35 y/o F w/ no significant pmhx presents to ED six hours after intentionally ingesting 25 tablets of acetaminophen. Pt is alert, vitals are stable, labs show an elevated acetaminophen level and mildly elevated AST/ALT.

Search question: In adults presenting to ED w/ acute acetaminophen overdose, does IV N-acetylcysteine compared to PO N-acetylcysteine more effectively prevent hepatotoxicity?

Question type: What kind of question is this?

Prevalence
Screening
Diagnosis
Prognosis
Treatment
Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

If systematic review or meta-analysis is not available for comparing IV versus PO N-acetylcysteine in adults with acetaminophen overdose, then RCTs would be the next best level of evidence, as they allow for direct comparison of the two treatment options. If RCTs are not available, then prospective cohort studies that follow patients receiving either IV or PO NAC can still provide useful insights about effectiveness and safety. Retrospective cohort studies wouldn't be as useful in this since they rely on existing records that may be incomplete, inconsistent, or inaccurately recorded, which can increase bias.

PICO search terms:

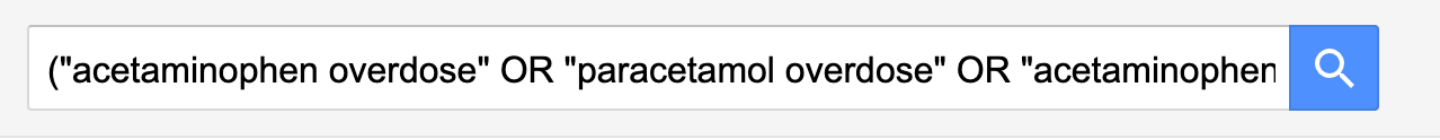
Population	Intervention	Comparison	Outcome
Adult(s)	IV N-acetylcysteine	PO N-acetylcysteine	Hepatotoxicity
ED setting	Intravenous N-acetylcysteine	Oral N-acetylcysteine	Liver injury
Acetaminophen overdose			Liver failure
Paracetamol overdose			Transaminase elevation
Acetaminophen poisoning			Liver disease

Search tools and strategy used: Please indicate what databases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters. Explain how you narrowed your choices to the few selected articles. For example, if your search returned 25 articles among the several databases used, what was the process used to determine which articles to use?

PubMed:

Query	Results
Search: **("acetaminophen overdose" OR "paracetamol overdose" OR "acetaminophen poisoning") AND (adult OR adults) AND ("emergency department" OR ED OR "ED setting") AND ("IV N-acetylcysteine" OR "intravenous N-acetylcysteine") AND ("PO N-acetylcysteine" OR "oral N-acetylcysteine") AND (hepatotoxicity OR "liver injury" OR "liver failure" OR "transaminase elevation" OR "liver disease" OR AST OR ALT OR "alanine aminotransferase" OR "aspartate aminotransferase")** Filters: **from 2011 - 2026**	4

Google Scholar:



About 15 results (**0.08** sec)

For this PICO assignment, I used a total of two databases to find the relevant articles: PubMed and Google Scholar. The initial search for PubMed returned 78 results, which I narrowed down to 4 by limiting the publication date to the last 15 years. Of those 4, I focused only on studies that directly compare IV and PO NAC in adults and were conducted in the US, leaving 2 relevant articles. In Google Scholar, the same keywords initially produced 263 results. By filtering for articles published in the last 6 years and selecting only review articles, I was able to reduce the list down to 15 articles. And from those, I chose the ones that were the most relevant to my PICO question, since some studies didn't include a direct comparison between the two routes and only addressed one route without the other.

1. N-Acetylcysteine for Preventing Acetaminophen-Induced Liver Injury: A Comprehensive Review

Citation: Licata A, Minissale MG, Stankevičiūtė S, Sanabria-Cabrera J, Lucena MI, Andrade RJ, Almasio PL. N-Acetylcysteine for Preventing Acetaminophen-Induced Liver Injury: A Comprehensive Review. Front Pharmacol. 2022 Aug 10; 13:828565.

Article Type: Systemic review

Aims: N-Acetylcysteine (NAC) is used as an antidote in acetaminophen (APAP) overdose to prevent and mitigate drug-induced liver injury (DILI). Our objective was to systematically review evidence of the use of NAC as a therapeutic option for APAP overdose and APAP-related DILI in order to define the optimal treatment schedule and timing to start treatment.

Methods: Bibliographic databases (PubMed, Web of Science, Embase, and MEDLINE) were searched for retrospective and prospective cohort studies, case series, and clinical trials. The prespecified primary outcomes were DILI-related mortality, hepatotoxicity, and adverse events (AEs).

Results: In total, 34 studies of NAC usage in APAP-related DILI cases with 19,580 patients were identified, of which 2,376 patients developed hepatotoxicities. The mortality rate across different studies ranged from 0 to 52%. Large variability of NAC regimens was found, i.e., intravenous (I.V.) (100–150 mg/kg) and oral (70–140 mg/kg), and length of treatment varied—12, 24, or 48 h for I.V. regimen and 72 h for oral administration. The timing of initiation of NAC treatment showed different results in terms of occurrence of hepatotoxicity and mortality; if started within 8 h and no more than 24 h from APAP overdose, either intravenously or orally, NAC administration was efficacious in terms of mortality. The most frequent AEs reported were anaphylactic reactions, followed by cutaneous AEs for the IV route and intestinal AEs for the oral one.

Conclusion: NAC improves hepatotoxicity and reduces mortality. Timing of treatment, ranging from 8 to 24 h from APAP overdose, regardless of the regimen or route of administration, is important to prevent or minimize liver damage, particularly in children and in elderly and obese patients.

Key points:

- Starting NAC within 8 h and no later than 24 h after ingestion was linked with better outcomes (less hepatotoxicity and improved survival) regardless of whether NAC was given IV or orally.
- Both IV and oral NAC were effective when given in an appropriate time window
    - The review does not show a clear superiority of one route over the other for preventing liver injury.
- IV NAC was more commonly associated with anaphylactic reactions and infusion-related effects, while oral NAC more often caused intestinal symptoms.

I decided to choose this article because, firstly, it is a recent (2022) systemic review that provides a comprehensive analysis of both IV and PO N-acetylcysteine regimens in adults w/ acetaminophen overdose. Secondly, it focuses on clinically important outcomes like liver injury and mortality, which directly relate to my PICO question. Overall, what this article suggests is that both routes are effective at treating acetaminophen overdose and at preventing hepatotoxicity when given promptly, with timing of administration being more critical than the route itself.

2. Oral and Intravenous Acetylcysteine for Treatment of Acetaminophen Toxicity: A Systematic Review and Meta-analysis

Citation: Green JL, Heard KJ, Reynolds KM, Albert D. Oral and Intravenous Acetylcysteine for Treatment of Acetaminophen Toxicity: A Systematic Review and Meta-analysis. West J Emerg Med. 2013 May;14(3):218-26.

Article Type: Systemic Review and Meta-analysis

Introduction: There are few reports summarizing the effectiveness of oral and intravenous (IV) acetylcysteine. We determined the proportion of acetaminophen poisoned patients who develop hepatotoxicity (serum transaminase > 1000 IU/L) when treated with oral and IV acetylcysteine.

Methods: Studies were double abstracted by trained researchers. We determined the proportions of patients who developed hepatotoxicity for each route using a random effects model. Studies were further stratified by early and late treatment.

Results: We screened 4,416 abstracts; 16 articles, including 5,164 patients, were included in the meta-analysis. The overall rate of hepatotoxicity for the oral and IV routes were 12.6% and 13.2%, respectively. Treatment delays are associated with a higher rate of hepatotoxicity.

Conclusion: Studies report similar rates of hepatotoxicity for oral and IV acetylcysteine, but direct comparisons are lacking. While it is difficult to disentangle the effects of dose and duration from route, our findings suggest that the rates of hepatotoxicity are similar for oral and IV administration.

Key points:

- Overall rates of hepatotoxicity (defined as serum transaminase >1000 IU/L) were similar between the two routes, with a rate of 12.6% for PO and 13.2% for IV
- Timing of treatment initiation is a far more significant factor in preventing liver injury than route of administration
- Patients who received early therapy (within 10 hours) had a hepatotoxicity rate of 5.7%, whereas those who received late therapy saw the rate jump to 26%
- PO NAC is associated with higher rates of nausea and vomiting, while IV NAC is associated with a higher frequency of anaphylactoid reactions

This article essentially echoes what was already noted in the previous review: both PO and IV N-acetylcysteine are similarly effective at preventing hepatotoxicity in adults with acetaminophen overdose, provided that treatment is initiated promptly. While minor differences exist in side effect profiles (PO more often causes N/V and IV may trigger anaphylactoid reaction), serious adverse events are rare so both options are safe to use. Overall, the choice of route is guided by patient factors and clinical practicality rather than clear superiority of one method over the other.

3. A Multi-center Comparison of the Safety of Oral versus Intravenous Acetylcysteine for Treatment of Acetaminophen Overdose

Citation: Bebarta VS, Kao L, Froberg B, Clark RF, Lavonas E, Qi M, Delgado J, McDonagh J, Arnold T, Odujebe O, O'Malley G, Lares C, Aguilera E, Dart R, Heard K, Stanford C, Kokko J, Bogdan G, Mendoza C, Mlynarchek S, Rhyee S, Hoppe J, Haur W, Tan HH, Tran NN, Varney S, Zosel A, Buchanan J, Al-Helial M. A multicenter comparison of the safety of oral versus intravenous acetylcysteine for treatment of acetaminophen overdose. Clin Toxicol (Phila).

Article Type: Observational study

Oral and intravenous (IV) acetylcysteine are used for treatment of acetaminophen poisoning. The objective of this multi-center study was to compare the safety of these two routes of administration.

METHODS

We conducted a multi-center chart review of all patients treated with acetylcysteine for acetaminophen poisoning. The primary safety outcome was the percentage of patients with of acetylcysteine-related adverse events.

RESULTS

A total of 503 subjects were included in the safety analysis (306 IV only, 145 oral only and 52 both routes).There were no serious adverse events related to acetylcysteine for either route. Nausea and vomiting were the most common related adverse events and were more common with oral treatment (23% vs 9%). Anaphylactoid reactions were more common with IV administration (6% vs 2%).

Conclusions

Intravenous and oral acetylcysteine are both associated with minimal side effects and are safe for treatment of acetaminophen toxicity.

Key points:

- For patients who present <10 hours post-ingestion, the estimated total cost of care with PO NAC is $5817, compared to $3765 for IV NAC.
- Difference in cost is largely driven by the longer duration of PO NAC regimen (72 hours) vs the shorter IV course (21 hours).

While this article may not be the highest level of evidence, it mentions an important point not discussed in the other two articles: the relative cost difference between PO and IV NAC. To summarize, administration of IV NAC is less expensive than PO NAC because of the shorter 21-hour treatment course compared to the 72-hour oral regimen. This shorter course ultimately reduces hospital stay and associated resource use. Since both routes are similar in effectiveness and safety, cost becomes an important factor to consider when deciding which route to use in clinical practice.

What is the clinical "bottom line" derived from these articles in answer to your question?

Acetaminophen is among one of the most commonly used over-the-counter medications worldwide and a leading cause of acute liver injury when overdosed. This makes timely recognition and effective treatment in the ED critical. There are currently two options available for treatment: PO and IV N-acetylcysteine. But the question remains which route is more effective and safer? Well, studies have shown that both PO and IV NAC are similarly effective at presenting hepatotoxicity when administered promptly (within 8-24 hours after ingestion), with minor differences in side effect profiles. PO NAC is more likely to cause nausea and vomiting, while IV NAC may trigger anaphylactoid reactions. Furthermore, in terms of cost, IV NAC is generally less expensive than PO NAC due to a shorter treatment course. With all these factors taken into account, the choice between PO and IV NAC should be tailored towards the patient. Are they able to tolerate PO? Do they have any accessible veins for IV administration? Is the patient likely to complete the full PO course?