ACMT | American College of Medical Toxicology

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# ACMT Practice Statement: Duration of Intravenous Acetylcysteine Therapy following Acetaminophen Overdose (2026 update)

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The position of the American College of Medical Toxicology (ACMT) is as follows:

Acetylcysteine (N-acetylcysteine, NAC) is indicated for the treatment of potentially toxic acetaminophen (APAP) ingestion in oral and intravenous (IV) formulations. The FDA approved a 72-h oral NAC regimen in 1985. However, evidence supports using shorter oral NAC courses if liver enzymes and synthetic function are normal or improving, and plasma APAP concentration is undetectable [1,2]. Intravenous NAC (Acetadote®, Cumberland Pharmaceuticals) was approved by the FDA in 2004 and is indicated to prevent or mitigate hepatic injury after potentially toxic APAP ingestion.

In 2016, ACMT published a position statement to address appropriate duration of NAC therapy for APAP hepatotoxicity [3]. This practice statement updates our previous document.

The prescribing information for IV NAC recommends administering the drug within 8 h of APAP ingestion for maximal efficacy, and to administer as soon as possible for patients who present later than 8 h [4]. The NAC treatment regimen described in the prescribing information was developed in the UK in the 1970s and delivers NAC 300 mg/kg, with half given as a loading dose, and the remainder infused over 20 h. The primary mechanism of action involves enhanced detoxification of N-acetyl-p-benzoquinone imine, a hepatotoxic APAP metabolite. Later investigations demonstrated improved mortality in APAP-induced liver failure, presumably via other mechanisms, even when IV NAC was administered after APAP had been eliminated from the blood [5,6].

Since approval of IV NAC in the USA, several reported cases have documented rising hepatic aminotransferase concentrations or persistent serum APAP concentrations despite 21 h of treatment [7–9]. With a short elimination half-life after therapeutic dosing, APAP is typically eliminated within 21 h after an acute overdose. However, hepatic injury can slow acetaminophen metabolism and prolong its apparent half-life [10]. In addition, altered absorption following massive ingestion [7] or coingestants that slow gastrointestinal motility [9] can result in persistently elevated acetaminophen concentrations.

In APAP poisoning, elevations in aminotransferases (AST or ALT equal or greater than 1000 U/L) precede laboratory markers of hepatic dysfunction. Many predictors of poor prognosis have been described in APAP poisoning. In practice, decreased pH, increased phosphate, increased

lactate, increases in prothrombin time/INR, and increases in serum creatinine are the most readily available predictors of poor prognosis [8,11,12]. Treatment with 21 h of IV NAC is highly effective at preventing hepatotoxicity in most patients following acute APAP overdose and in reducing mortality in those with established hepatotoxicity [13]. However, continuing NAC past 21 hours is essential in some circumstances and it is vitally important to evaluate evidence of hepatic injury (AST or ALT elevation), hepatic failure (INR, mental status), and unmetabolized APAP prior to stopping any NAC protocol.

Shorter protocols have been used successfully in selected low-risk patients under clinical investigation [14–16] but are not evaluated here. The use of double and triple dose of NAC may be appropriate after massive APAP overdose [17,18]. In such cases, authors have recommended increasing the dose of the final NAC infusion in proportion to the APAP ingestion or APAP concentration [17]. The infusion rate should also be increased if hemodialysis is concurrently being performed [19].

The administration of an additional NAC bolus or extending the duration of the 6.25 mg/kg/h infusion (the final infusion rate in the FDA-approved protocol) may be appropriate in certain clinical scenarios [20–23]. Treatment beyond 21 h is indicated when patients have evidence of hepatotoxicity evidenced by elevations in aminotransferases, abnormalities in predictors of poor prognosis, or persistent APAP detected by laboratory testing. Laboratories use different reporting limits for APAP concentrations. Although the scientific literature does not establish one APAP reporting cutoff to be superior to another, we recommend using a cutoff of <10mcg/mL for alignment with other authors [19].

The presence of rising liver aminotransferases, markers of poor prognosis, or persistent acetaminophen concentrations should prompt continued IV NAC administration.

The American College of Medical Toxicology (ACMT) strongly recommends all the following criteria be present for discontinuation of IV NAC [19]:

- Undetectable acetaminophen concentration (<10 µg/mL).
- Improving hepatic aminotransferases, defined as ALT/AST at baseline for patient or if elevated, have decreased from peak (25%-50%).
- INR < 2.0.
- Improving prognostic markers (e.g., creatinine, lactate, pH, phosphate).

ACMT supports the principle of individualizing therapy, guided by patients' clinical condition, in consultation with a medical toxicologist or other expert. This includes the following: 1-bag, 2-bag, or 3-bag NAC protocols, high dose NAC regiments, hemodialysis clinical indications,

4-methylpyrazole (fomepizole) administration, and consultation with liver transplant team as indicated [19].

The development of hepatotoxicity or liver failure despite IV NAC therapy should prompt evaluation and monitoring of acid–base status, coagulation parameters, renal function, and level of consciousness. Consider consultation with a medical toxicologist, a regional poison center, and/or individual or institution with expertise in managing patients with severely compromised hepatic function.

**Disclaimer**

While individual practitioners may differ, these are the positions of the American Academy of Clinical Toxicology (AACT) and the American College of Medical Toxicology (ACMT) at the time written, after a review of the issue and pertinent literature.

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**Reference**

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