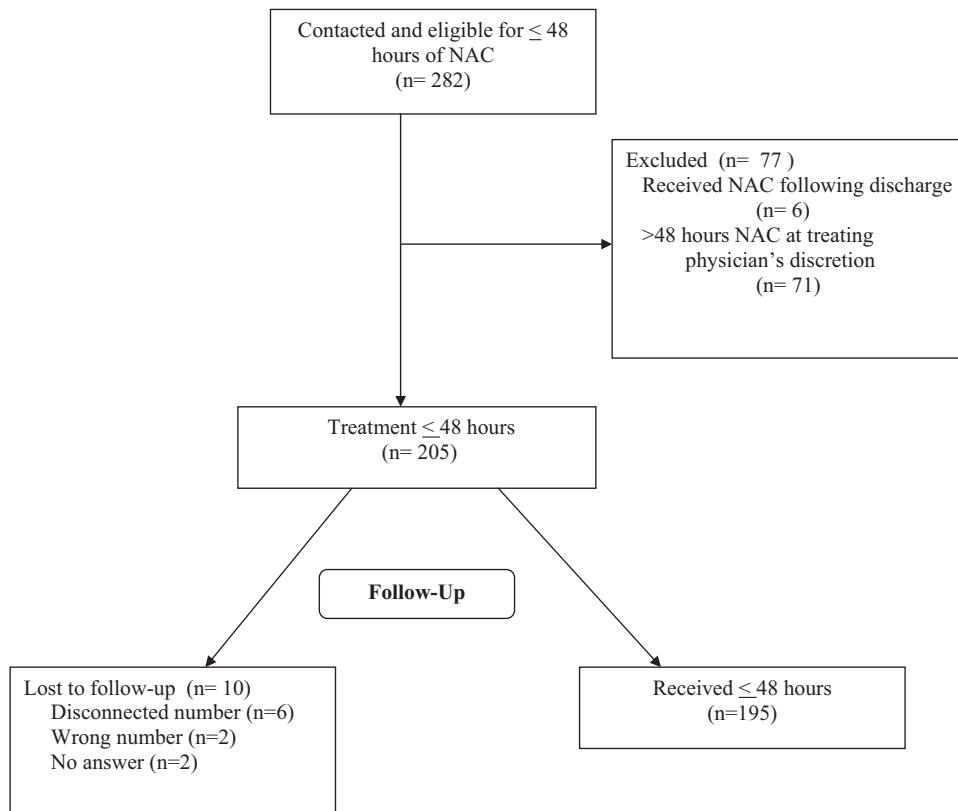
### Primary Data Analysis

Categorical data are expressed as the percentage frequency of occurrence. Ninety-five percent confidence intervals (CIs) are provided. Continuous data are expressed as means with SDs. Statistical differences between the means of continuous variables were analyzed with the unpaired 2-tailed Student *t* test. A  $P < .05$  was considered significant for all tests.

## RESULTS

### Characteristics of Study Subjects

Two hundred eighty-two individuals met laboratory criteria for shortened course *N*-acetylcysteine and had follow-up telephone numbers obtained. Seventy-one patients received greater than 48 hours of treatment while hospitalized, despite poison specialists' recommendations for *N*-acetylcysteine discontinuation (as appropriate laboratory criteria were met) at the treating physician's discretion. Six individuals receiving 48



**Figure 1.** Disposition of patients eligible for shortened course of oral *N*-acetylcysteine. *NAC*, *N*-acetylcysteine.

hours or less of treatment while hospitalized were discharged or transferred to psychiatric care, with additional *N*-acetylcysteine to complete the full 72-hour course of treatment, and were also excluded. The remaining 205 patients received 48 hours of *N*-acetylcysteine treatment or less ( $\leq 13$  doses) and make up the study cohort. Follow-up information was available by telephone from 195 of the 205 shortened-course oral *N*-acetylcysteine-treated subjects (Figure 1). Demographic characteristics of the study cohort and information pertaining to other ingested substances are summarized in Table 1.

**MAIN RESULTS**

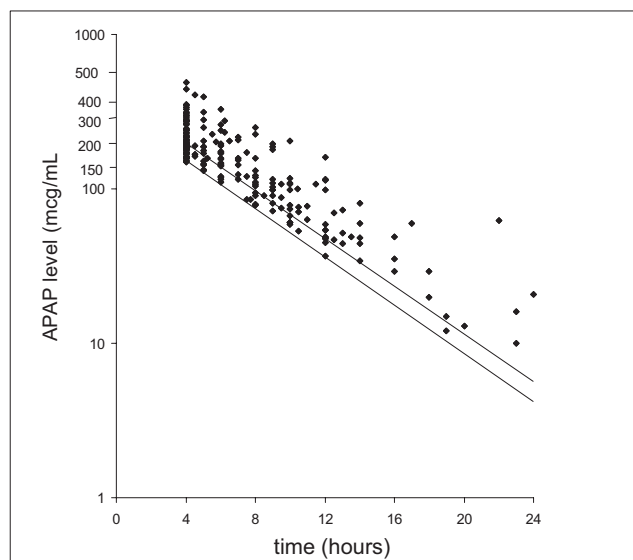
One hundred twenty-five (61.0%) individuals had measured acetaminophen concentrations that corresponded to “probable” toxic ingestions, and 80 (39.0%) study subjects had “possible” toxic ingestions (Figure 2). *N*-Acetylcysteine treatment was initiated a mean of 5.2 hours (SD 6.8 hours) (range 1 to 24 hours) from ingestion in the 194 of 205 patients for whom poison center specialists recorded a specific time of initial *N*-acetylcysteine administration. One hundred forty-two (63%) subjects received their first dose of oral *N*-acetylcysteine by 10 hours from ingestion, with a mean treatment duration of 35.3 hours (SD 7.7 hours) (range 20 to 48 hours), whereas 52 (27%) individuals received treatment initiated greater than 10 hours from ingestion, with a mean treatment duration of 36.9 hours (SD 7.3 hours) (range 20 to 48 hours;  $P=.31$ ) (Table 2).

**Table 1.** Characteristics of subjects treated with oral *N*-acetylcysteine for fewer than 48 hours.

Patient/Ingestion Characteristics	Number of Subjects (%)
<b>Age, y, mean (range) (n=204)</b>	32 (18 mo to 81 y)
Age distribution, y (%)	
0–5	5 (2.5)
5–10	0 (0)
10–20	98 (48.0)
20–30	57 (27.9)
30–40	19 (9.3)
40–60	21 (10.3)
$\geq 60$	4 (2.0)
<b>Sex: female (%)</b>	139/205 (67.8)
<b>Acetaminophen formulation, No. (%)</b>	
Acetaminophen	113 (51.8)
Acetaminophen+opioids	25 (11.5)
Acetaminophen+antihistamines	50 (22.9)
Acetaminophen, extended relief	1 (0.4)
Acetaminophen (unknown)	29 (13.3)
<b>Coingestants (%)*</b>	57/205 (27.8)

\*Coingested nonacetaminophen-containing product taken at time of acetaminophen ingestion.

The overall mean duration of treatment for individuals treated with shortened course oral *N*-acetylcysteine was 36.1 hours (SD 8.0 hours) (range 20 to 48 hours), with no significant difference between those with “probable” toxic levels,



**Figure 2.** Acetaminophen level distribution as plotted on the modified Rumack-Matthew nomogram. If more than 1 acetaminophen level was obtained within the first 24 hours, the level that was the greatest distance from the potentially toxic line has been plotted. APAP, acetaminophen.

35.6 hours (SD 8.0 hours) (range 20 to 48 hours), and “possible” toxic levels, 36.9 hours (SD 7.4 hours) (range 20 to 48 hours;  $P=0.26$ ) (Table 2). Eleven percent (22/205) of patients had the time of *N*-acetylcysteine discontinuation reported as “yesterday” by the poison specialist and were assumed to have had *N*-acetylcysteine discontinued the previous day at 10 PM. Overall, 31.7% of individuals were treated with 20 to 32 hours’ worth of *N*-acetylcysteine, 35.6% were treated for 32 to 40 hours, and 32.7% were treated with *N*-acetylcysteine for 40–48 hours. At *N*-acetylcysteine discontinuation, complete laboratory data, including acetaminophen, transaminase, and INR levels, were recorded by poison specialists for 21.5% (44/205) of patients treated with shortened course *N*-acetylcysteine. Of the total case patients, 44.9% (92/205) had only transaminase and acetaminophen levels reported, 3.9% (8/205) had transaminase and INR levels alone reported, 15.1% (31/205) had transaminase levels alone reported, 2.9% (6/205) had acetaminophen levels alone reported, and 11.7% (24/205) had no laboratory studies recorded. In 5.4% (11/205) of cases, *N*-acetylcysteine was discontinued at the treating physician’s discretion despite poison specialists’ recommendations, with laboratory studies recorded before discharge that ranged above those considered to be appropriate for shortened course *N*-acetylcysteine treatment: AST (63 to 96 IU/L), ALT (76 to 138 IU/L), and INR (1.4 to 1.8).

Of 205 patients who received shortened course oral *N*-acetylcysteine, 10 were unable to be contacted at follow-up. Six had disconnected numbers at the initial call, 2 had wrong

numbers provided, and the remaining 2 had no answer obtained despite multiple attempts. Of those individuals in which telephone contact was made, 187 (95.9%) reported no adverse effects after discharge, whereas 8 individuals (4.1%) reported abdominal pain ( $n=6$ ) or vomiting ( $n=3$ ) (Table 3). None of these 8 individuals with abdominal pain or vomiting were rehospitalized or administered further *N*-acetylcysteine treatment. There were no known individuals (0/195) in which the follow-up telephone call revealed death of the patient or need for transplant (0%; 95% CI 0% to 1.9%). Lethargy, confusion, and jaundice were not reported by any subjects at follow-up. A search of the California State Death Index did not identify any of the 10 individuals who were lost to follow-up within 30 days from overdose. The search of the Scientific Registry of Transplant Recipients identified none of the 205 patients treated with *N*-acetylcysteine for 48 hours or less as later being registered for a liver transplant within 30 days after their ingestion.

## LIMITATIONS

Ten individuals (4.9%) receiving shortened duration oral *N*-acetylcysteine treatment were unable to be contacted after discharge. These individuals were not listed on the statewide death index or in the national transplant registry; however, we cannot assume with certainty that these patients did not develop liver injury. Death after acetaminophen poisonings is uncommon, with mortality rates from 0.54% in patients receiving *N*-acetylcysteine to 3% in historical controls in which *N*-acetylcysteine was not given.<sup>4</sup> The development of subsequent hepatic failure in any individual after receiving this shortened duration treatment would be considered a failure of the treatment protocol. Although this study represents the largest reported series of patients treated with oral *N*-acetylcysteine for fewer than 72 hours, given the low rate of mortality in those treated with conventional 18-dose treatment and even in those untreated, conclusions and comparisons of the effectiveness of shortened course *N*-acetylcysteine remain limited according to our study size of 205 patients.

The California Poison Control System has made recommendations for shortened duration oral *N*-acetylcysteine treatment as our standard treatment protocol for approximately 10 years, with no known poor outcomes. However, before this study, the California Poison Control System did not have follow-up obtained after discharge in all cases, and the discovery of treatment failures with shortened course oral *N*-acetylcysteine would come solely from health care providers voluntarily contacting the poison center about the need for additional treatment. Some variation in the minimum treatment duration recommendations may exist among poison specialists at each division of the statewide poison center, making it difficult to compare differences in treatment durations between the separate poison center divisions.

Laboratory studies were not routinely obtained after discharge. The presence of an increase in serum transaminase levels after acetaminophen’s metabolism to a level of less than

**Table 2.** Treatment duration characteristics of acetaminophen-poisoned patients treated with 48 hours of *N*-acetylcysteine treatment.

Treatment Duration Characteristics	Potentially Toxic Ingestion	Possible Toxicity	Probable Toxicity	P Value*
<b>Subjects</b>	205	80	125	
Early treatment		63	79	
Late treatment		12	40	
<b>Mean treatment duration (SD)</b>	36.1 (8.01)	36.9 (7.37)	35.6 (8.04)	.26
Early treatment (range)	35.6 (7.94)	36.6 (7.32) (20–48 h)	34.8 (8.36) (20–48 h)	.19
Late treatment (range)	37.1 (8.07)	36.4 (8.01) (23.5–47.5 h)	37.4 (8.18) (20–48 h)	.73
<b>Treatment distribution, h (%)</b>				
20–32	65 (31.7)	19 (23.8)	46 (36.8)	
>32–40	73 (35.6)	35 (43.8)	38 (30.4)	
>40–48	67 (32.7)	26 (32.5)	41 (32.8)	

\*Statistical difference between mean treatment durations of possible and probable toxic ingestions.

**Table 3.** Characteristics of individuals with symptoms reported at follow-up.

Age/Sex	Possible/Probable Toxicity	Treatment Initiation, h	Duration of <i>N</i> -Acetylcysteine Treatment, h	Laboratory Values*	Complaint at Follow-up
16 M	Probable	6.25	33	APAP <10, AST 63, ALT 138	Abdominal pain
39 F	Possible	13	24	APAP <10, AST/ALT “normal”	Abdominal pain
15 F	Possible	3	34	“Normal laboratory results”	Abdominal pain
34 F	Probable	5.5	26	APAP <10, AST 12, SPGT 11	Abdominal pain
15 F	Possible	4	24.5	APAP 13, AST 14, ALT 21	Abdominal pain/vomiting
18 F	Possible	6	30	APAP <10, AST/ALT/INR “normal”	Abdominal pain
22 F	Possible	6	30	APAP 6, AST 12, ALT 5	Vomiting
22 F	Possible	23	32	APAP <10, AST/ALT/INR “normal”	Vomiting

\*Laboratory values are last reported values recorded by poison specialists before *N*-acetylcysteine discontinuation.

10  $\mu\text{g/mL}$  cannot be excluded. Telephone follow-up involves inherent limitations by asking individuals to clinically assess themselves. A trained health care professional evaluation that may have unmasked subtle manifestations of hepatotoxicity was not performed. The questionnaire used by study investigators has not been previously validated as a measure of determining the presence of progressive hepatic failure. Patients were excluded who were unable to provide the study authors with a follow-up telephone number, potentially excluding individuals of a lower socioeconomic class who may have higher rates of malnourishment, chronic substance abuse, and other chronic medical conditions.

Although individuals reporting transient abdominal pain and vomiting were improved at the second follow-up telephone call, these individuals did not all follow up with health care professionals as recommended and potentially had physical signs and laboratory studies that would warrant further treatment. The precise time of *N*-acetylcysteine treatment initiation, discontinuation, and number of doses was not clearly recorded in many cases, leading investigators to extrapolate the total duration of treatment from the poison specialists' reports. Although poison specialists' recommendations did adhere to the treatment protocol, given the method of data extraction

from the poison center database and the uncertainty of the actual time of *N*-acetylcysteine dosing, an overestimation of treatment duration may have occurred in some cases. Our method of reporting treatment duration was performed so that the effectiveness of the shortened *N*-acetylcysteine treatment regimen was assumed to have resulted from a longer duration of treatment rather than an underestimation of time of treatment.

## DISCUSSION

Since gaining US Food and Drug Administration approval in 1985, oral *N*-acetylcysteine has traditionally been administered in the United States as an 18-dose, 72-hour protocol. A shortened duration of treatment has been advocated by many clinicians. A 2002 survey of poison center directors throughout North America and Europe reported that 36.7% who routinely recommended oral *N*-acetylcysteine would consider early *N*-acetylcysteine discontinuation after toxic acetaminophen ingestion under certain circumstances.<sup>16</sup> Twenty percent routinely recommend early discontinuation with normalization of laboratory studies.

Acetaminophen-induced hepatotoxicity is considered to be primarily a result of the production and action of *N*-acetyl-*p*-

benzoquinone imine (NAPQI), a toxic metabolite of acetaminophen produced by oxidation by the hepatic cytochrome P450 enzyme system (CYP 2E1). NAPQI binds to intracellular proteins, leading to rapid subsequent hepatocyte damage.<sup>17</sup> After the elimination of acetaminophen by metabolism through this and other nontoxic pathways (sulfation and glucuronidation), no further NAPQI should be produced. Given this well-accepted mechanism of toxicity, the development of transaminase increase to any level of clinical significance would seem unlikely in the absence of acetaminophen. Concentrations of acetaminophen may be present at levels undetected by typical laboratory methods (<10 µg/mL), resulting in small amounts of NAPQI production after *N*-acetylcysteine has been discontinued; however, we believe this would be insufficient to produce clinically significant hepatocyte damage.

The reported effectiveness of shorter duration intravenous *N*-acetylcysteine (20 to 48 hours) as given worldwide throughout the past 2 decades would appear to lend further support to shorter duration oral *N*-acetylcysteine use as well. After absorption, oral *N*-acetylcysteine is pharmacologically identical to intravenous *N*-acetylcysteine. The large amount of oral *N*-acetylcysteine traditionally given in the first 20 hours (490 mg/kg) has been long assumed to be more than sufficient to replenish glutathione stores depleted by NAPQI production.

Ease of standard oral *N*-acetylcysteine dosing may offer further benefit, especially in the pediatric population in which changes in preparation of intravenous *N*-acetylcysteine preparations may be required. Ensuring that *N*-acetylcysteine discontinuation occurs only when all appropriate laboratory criteria are met may be challenging with the introduction of a somewhat more complicated treatment protocol that varies from the standard 72-hour oral course. Despite our recommendations to the health care team, it appears that in 5.4% (11/205) of the total shortened-course *N*-acetylcysteine cases followed and in 1 of the 8 symptomatic patients, *N*-acetylcysteine was discontinued, with laboratory studies that were out of the range deemed acceptable for *N*-acetylcysteine discontinuation.

A shortened duration of oral *N*-acetylcysteine administration to selected patients may offer benefits by reducing medication costs and shortening the length of hospital stay, thereby allowing limited health care resources to focus on more severely ill patients.<sup>18</sup> Tailoring treatment duration according to the fulfillment of laboratory criteria would allow a further benefit of consideration of a shortened treatment duration under certain circumstances in those presenting more than 8 to 10 hours after ingestion, a subset of patients that often may require treatment with *N*-acetylcysteine beyond 20 to 48 hours.

Treatment with oral *N*-acetylcysteine for fewer than 72 hours after acetaminophen poisoning has gained acceptance among many medical toxicologists. An understanding of acetaminophen toxicity suggests that a shortened duration

of treatment may be effective in many circumstances. The accumulation of additional reports of acetaminophen-poisoned individuals given shortened oral *N*-acetylcysteine treatment will provide further information about the appropriateness of these recommendations.

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*Author contributions:* DPB was principal investigator. DPB, FLC, SRW, and RFC conceived and designed the study. DPB, SCT, and RFC identified eligible study participants and collected and recorded all data. SRW and RFC supervised data collection and analysis. DPB drafted the article, and FLC, SRW, and RFC contributed substantially to its revisions. DPB is responsible for the paper as a whole.

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