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

Note: Active Table of Contents – Click each header below to jump to the section of interest

Table of Contents

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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.[1] These mechanisms of action have led to FDA-labeled indications for N-Acetylcysteine as an acetaminophen overdose antidote and as a mucolytic agent.[1]

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. There is evidence to support N-acetylcysteine use for non-acetaminophen-induced acute liver failure (NAI-ALF), alcohol-induced liver failure (AILF), and radiographic contrast agent nephropathy prophylaxis.

Additional off-label uses with insufficient evidence to support N-acetylcysteine use includes prophylaxis of acute renal failure in patients with chronic renal insufficiency undergoing cardiac surgery; acute respiratory distress syndrome; administration of anesthesia for procedures; bezoar; blepharitis; cancer; cystinosis; treatment and prophylaxis of cytotoxicity; drug allergies; drug tolerance to nitrates; prophylaxis of hemorrhagic cystitis; hepatic ischemia-reperfusion injury[2]; hepatorenal syndrome; HIV infection; lamellar ichthyosis; malaria; meconium ileus; prophylaxis of multiple organ failure; mucolysis associated with occlusion of the ureter; otitis media; respiratory tract infection; Sjogren's syndrome; and Unverricht-Lundborg syndrome.

Scope

Intended Users: Physicians, advanced practice providers, pharmacists, and nurses.

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

Target Population:

- Adult and pediatric patients with acetaminophen overdose
- Adult and pediatric patients with non-acetaminophen-induced acute liver failure (NAI-ALF)
- Adult patients with alcohol-induced liver failure (AILF)
- Adult and pediatric patients at risk for contrast induced nephropathy (CIN)

Clinical Questions Considered:

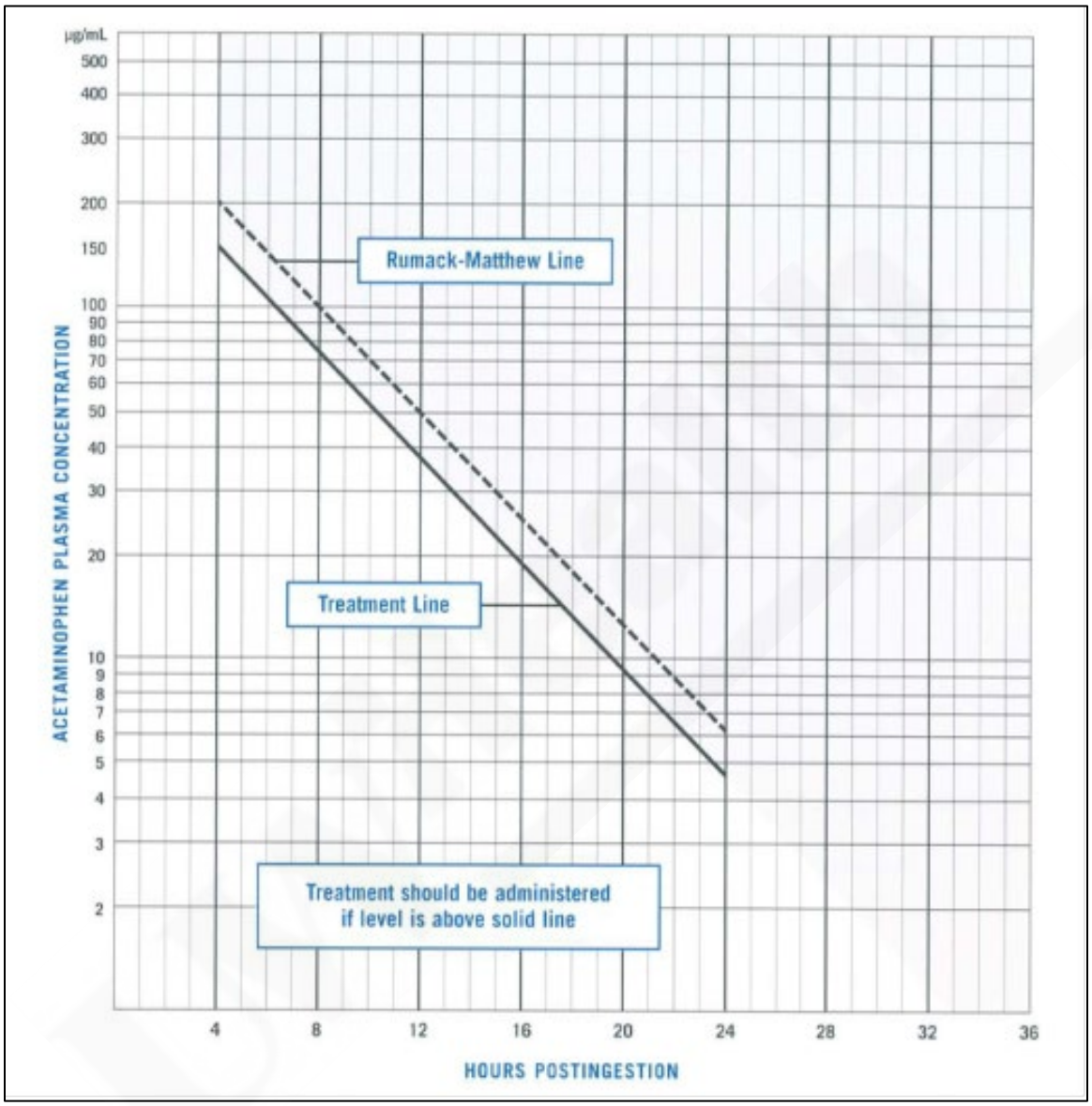
1. What are the indications to support N-acetylcysteine use?
2. What are the dosing regimens of N-acetylcysteine for its indicated disease states?

Definitions

- AILF: Alcohol-induced liver failure
  - also referred to as alcoholic hepatitis[3]
- CIN: contrast induced nephropathy
- LFT: liver function test
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
  - Alkaline phosphatase
  - Bilirubin
- N-acetylcysteine: N-Ac or acetylcysteine
- NAI-ALF: Non-acetaminophen-induced acute liver failure[4,5]
  - includes liver failure etiologies of hepatitis B; other non-acetaminophen, drug-induced hepatotoxicity; and autoimmune hepatitis
  - excludes alcohol-induced liver failure

- Rumack-Matthew Nomogram (Figure 1); used for interpretation of acetaminophen concentrations in association with potential acetaminophen overdose[6,7]

Figure 1. Rumack-Matthew Nomogram



Recommendations

1. **General dosing recommendations**
   - 1.1. It is reasonable to use enteral N-acetylcysteine regimens preferentially over intravenous regimens, unless a patient is unable to tolerate an enteral regimen, as the enteral regimen is equally efficacious and less expensive.[8-11] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)
     - 1.1.1. Enteral N-acetylcysteine provides favorable absorption, delivering antidote directly to the liver[1,8]
     - 1.1.2. Inability to tolerate enteral therapy may include nausea or vomiting despite antiemetic therapy, receiving gastrointestinal decontamination, suspected or confirmed gastrointestinal bleed, possible obstruction, or surgical conditions that preclude enteral administration.
   - 1.2. For the management of acetaminophen overdose, N-acetylcysteine should be dosed on actual weight up to a maximum of 100 kg for IV administration[1] (*UW Health Strong Recommendation, High Quality of Evidence*) and it is reasonable to dose up to a maximum of 110 kg for enteral administration. (*UW Health Conditional Recommendation, Low Quality of Evidence*)
   - 1.3. 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 enteral administration. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)

2. **Confirmed acetaminophen ingestion/overdose management[1,12]**
   - 2.1. N-acetylcysteine should be used in the management of acetaminophen overdose for adults and pediatrics. (*UW Health Strong Recommendation, High Quality of Evidence)*
   - 2.2. In patients with confirmed acetaminophen overdose, no further acetaminophen should be ordered upon admission. (*UW Health Strong Recommendation, Moderate Quality of Evidence*)
   - 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 1). 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.[7] (*UW Health Strong Recommendation, High Quality of Evidence*)
     - 2.3.1. Administration should be initiated within 8 hours of ingestion or as soon as possible after ingestion. (*UW Health Strong Recommendation, High Quality of Evidence)*
     - 2.3.2. If ingestion time is unknown or there have been multiple acetaminophen ingestions, N-acetylcysteine should be administered if there is any evidence to suggest significant acetaminophen overdose and detectable acetaminophen levels or any degree of transaminitis. (*UW Health Strong Recommendation, Low Quality of Evidence*)
     - 2.3.3. 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. (*UW Health Strong Recommendation, High Quality of Evidence*)
   - 2.4. See Table 1 for dosing recommendations.
     - 2.4.1. Enteral N-acetylcysteine dosing is 140 mg/kg load, followed by 70 mg/kg every four hours for 17 doses.[1,8] (*UW Health Strong Recommendation, High Quality of Evidence*)
       - 2.4.1.1. If the patient vomits within one hour of administration, consider readministering dose.[1] (*UW Health Strong Recommendation, Low Quality of Evidence*)
       - 2.4.1.2. To improve palatability, may put N-acetylcysteine over ice[1] or dilute N-acetylcysteine with water or soft drink.[13] (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

2.4.2. IV N-acetylcysteine dosing is 150 mg/kg load over one hour, followed by a continuous infusion at 12.5 mg/kg/hr for 20 hours or more.[8,14] (*UW Health Conditional Recommendation, Low Quality of Evidence*)

2.4.2.1. Multiple dosing regimens for IV N-acetylcysteine have been evaluated, but the above recommendation from the Wisconsin Poison Center (WPC) has been adopted as it decreases adverse effects and medication errors,[8,15-23] while maintaining clinical efficacy in managing acetaminophen toxicity in comparison to other dosing schemes.[14]

2.5. The enteral route is as effective as intravenous.[9,10] Enteral route provides favorable absorption, higher cumulative dosing leading to higher levels in the liver, and less expense.[1,8] Therefore, enteral administration is preferable as it is less invasive and has a lower potential for anaphylaxis than does the intravenous regimen. (*UW Health Strong Recommendation, High Quality of Evidence*)

2.5.1. Shorter courses of enteral 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.[24-27] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

2.6. Therapy duration should be guided by patient condition, resolution of transaminase elevation, and completion of acetaminophen metabolism.[28] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

2.7. Patients should have serial acetaminophen levels and LFTs measured before completion of N-acetylcysteine.[29] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

2.7.1. The first repeat acetaminophen concentration should be drawn four to six hours after the baseline.[12] (*UW Health Conditional Recommendation, Low Quality of Evidence*)

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. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)

2.9. N-acetylcysteine should be continued if acetaminophen levels remain greater than 10 mcg/mL or if the aminotransferases (AST, ALT) remain elevated.[29,30] (*UW Health Conditional Recommendation, High Quality of Evidence*)

2.9.1. Maintenance treatment courses may be extended beyond 17 doses or 20 hours for enteral or intravenous N-acetylcysteine therapy, respectively, if clinically warranted, especially in patients with liver injury.[31] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

2.9.2. Patient status should be reevaluated 12 hours after initiation of continuation of N-acetylcysteine.[29] (*UW Health Conditional Recommendation, High Quality of Evidence*)

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).[28] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

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/L or may be discontinued at the discretion of the provider.[12,26] (*UW Health Conditional Recommendation, Low Quality of Evidence*)

2.10.1. Drawing no further acetaminophen concentrations beyond thirty-six hours may be reasonable.[12,26] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)

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

2.10.3. INR may be considered to evaluate liver injury. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)

3. **Non-acetaminophen-induced acute liver failure (NAI-ALF) management**
   - 3.1. N-acetylcysteine use is reasonable for use in adults for NAI-ALF management.[5,32-34] (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)
   - 3.2. N-acetylcysteine use may be considered in pediatric patients for NAI-ALF management.[33,35,36] (*UW Health Conditional Recommendation, Low Quality of Evidence*)
   - 3.3. See Table 1 for dosing recommendations.[5,37]
     - 3.3.1. Enteral N-acetylcysteine dosing is 140 mg/kg load, followed by 70 mg/kg every four hours for 17 doses. (*UW Health Conditional Recommendation, Moderate Quality of Evidence)*
     - 3.3.2. IV N-acetylcysteine dosing is 150 mg/kg load over one hour, followed by 12.5 mg/kg/hr for four hours, then 6.25 mg/kg/hr for 67 hours. (*UW Health Conditional Recommendation, Moderate Quality of Evidence)*
   - 3.4. N-acetylcysteine treatment discontinuation may be considered if AST has fallen below the threshold of five times the upper limit of normal or may be discontinued at the discretion of the provider. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)

4. **Alcohol-induced liver failure (AILF) management**[38-40]
   - 4.1. N-acetylcysteine may be reasonable for alcohol-induced liver failure management. (*intravenous: UW Health Conditional Recommendation, Moderate Quality of Evidence; enteral: UW Health Conditional Recommendation, Very Low Quality of Evidence*)
     - 4.1.1. Data supporting the use of IV N-acetylcysteine for AILF is not robust, but may provide some benefit when combined with corticosteroids.[38]
     - 4.1.2. N-acetylcysteine in addition to adequate enteral nutritional support[40] or antioxidant demonstrated no survival benefit.[41]
     - 4.1.3. Increased risk of infection may be associated with N-acetylcysteine use alone; however, the combination of N-acetylcysteine and corticosteroids may be associated with decreased risk of infection.[39]
   - 4.2. See Table 1 for dosing recommendations.
     - 4.2.1. Enteral N-acetylcysteine dosing is 140 mg/kg load, followed by 70 mg/kg every four hours for 17 doses. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)
     - 4.2.2. IV N-acetylcysteine dosing is 150 mg/kg load over one hour, followed by 12.5 mg/kg/hr for four hours, then 6.25 mg/kg/hr for 16 hours on day 1. On days 2-5, IV dosing is 4.17 mg/kg/hr. (*UW Health Conditional Recommendation, Moderate Quality of Evidence*)
   - 4.3. N-acetylcysteine discontinuation may be considered at the discretion of the provider or if there is no improvement of total bilirubin at day seven of treatment. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)

5. **Therapeutic use as a mucolytic**[1]
   - 5.1. N-acetylcysteine is recommended as a mucolytic agent. (*UW Health Strong Recommendation, High Quality of Evidence*)
   - 5.2. Nebulize via face mask, mouth piece or into a tracheostomy.
   - 5.3. Use 1 to 10 mL of 20% N-acetylcysteine solution every two 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, NAI-ALF, or AILF[A]

		Adult	Pediatric
Confirmed acetaminophen ingestion or overdose	Enteral Loading Dose[B]	140 mg/kg	140 mg/kg
	Enteral Maintenance Dose[B]	Following loading dose, 70 mg/kg every 4 hours for 17 doses	Following loading dose, 70 mg/kg every 4 hours for 17 doses
	Intravenous Loading Dose[C]	150 mg/kg over 60 minutes	150 mg/kg over 60 minutes
	Intravenous Maintenance Dose[C]	12.5 mg/kg/hr for 20 hours or more	12.5 mg/kg/hr for 20 hours or more
		Adult	
NAI-ALF	Enteral Loading Dose[B]	140 mg/kg	
	Enteral Maintenance Dose[B]	Following loading dose, 70 mg/kg every 4 hours for 17 doses	
	Intravenous Loading Dose[C]	150 mg/kg over 60 minutes	
	Intravenous Maintenance Dose[C]	12.5 mg/kg/hr for 4 hours, then 6.25 mg/kg/hr for 67 hours	
		Adult	
AILF	Enteral Loading Dose[B]	140 mg/kg	
	Enteral Maintenance Dose[B]	Following loading dose, 70 mg/kg every 4 hours for 17 doses	
	Intravenous Loading Dose[C]	150 mg/kg over 60 minutes	
	Intravenous Maintenance Dose[C]	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	

[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

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This 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.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence/Select the Evidence:
The following criteria were used by the guideline authors and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: 2015 to 2018

Search Terms:

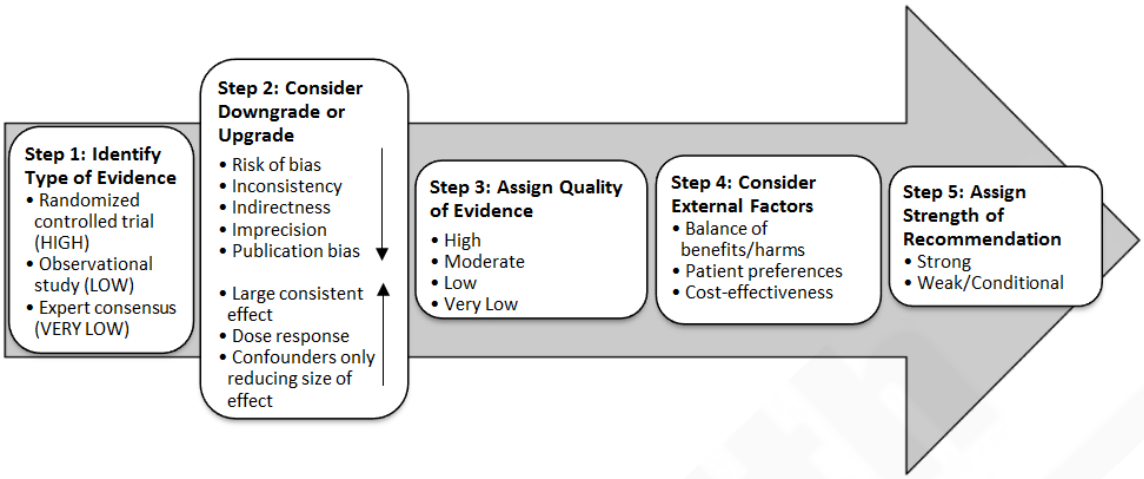
- N-acetylcysteine
- Acetaminophen overdose
- Non-acetaminophen acute liver failure
- Alcohol induced liver failure
- Monitoring

For the first version of this guideline and subsequent 2018 revision, an extensive evidence review was performed through August 2018. 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. Search terms included n-acetylcysteine and treatment, acetaminophen overdose, non-acetaminophen acute liver failure, alcohol-induced liver failure, monitoring, administration, and dosing. References from the articles were also searched. The 2018 revision evaluated new clinical evidence published between 2015 and 2018.

Methods Used to Formulate the Recommendations:
The workgroup members created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 2**).

Figure 2. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong	The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.
Conditional	Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.

Recognition of Potential Health Care Disparities: No health care disparities identified.

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics

Successful management of patients treated with n-acetylcysteine include achievement of undetectable acetaminophen levels, normalization of liver function tests, and incidence of acute liver failure and subsequent transplant.

Order Sets & Smart Sets

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

Clinical Practice Guidelines

UW Health Prevention of Contrast Induced Nephropathy – Adult – Inpatient/Ambulatory – Clinical Practice Guideline

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