Acetylcysteine (N-acetylcysteine) – Adult/Pediatric – Emergency Department/Inpatient Clinical Practice Guideline

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Executive Summary
Guideline Overview
This document is intended to guide the use of N-acetylcysteine for the treatment of confirmed acetaminophen overdoses, non-acetaminophen acute liver failure, and alcohol-induced liver failure.

Target Population
Adult and pediatric patients receiving N-acetylcysteine.

Key Practice Recommendations
Intravenous and oral dosing of N-acetylcysteine for the treatment of confirmed acetaminophen overdoses, non-acetaminophen acute liver failure, and alcohol-induced liver failure.

Companion Documents
ED/IP – Acetylcysteine Administration – Adult – Supplemental Order Set [3528]

Pertinent UWHC Policies & Procedures
UWHC Prevention of Contrast-Induced Nephropathy – Adult – Inpatient/Ambulatory – Clinical Practice Guideline
Scope

Disease/Condition(s):
- Treatment of confirmed acetaminophen overdose
- Non-acetaminophen acute liver failure (NAALF) management in adult patients
- Alcohol-induced liver failure

Clinical Specialty/Intended Users:
- Medicine
- Hepatology
- Nephrology
- Respiratory/Pulmonary
- Pediatrics

CPG objective:
To guide the use of N-acetylcysteine for appropriate indications and dosing.

Target Population:
- Adult and pediatric with acetaminophen overdose
- Adult patients with non-acetaminophen acute liver failure
- Adult patients with alcohol-induced liver failure
- Adult and pediatric patients at risk for contrast induced nephropathy

Major Outcomes Considered:
- Survival to discharge
- Transplant-free survival
- Improvement in coma grade score

Guideline Metrics:
- Normalization of LFTs to baseline (AST, ALT, Bilirubin, INR)

Methodology

Methods Used to Collect/Select the Evidence:
An extensive evidence review through October 2014. Searches were extended to studies, reviews, and other evidence that were conducted in human subjects, published in English, and accessible via PubMed, EMBASE, Cochrane, Agency for Healthcare Research and Quality Reports, and other selected databases relevant to this guideline.

Methods Used to Assess the Quality and Strength of the Evidence:
A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology (Figure 1) was used to assess the quality and strength of the evidence and recommendations.
**Definitions**

- **NAALF**: Non-acetaminophen acute liver failure\(^2\,^3\)
  - includes liver failure etiologies of hepatitis B; other non-acetaminophen, drug-induced hepatotoxicity; and autoimmune hepatitis
  - excludes alcohol-induced liver failure
- **N-acetylcysteine**: N-Ac or acetylcysteine
- **Rumack-Matthew Nomogram** (Figure 2); used for interpretation of acetaminophen concentrations in association with potential acetaminophen overdose\(^4\,^5\)
Introduction
Acetylcysteine (N-Acetylcysteine or N-Ac) is a derivative of cysteine. It has mucolytic activity that is exerted through physical disruption of chemical bonds in mucous that results in decreased mucous viscosity. N-acetylcysteine also acts as an antidote to acetaminophen toxicity by enhancing glutathione stores, providing a glutathione substitute, and enhancing disposition by nontoxic sulfate conjugation. N-acetylcysteine has also been implicated in free radical scavenging antioxidant activity and subsequent cytoprotection. These mechanisms of action have led to FDA-labeled indications for N-Ac as an acetaminophen overdose antidote and as a mucolytic agent.

The diverse mechanisms of action demonstrated by N-acetylcysteine, particularly its antioxidant effects, have resulted in substantive off-label use of this agent for numerous clinical health states. The most common off-label uses include: NAALF, alcohol-induced liver failure, hemorrhagic cystitis, hepatorenal syndrome, radiographic contrast agent nephropathy prophylaxis, and multiple organ failure prophylaxis.
Recommendations

1. Appropriate indications for use:\(^6,7\):
   1.1. Treatment of confirmed acetaminophen overdose. (I, A)
   1.2. Treatment of conditions that involve significant, abnormal, viscid mucus secretions are generally managed with nebulized hypertonic saline. In pediatric neuromuscular disorders with atelectasis due to mucus obstruction N-Ac may be a more appropriate option than hypertonic saline.\(^6,7\) (I, A)
   1.3. NAALF management in adult patients (IIa, B)\(^2,3,9,10\)
   1.4. Alcohol-induced liver failure. (IIa, B)\(^11,12\)
   1.5. Contrast Induced Nephropathy (CIN): refer to UWHC Prevention of Contrast-Induced Nephropathy – Adult – Inpatient/Ambulatory – Clinical Practice Guideline

2. The following indications have insufficient evidence to support their use (IIb, C)\(^6,7\):
   2.1. Acute renal failure, in patients with chronic renal insufficiency undergoing cardiac surgery; Prophylaxis
   2.2. Acute respiratory distress syndrome
   2.3. Administration of anesthesia for procedures
   2.4. Bezoar
   2.5. Blepharitis
   2.6. Cancer
   2.7. Cystinosis
   2.8. Treatment and prophylaxis of cytotoxicity
   2.9. Drug allergies
   2.10. Drug tolerance to nitrates
   2.11. Prophylaxis of hemorrhagic cystitis
   2.12. Hepatic ischemia-reperfusion injury\(^13\)
   2.13. Hepatorenal syndrome
   2.14. HIV infection
   2.15. Lamellar ichthyosis
   2.16. Malaria
   2.17. Meconium ileus
   2.18. Prophylaxis of multiple organ failure
   2.19. Mucolysis associated with occlusion of the ureter
   2.20. Otitis media
   2.21. Respiratory tract infection
   2.22. Sjogren's syndrome
   2.23. Unverricht-Lundborg syndrome

3. Dosing for Recommended Indications
   3.1. General recommendations
   3.1.1. For the management of acetaminophen overdose, N-acetylcysteine should be dosed on actual weight up to a maximum of 100 kg for IV administration\(^6\) (I, A) and it is reasonable to dose up to a maximum of 110 kg for oral administration. (IIa, C)
   3.1.2. For other indications, it is reasonable to dose on actual weight up to a maximum of 100 kg for IV administration and up to a maximum of 110 kg for oral administration. (IIa, C)
   3.1.3. It is reasonable to use enteral N-acetylcysteine regimens preferentially over intravenous regimens unless a patient is unable to tolerate an enteral regimen. (IIa, C)

3.2. Treatment of confirmed acetaminophen overdose\(^6,14\)
   3.2.1. N-acetylcysteine should be used in the management of acetaminophen overdose (I, A)
3.2.2. In patients with confirmed acetaminophen overdose, no further acetaminophen should be ordered upon admission \((I, A)\).

3.2.3. An acetaminophen concentration should be obtained four hours or greater after acetaminophen overdose ingestion. This acetaminophen concentration should be interpreted according to the Rumack-Matthew nomogram (See Figure 2). If the measured acetaminophen concentration falls on or above the solid line (the FDA 25% safety line), then the concentration is considered toxic and N-acetylcysteine treatment is warranted. \((I, A)\)

3.2.3.1. Administration should be initiated within 8 hours of ingestion or as soon as possible after ingestion \((I, A)\)

3.2.3.2. The Rumack-Matthew nomogram should not be applied to patients with evidence of hepatotoxicity, multiple acetaminophen ingestions (i.e. not a single ingestion event), or patients with an uncertain time of acetaminophen ingestion \((I, A)\)

3.2.4. See Table 1 for dosing recommendations.

3.2.5. The oral protocol is as effective as the intravenous one.\(^{15,16}\) Therefore, oral administration is preferable as it is less invasive and has a lower potential for anaphylaxis than does the intravenous regimen. \((I, A)\)

3.2.5.1. Shorter courses of oral N-acetylcysteine lasting at least 20 hours may be considered in the setting repeat acetaminophen concentrations below 10 mcg/mL and no increase in ALT/AST or INR\(^{17-20}\) \((IIb, B)\)

3.2.6. Therapy should be guided by patient condition, resolution of transaminase elevation, and completion of acetaminophen metabolism.\(^ {21}\) \((IIa, B)\)

3.2.7. Patients should have serial acetaminophen levels and LFTs measured before completion of N-acetylcysteine.\(^ {22} \) \((IIa, B)\)

3.2.7.1. The first repeat acetaminophen concentration should be drawn 4-6 hours after the baseline.\(^ {14} \) \((IIa,C)\)

3.2.8. Periodic acetaminophen concentrations should be drawn while N-acetylcysteine is being continued with a goal of decreasing the acetaminophen concentration below 10 mcg/mL. \((IIb, C)\)

3.2.9. N-acetylcysteine should be continued if acetaminophen levels remain greater than 10 mcg/mL or if the aminotransferases (AST, ALT) remain elevated.\(^ {22,23} \) \((IIa, A)\)

3.2.9.1. Maintenance treatment courses may be extended beyond 17 doses or 16 hours for oral or intravenous N-acetylcysteine therapy, respectively, if clinically warranted, especially in patients with liver injury.\(^ {24}\) \((IIa, B)\)

3.2.9.2. Status should be reevaluated 12 hours after initiation of continuation of N-acetylcysteine.\(^ {22} \) \((IIa, A)\)

3.2.9.3. With extended courses of N-acetylcysteine, therapeutic endpoints to monitor include INR normalization, encephalopathy resolution, and decreasing AST (to a level at least below 1000 units/L).\(^ {21} \) \((IIa, B)\)

3.2.10. N-acetylcysteine treatment discontinuation may be considered when a single acetaminophen concentration is below 10 mcg/mL and AST has decreased to fewer than 1000 units/mL or may be discontinued at the discretion of the physician.\(^ {14,19} \) \((IIb, C)\)

3.2.10.1. Drawing no further acetaminophen concentrations beyond thirty-six hours may be reasonable.\(^ {14,19} \) \((IIb, B)\)

3.2.10.2. ALT and total bilirubin, if elevated in the setting of acetaminophen overdose, will resolve more slowly in comparison to AST.

3.2.10.3. INR may be considered to evaluate liver injury \((IIb, C)\)

3.3. NAALF management

3.3.1. N-acetylcysteine use is reasonable for use in adults for NAALF management.\(^ {3,25} \) \((IIa, B)\)

3.3.2. N-acetylcysteine use may be considered in pediatric patients for NAALF management\(^ {26,27} \) \((IIb, B)\)

3.3.3. See Table 1 for dosing recommendations.
3.3.4. N-acetylcysteine treatment discontinuation may be considered AST has fallen below the threshold of five times the upper limit of normal or may be discontinued at the discretion of the physician. (IIb, C)

3.4. **Alcohol-induced liver failure**

3.4.1. N-acetylcysteine use is reasonable for alcohol-induced liver failure management. (*intravenous*: IIa, B; *enteral*: IIb, C)

3.4.2. See Table 1 for dosing recommendations.

3.4.3. N-acetylcysteine discontinuation may be considered at the discretion of the physician or if there is no improvement of total bilirubin at day seven of treatment. (IIb, C)

3.5. **Therapeutic use as a mucolytic**

3.5.1. Nebulize via face mask, mouth piece or into a tracheostomy

3.5.2. Use 1-10 mL of 20% N-acetylcysteine solution every one to six hours. Frequency and volume of medication administration will vary within this range depending on health condition or surgical procedure necessitating mucolytic therapy.
Table 1. N-acetylcysteine dosing for confirmed acetaminophen overdose, NAALF, or alcohol-induced liver failure

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed acetaminophen overdose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Loading Dose</td>
<td>140 mg/kg</td>
<td>140 mg/kg</td>
</tr>
<tr>
<td>Oral Maintenance Dose</td>
<td>Following loading dose, 70 mg/kg every 4 hours for 17 doses</td>
<td>Following loading dose, 70 mg/kg every 4 hours for 17 doses</td>
</tr>
<tr>
<td>Intravenous Loading Dose</td>
<td>150 mg/kg over 60 minutes</td>
<td>150 mg/kg over 60 minutes</td>
</tr>
<tr>
<td>Intravenous Maintenance Dose</td>
<td>12.5 mg/kg/hr for 4 hours, then 6.25 mg/kg/hr</td>
<td>12.5 mg/kg/hr for 4 hours, then 6.25 mg/kg/hr</td>
</tr>
<tr>
<td><strong>NAALF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Loading Dose</td>
<td>140 mg/kg</td>
<td></td>
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<td>Intravenous Loading Dose</td>
<td>150 mg/kg over 60 minutes</td>
<td></td>
</tr>
<tr>
<td>Intravenous Maintenance Dose</td>
<td>12.5 mg/kg/hr for 4 hours, then 6.25 mg/kg/hr for 67 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol-induced liver failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Loading Dose</td>
<td>140 mg/kg</td>
<td></td>
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<td>150 mg/kg over 60 minutes</td>
<td></td>
</tr>
<tr>
<td>Intravenous Maintenance Dose</td>
<td>1) Day 1: 12.5 mg/kg/hr for 4 hours, then 6.25 mg/kg/hr for 16 hours 2) Days 2-5: 4.17 mg/kg/hr for 4 days</td>
<td></td>
</tr>
</tbody>
</table>

A See text for specific recommendations regarding enteral and parenteral administration; enteral is acceptable for any patient who may tolerate it.

B Use actual body weight up to a maximum of 110 kg.

C Use actual body weight up to a maximum of 100 kg.
4. N-acetylcysteine monitoring for recommended indications

4.1. General (IIa, B)

4.1.1. Laboratory

4.1.1.1. Evaluate liver function (AST, ALT, bilirubin, PT/INR), renal function (creatinine, BUN), blood glucose, hemoglobin, hematocrit, and electrolytes prior to initiating N-acetylcysteine and daily during continuation N-acetylcysteine therapy

4.1.2. Physical findings and symptom assessment

4.1.2.1. Mucolytic agent: mucous viscosity, respirations

4.1.2.2. Hepatic indications: encephalopathy grade

4.1.3. Anaphylactoid reaction assessment: assessment for the emergence of rash, hypotension, wheezing, and shortness of breath shortly after intravenous infusion initiation

4.1.3.1. Anaphylactic reactions should be managed with antihistamines and epinephrine, as necessary

UW Health Implementation

Potential Benefits/Harms:
The predominant benefit with guideline implementation will be standardization of can-acetylcysteine use to promote safety and adherence to evidence-based use in managing patients. Additionally, when utilized for acetaminophen overdoses, avoidance of fulminant liver failure, possible liver transplant or death may be avoided.

Implementation Plan

A. The restriction of N-acetylcysteine use to appropriate, evidence-based indications will be operationalized by linking the guideline to the medication orders

B. An N-acetylcysteine order set is available to assist practitioners in ordering N-acetylcysteine for various indications: ED/IP – Acetylcysteine Administration – Adult – Supplemental Order Set [3528]

C. Decentralized clinical pharmacists will be educated about this guideline through pharmacy team meetings.

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
References


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