

CADTH Health Technology Review

# Point-of-Care Testing and N-Acetylcysteine for Acute Acetaminophen Overdose

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## Abbreviations

<b>GRADE</b>	Grades of Recommendation Assessment, Development and Evaluation
<b>NAC</b>	N-acetylcysteine
<b>UW</b>	University of Wisconsin

## Key Messages

- Evidence on the clinical utility and cost-effectiveness of point-of-care devices could not be identified.
- Two evidence-based guidelines recommend a 2-bag regimen of N-acetylcysteine, consisting of both a loading dose and maintenance dose, administered by IV for patients with acute acetaminophen overdose.

## Context and Policy Issues

Acetaminophen, also called paracetamol or N-acetyl-p-aminophenol, is a popular drug used to temporarily reduce pain and fever.<sup>1</sup> It is available in different strengths and forms, and for a wide range of populations, from children to elderly people.<sup>1</sup> The maximum amount of acetaminophen allowed per day is 4,000 mg for adults and children aged 12 years and older.<sup>1</sup> Although acetaminophen is safe when used as directed, long-term use and exceeding the maximum recommended daily dose can cause acetaminophen toxicity and liver damage.<sup>1</sup>

Due to the popularity and accessibility of acetaminophen, the risk of acetaminophen overdose, either by accident or on purpose, is relatively common and it is the leading cause of acute liver failure in Canada and around the world.<sup>1</sup> Approximately 4,500 individuals are hospitalized each year in Canada due to acetaminophen overdose, and about 6% of patients hospitalized for acetaminophen overdose develop liver injuries including acute liver failure that may require a liver transplant or lead to death.<sup>1</sup>

The diagnosis of liver toxicity is based on serum levels of acetaminophen and other laboratory tests including liver function tests and a coagulation profile.<sup>2</sup> The Rumack-Matthew nomogram, based on large data of patients not treated with antidote, plots acetaminophen concentration against time of ingestion as a predictor of hepatotoxicity and mortality.<sup>2,3</sup> When the serum concentration of acetaminophen is above the curve at 200 mg/L at 4 hours and 25 mg/L at 16 hours, patients would have 60% incidence of severe hepatotoxicity and 5% rate of mortality.<sup>3</sup> With 300 mg/L serum acetaminophen concentration at 4 hours and 37.5 mg/L at 16 hours, the incidence of severe hepatotoxicity would be up to 90%, and the rate of mortality would be up to 24%.<sup>3</sup> Using this approach, patients with serum acetaminophen concentration greater than 140 mg/L at 4 hours after ingestion are considered having possible risk of hepatotoxicity, and treatment with N-acetyl-cysteine (NAC) is required.<sup>2,3</sup> NAC has been indicated in Canada as an acetaminophen poisoning antidote.<sup>4</sup>

Several analytical methods for determining acetaminophen levels in human serum/plasma have been reported in the literature including high-performance liquid chromatography,<sup>5</sup> UV-visible spectrophotometry,<sup>6</sup> spectrofluorometric,<sup>7</sup> and gas chromatography-mass spectrometry.<sup>8</sup> When a patient is admitted to hospital or emergency department with actual or suspected acetaminophen overdose, blood samples are taken and sent to central laboratory for analysis of acetaminophen levels in the blood, and the diagnosis is delayed while waiting for the laboratory results. Point-of-care tests, also called bed-side tests or near-patient tests, are quick screening tests that could potentially improve the management of these patients. Several point-of-care tests for acetaminophen detection are reported in the literature,<sup>9,10</sup> however, their clinical utility compared with laboratory-based diagnostic tests is unclear.

This report aims to review the clinical utility and cost-effectiveness of point-of-care devices that measure acetaminophen toxicity for patients with suspected overdose. The report also summarizes the recommendations from evidence-based guidelines regarding the administration of IV N-acetylcysteine for patients with acute acetaminophen overdose.

## Research Questions

1. What is the clinical utility of point-of-care devices that measure acetaminophen toxicity for patients with suspected overdose?
2. What is the cost-effectiveness of point-of-care devices that measure acetaminophen toxicity for patients with suspected overdose?
3. What are the evidence-based guidelines regarding the administration of IV N-acetylcysteine for patients with acute acetaminophen overdose?

## Methods

### Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were acetaminophen, overdose, and n-acetylcysteine. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses; randomized controlled trials, controlled clinical trials, or any other type of clinical trial; economic studies; and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and June 15, 2021.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#), they were duplicate publications, or were published before 2016. Guidelines with unclear methodology were also excluded.

## Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument<sup>11</sup> for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 477 citations were identified in the literature search. Following screening of titles and abstracts, 467 citations were excluded and 10 potentially relevant report from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 9 publications were excluded for various reasons, and 2 publications met the inclusion criteria and were included in this report. These were both evidence-based guidelines. [Appendix 1](#) presents the PRISMA<sup>12</sup> flow chart of the study selection. Additional references of potential interest are provided in [Appendix 5](#).

### Summary of Study Characteristics

The detailed characteristics of the included guidelines by Chiew et al. (2020)<sup>13</sup> and the University of Wisconsin (UW) Health (2019)<sup>14</sup> are provided in [Appendix 2 \(Table 2\)](#).

### Study Design

Both included guidelines<sup>13,14</sup> were clinical practice guidelines, which were developed to provide recommendations on the use of NAC for the management of acetaminophen

**Table 1: Selection Criteria**

Criteria	Description
<b>Population</b>	Patients with suspected acute acetaminophen overdose.
<b>Intervention</b>	Q1, Q2: Any point-of-care device to measure acute acetaminophen overdose. Q3: IV NAC for acute acetaminophen overdose.
<b>Comparator</b>	Q1, Q2: Laboratory-based diagnostic tests or any other diagnostic tests that measure acute acetaminophen overdose. Q3: Not applicable.
<b>Outcomes</b>	Q1: Clinical utility (e.g., time to overdose treatment, incidence of overdose-related adverse events, safety, overdose-related mortality). Q2: Cost-effectiveness (e.g., cost-benefit of point-of-care testing vs. usual diagnostic test, costs associated with acetaminophen toxicity treatment, QALYs gained, ICERs). Q3: Recommendations regarding the use of IV NAC for patients with acute acetaminophen overdose.
<b>Study designs</b>	HTA, SR, RCT, non-randomized studies, economic evaluations, and evidence-based guidelines.

HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; NAC = N-acetylcysteine; RCT = randomized controlled trial; SR = systematic review.

overdose. A systematic search of the literature was conducted, and the quality of evidence and the strength of recommendations were assessed and graded using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) in both guidelines. The UW Health guideline<sup>14</sup> rated the level of evidence from high to very low, and the recommendations as either strong or conditional. The wordings are presented in the footnotes of [Table 2](#) in [Appendix 2](#). The guideline by Chiew et al, (2020)<sup>13</sup> did not provide the rating scheme for the strength of the evidence and recommendations. Recommendations in both guidelines were developed by expert panels, and the guidelines were reviewed by external reviewers and were published either on their websites or peer-reviewed journals.

### Country of Origin

The guidelines were conducted by authors from Australia and New Zealand,<sup>13</sup> and the US.<sup>14</sup>

### Patient Population

The target population of both guidelines<sup>13,14</sup> are adult and pediatric patients with acetaminophen overdose. The intended guideline users were health care providers involved in the management of acute acetaminophen overdose.

### Interventions and Comparators

The dosing regimens of NAC for treatment of acetaminophen overdose were considered in both guidelines.<sup>13,14</sup>

### Outcomes

Both guidelines<sup>13,14</sup> considered evidence based on efficacy and safety outcomes of NAC for the treatment of acetaminophen overdose for the development of the recommendations. The clinical efficacy outcomes of NAC included lowering acetaminophen plasma concentration, lowering liver enzyme levels, and therefore preventing liver toxicity.<sup>15</sup> The common adverse events of IV NAC were anaphylactoid reactions, such as rash, pruritus, angioedema, bronchospasm, tachycardia, and hypotension.<sup>15</sup>

## Summary of Critical Appraisal

The detailed quality assessments of the included guidelines<sup>13,14</sup> ([Table 3](#)) are presented in [Appendix 3](#).

Both guidelines<sup>13,14</sup> were explicit in terms of scope and purpose (i.e., objectives, health questions and populations), and had clear presentation (i.e., specific, and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). In terms of stakeholder involvement, both guidelines<sup>13,14</sup> clearly defined target users and the development groups; however, it was unclear if the views and preferences of the patients were sought in the guideline by Chiew et al. (2020).<sup>13</sup> For rigour of development, both guidelines<sup>13,14</sup> reported systematic methods used to search for evidence, criteria for selecting evidence, explicit link between recommendations and the supporting evidence, and methods of formulating the recommendations. Both guidelines<sup>13,14</sup> considered health benefits, side effects, and risks in formulating the recommendations, were peer-reviewed before publication, and provided a procedure for updating. Both guidelines<sup>13,14</sup> used GRADE methodology to assess and grade their recommendations. For clarity, the recommendations in both guidelines<sup>13,14</sup> are specific and unambiguous, provide different options for management of the condition, and are easily identifiable. For applicability, both

guidelines<sup>13,14</sup> were explicit in terms of facilitators and barriers to application (e.g., confirmed acetaminophen ingestion/management in a clinical setting, and seeking advice from a poisons information centre), advice and/or tools on how the recommendations can be put into practice (e.g., acetaminophen management flow charts), and resource implications (e.g., considering costs in recommendations). However, neither guideline<sup>13,14</sup> presented monitoring and or auditing criteria for auditing or monitoring the use of the guideline. For editorial independence, competing interests of guideline development group members were reported, but it was unclear if the views of the funding body have influenced the content of the guidelines. Overall, both included guidelines<sup>13,14</sup> were of good methodological quality.

## Summary of Findings

The summary of guideline recommendations is presented in [Appendix 4 \(Table 4\)](#).

### Clinical Utility of Point-of-Care Devices

No clinical utility studies of point-of-care devices that measure acetaminophen toxicity for patients with suspected overdose were identified; therefore, no summary can be provided.

### Cost-Effectiveness of Point-of-Care Devices

No cost-effectiveness studies of point-of-care devices that measure acetaminophen toxicity for patients with suspected overdose were identified; therefore, no summary can be provided.

## Guidelines

The Australia and New Zealand guideline by Chiew et al. (2020)<sup>13</sup> recommends NAC administered as a 2-bag regimen. Initial loading dose is 200 mg/kg over 4 hours followed by 100 mg/kg over 16 hours; this is a strong recommendation based on low-level evidence. For patients with initial acetaminophen concentration greater than double the nomogram line, the second bag in the 2-bag regimen should be doubled (i.e., 200 mg/kg IV NAC over 16 hours). Patients with initial acetaminophen concentration that is greater than or equal to triple the nomogram line may benefit from higher NAC doses; this is a strong recommendation based on low-level evidence. NAC should be continued if the concentration of acetaminophen is greater than 10 mg/L (66 µmol/L) or alanine transferase is elevated and increasing (> 50 units/L); this is a strong recommendation based on low-level evidence.

The UW Health guideline<sup>14</sup> recommends enteral NAC regimens be preferred over IV regimens because the enteral regimen is equally efficacious and less expensive, unless the patient is unable to tolerate an enteral regimen; this is a strong recommendation based on high-level evidence. For IV administration, the NAC dosing is 150 mg/kg load over 1 hour, followed by a continuous infusion at 12.5 mg/kg/hour for 20 hours or more; this is a conditional recommendation based on low-level evidence. NAC treatment may be discontinued when acetaminophen concentration is below 10 mg/L and aspartate aminotransferase has decreased to less than 1,000 units/L; this is a conditional recommendation based on moderate-level evidence.

## Limitations

This review did not identify any clinical utility studies or economic evaluation studies of point-of-care devices that measure acetaminophen toxicity for patients with suspected overdose, therefore no conclusions can be formed on these research questions. There were no significant methodological limitations of both included guidelines. The recommendations

from the Australia and New Zealand guideline by Chiew et al. (2020)<sup>13</sup> were mostly based on low-level evidence. Both included guidelines were conducted in Australia and New Zealand, and the US, and it is unclear whether the recommendations could be generalized to the Canadian context.

## Conclusions and Implications for Decision- or Policy-Making

This report identified 2 evidence-based guidelines<sup>13,14</sup> regarding the administration of IV NAC for patients with acute acetaminophen overdose. No relevant evidence was identified regarding the clinical utility or cost-effectiveness of point-of-care devices that measure acetaminophen toxicity for patients with suspected overdose.

Both guidelines recommend a 2-bag NAC IV regimen for the management of acetaminophen overdose. The NAC dose and the length of infusion were slightly different between guidelines. For instance, the Australia and New Zealand guideline<sup>13</sup> slows the loading dose of NAC (i.e., 200 mg/kg for 4 hours), while the UW Health guideline<sup>14</sup> recommends a loading dose of 150 mg/kg over 1 hour. For continuous infusion, the guideline by Chiew et al. (2020)<sup>13</sup> recommends 100 mg/kg over 16 hours, while the UW Health guideline<sup>14</sup> recommends 12.5 mg/kg/hour for 20 hours or more. However, conditions for the discontinuation of NAC treatment in both guidelines were similar (i.e., acetaminophen concentration is below 10 mg/L or liver enzyme levels return to normal). For patients with acetaminophen concentration many times higher than the nomogram line, a threshold for acetaminophen toxicity in the Rumack-Matthew graph plotting serum acetaminophen concentration against hours after ingestion, the Australian and New Zealand guideline<sup>13</sup> suggests an even higher doses of continuous infusion of NAC (i.e., 200 mg/kg for 16 hours, instead of 160 mg/kg for 16 hours). The UW Health guideline<sup>14</sup> favours enteral NAC regimen over IV regimen, as the enteral regimen is equally efficacious and less expensive. The recommendations of 1 guideline<sup>13</sup> were based on evidence the authors assessed as low quality, while those in the other guideline<sup>14</sup> were based on a mix of evidence the authors assessed to be low to high quality.

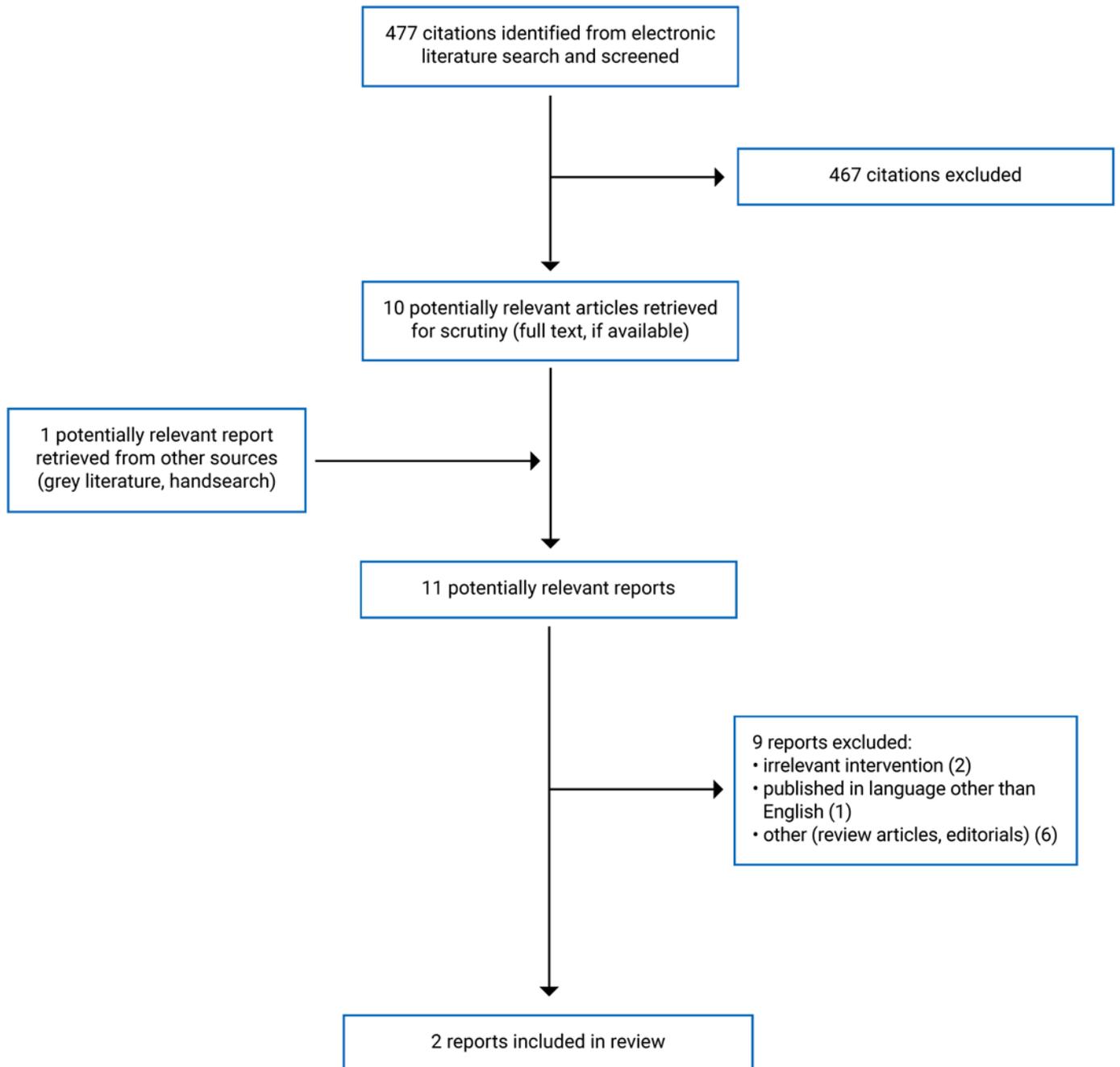
CADTH previously published 2 Rapid Response reports: 1<sup>16</sup> on the clinical effectiveness and cost-effectiveness of point-of-care devices to measure acetaminophen toxicity, and the other<sup>17</sup> on the evidence-based guidelines regarding the administration of IV NAC for patients with acute acetaminophen overdose in the pre-hospital setting. The first report<sup>16</sup> identified 3 clinical studies on point-of-care tests, and no economic evaluations. The second report<sup>17</sup> identified 1 guideline, which recommends NAC treatment for all patients experiencing acetaminophen overdose who were at risk of hepatotoxicity; however, this report did not include the strength of the recommendation, and it did not assess the strengths and limitations of the guideline. None of the previous CADTH reports examined the clinical utility of point-of-care devices that measure acetaminophen toxicity for patients with suspected overdose. Thus, there is a need for future research on the clinical utility and cost-effectiveness of point-of care devices for management of acetaminophen toxicity.

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## Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



## Appendix 2: Characteristics of Included Publications

**Table 2: Characteristics of Included Guidelines**

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
<b>Chiew et al. (2020)<sup>13</sup></b>						
<p><b>Intended users: All health care providers involved in the management of acute acetaminophen overdose.</b></p> <p>Target population: Adult and pediatric patients with acetaminophen overdose.</p>	NAC regimens for the management of acetaminophen poisoning.	Health benefits and side effects of NAC in protecting against acetaminophen toxicity.	The evidence from literature was systematically identified.	The level of evidence and the strength of recommendations were graded using GRADE methodology. The rating scheme for the strength of evidence and recommendations were not reported.	Members of the Treatment of Paracetamol Poisoning Writing group completed a detailed literature review and critically appraised the existing evidence. Drafts of the evidence-based recommendations were developed. The summary recommendations follow the NHMRC guidance <sup>18</sup>	Externally peer reviewed. Published in a peer-reviewed journal.
<b>UW Health (2019)<sup>14</sup></b>						
<p><b>Intended Users: Physicians, advanced practice providers, pharmacists, and nurses</b></p> <p>Target Population: Adult and pediatric patients with acetaminophen overdose, with non-acetaminophen–</p>	NAC for appropriate indication and dosing. Different indications considered in this guideline include acetaminophen overdose, non-acetaminophen-induced acute liver failure, alcohol-induced liver failure, and at risk	Health benefits and side effects of NAC in protecting against acetaminophen toxicity.	The evidence from the literature was systematically identified, including RCT (high quality), observational study (low quality), and expert consensus (very low quality).  Quality of evidence was assigned, and external factors	The level of evidence <sup>a</sup> and the strength of recommendations <sup>b</sup> are graded using GRADE methodology.	The guideline is managed by the centre for Clinical Knowledge Management, which regularly review the content to ensure up-to-date evidence. Clinicians and non-clinicians are involved in the development of the guideline. The recommendations were created via a consensus process.	The guideline was reviewed by external reviewers. Published in UW Health website.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
induced acute liver failure, alcohol-induced liver failure, and at risk for contrast induced nephropathy.	for contrast induced nephropathy.		were considered such as balance of benefits and harms, patient preferences, and cost-effectiveness.			

GRADE = Grades of Recommendation Assessment, Development and Evaluation; NAC = N-acetylcysteine; NHMRC = National Health and Medical Research Council; RCT = randomized controlled trial; UW = university of Wisconsin.

Note: this table has been formatted for accessibility but has not been copy-edited.

<sup>a</sup>Level 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.<sup>14</sup> (p. 11)

<sup>b</sup>Strength of recommendations.

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.<sup>14</sup> (p. 11)

## Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has been formatted for accessibility but has not been copy-edited.

**Table 3: Strengths and Limitations of Guidelines Using AGREE II<sup>11</sup>**

Item	Chiew et al. (2020) <sup>13</sup>	UW Health (2019) <sup>14</sup>
<b>Domain 1: Scope and Purpose</b>		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
<b>Domain 2: Stakeholder Involvement</b>		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Unclear	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes
<b>Domain 3: Rigour of Development</b>		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts before its publication.	Yes	Yes
14. A procedure for updating the guideline is provided.	Yes	Yes
<b>Domain 4: Clarity of Presentation</b>		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes
<b>Domain 5: Applicability</b>		
18. The guideline describes facilitators and barriers to its application.	Yes	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes

Item	Chiew et al. (2020) <sup>13</sup>	UW Health (2019) <sup>14</sup>
20. The potential resource implications of applying the recommendations have been considered.	Yes	Yes
21. The guideline presents monitoring and/or auditing criteria.	No	No
<b>Domain 6: Editorial Independence</b>		
22. The views of the funding body have not influenced the content of the guideline.	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; UW = university of Wisconsin.

## Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix has been formatted for accessibility but has not been copy-edited.

**Table 4: Summary of Recommendations in Included Guidelines**

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<b>Chiew et al. (2020)<sup>13</sup></b>	
<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."<sup>13</sup> (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."<sup>13</sup> (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 (&gt; 50 U/L) and increasing (if baseline ALT &gt; 50 U/L)."<sup>13</sup> (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>
<b>UW Health (2019)<sup>14</sup></b>	
<p>"N-acetylcysteine should be used in the management of acetaminophen overdose for adults and pediatrics."<sup>14</sup> (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."<sup>14</sup> (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>
<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"<sup>14</sup> (p. 5)</p> <p>This recommendation was developed based on evidence from 1 UptoDate review.</p>	<p>Level of evidence: High Strength of recommendation: Strong</p>

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<p><b>“Administration (of N-acetylcysteine) should be initiated within 8 hours of ingestion or as soon as after ingestion (of acetaminophen).”<sup>14</sup> (p. 5)</b></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 Strength of recommendation: Strong</p>
<p><b>“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.”<sup>14</sup> (p. 5)</b></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 Strength of recommendation: Strong</p>
<p><b>“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.”<sup>14</sup> (p. 6)</b></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 Strength of recommendation: Conditional</p>
<p><b>“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.”<sup>14</sup> (p. 6)</b></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 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.

## Appendix 5: References of Potential Interest

### Previous CADTH Reports

1. Point of Care Devices for Assessing Acetaminophen Toxicity. Ottawa (ON): CADTH; 2007: [Microsoft Word - 0246\\_POC for Acetaminophen Toxicity\\_final.doc \(cadth.ca\)](https://www.cadth.ca/media/pdf/htis/Point%20of%20Care%20Devices%20for%20Acetaminophen%20Toxicity.pdf) <https://www.cadth.ca/media/pdf/htis/Point%20of%20Care%20Devices%20for%20Acetaminophen%20Toxicity.pdf>. Accessed 19 Jul 2021.
2. N-Acetylcysteine for Acute Acetaminophen Overdose in the Pre-Hospital Setting: Guidelines. Ottawa (ON): CADTH; 2015: <https://www.cadth.ca/sites/default/files/pdf/htis/june2015/RB0876%20Acetylcysteine%20Infusion%20Final.pdf>. Accessed 19 Jul 2021.

### Additional References

3. BC Emergency Medicine Network. Acetaminophen Overdoses. *Point-of-care emergency clinical summary*. 2020; [https://www.bcemergencynetwork.ca/clinical\\_resource/acetaminophen-overdoses/](https://www.bcemergencynetwork.ca/clinical_resource/acetaminophen-overdoses/). Accessed 19 Jul 2021.