

Table 4: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Chiew et al. (2020)¹³	
<p>"A two-bag acetylcysteine regimen slows the initial loading dose and simplifies the protocol (i.e., 200 mg/kg over 4 h followed by 100 mg/kg over 16 h). This is widely used in toxicology units around Australia and has been shown to significantly reduce the rates of adverse reactions."¹³ (p. 176)</p> <p>Evidence supporting this recommendation came from 4 observational studies and 1 conference abstract on the efficacy of 2-bag NAC regimen to treat acetaminophen overdose.</p>	<p>Level of evidence: Low Strength of recommendation: Strong</p>
<p>"Those with an initial paracetamol concentration greater than double the nomogram line may benefit from an increased dose of acetylcysteine. The second bag in the two-bag acetylcysteine regimen should be doubled to 200 mg/kg intravenous acetylcysteine over 16 hours (instead of 100 mg/kg over 16 h). Patients with even higher concentrations (e.g., ≥ triple the nomogram line) may benefit from even higher acetylcysteine doses. These patients should be discussed with a clinical toxicologist or a Poisons Information Centre."¹³ (p. 176)</p> <p>This recommendation was developed based on evidence from a narrative review of acetaminophen and NAC dose and duration and an observational study assessing the effect of increased NAC dose for treatment of massive acetaminophen overdose.</p>	<p>Level of evidence: Low Strength of recommendation: Strong</p>
<p>"Acetylcysteine should be continued if the paracetamol concentration is greater than 10 mg/L (66 µmol/L) or ALT is elevated (> 50 U/L) and increasing (if baseline ALT > 50 U/L)."¹³ (p. 176)</p> <p>Three narrative reviews and 1 observational study provided evidence for this recommendation. The observational study assessed a dose-dependent relationship between plasma acetaminophen concentration and liver injury despite prompt treatment with NAC.</p>	<p>Level of evidence: Low Strength of recommendation: Strong</p>
UW Health (2019)¹⁴	
<p>"N-acetylcysteine should be used in the management of acetaminophen overdose for adults and pediatrics."¹⁴ (p. 5)</p> <p>This recommendation was developed based on evidence from 2 narrative reviews, including an UptoDate review.</p>	<p>Level of evidence: High Strength of recommendation: Strong</p>
<p>"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."¹⁴ (p. 5)</p> <p>Three narrative reviews and 1 observational study on the efficacy of oral NAC vs. IV NAC provided evidence for this recommendation.</p>	<p>Level of evidence: Moderate Strength of recommendation: Conditional</p>

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<p>“For the management of acetaminophen overdose, N-acetylcysteine should be dosed on actual weight up to a maximum of 100 kg for IV administration”¹⁴ (p. 5)</p> <p>This recommendation was developed based on evidence from 1 UptoDate review.</p>	<p>Level of evidence: High</p> <p>Strength of recommendation: Strong</p>
<p>“Administration (of N-acetylcysteine) should be initiated within 8 hours of ingestion or as soon as after ingestion (of acetaminophen).”¹⁴ (p. 5)</p> <p>Two narrative reviews and 1 clinical policy in the management of patients with acetaminophen overdose presenting to the emergency department provided evidence for this recommendation.</p>	<p>Level of evidence: High</p> <p>Strength of recommendation: Strong</p>
<p>“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.”¹⁴ (p. 5)</p> <p>This recommendation was developed based information from 2 narrative reviews and 1 clinical policy in the management of patients with acetaminophen overdose presenting to the emergency department.</p>	<p>Level of evidence: Low</p> <p>Strength of recommendation: Strong</p>
<p>“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.”¹⁴ (p. 6)</p> <p>This recommendation was developed based on evidence from 1 narrative review on NAC dosing recommendations in acetaminophen toxicity and 1 observational study on the effect of increased NAC dose for massive acetaminophen overdose.</p>	<p>Level of evidence: Low</p> <p>Strength of recommendation: Conditional</p>
<p>“N-acetylcysteine treatment discontinuation may be considered when a single acetaminophen concentration is below 10 mcg/mL and AST has decreased to fewer than 1,000 units/L.”¹⁴ (p. 6)</p> <p>Evidence from 1 narrative review and 1 observational study on the duration of NAC therapy for acute acetaminophen overdose provided evidence for the development of this recommendation.</p>	<p>Level of evidence: Moderate</p> <p>Strength of recommendation: Conditional</p>

APAP = N-acetyl-*p*-aminophenol; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GRADE = Grades of Recommendation Assessment, Development and Evaluation; NAC = N-acetylcysteine; UW = university of Wisconsin.