

# POISON PEARLS



## Toxicology Topics for the Healthcare Team of a Poisoned Patient

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# 2-Bag vs 3-Bag N-Acetylcysteine

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### Background

N-acetylcysteine (NAC) remains a mainstay antidote for acetaminophen-induced hepatotoxicity since an oral 72-hour regimen was approved by the U.S. Food and Drug Administration (FDA) in 1985. In 2004, the FDA approved an intravenous (IV) formulation administered in a three-bag protocol totaling 300 mg/kg over 21 hours: 150 mg/kg over 15 minutes, 50 mg/kg over 4 hours, and 100 mg/kg over 16 hours. The initial rapid infusion of 150 mg/kg over 15 minutes was frequently associated with rate-dependent, non-IgE-mediated anaphylactoid reactions, also called non-allergic anaphylactic reactions (NAARs). Subsequent post marketing surveillance and clinical data suggested that prolonging the duration of the initial infusion decreased the incidence of adverse effects. Accordingly, in 2011, the FDA recommended extending the duration of the first infusion from 15 minutes to one hour. Despite this modification, the complexity of preparing and administering three separate infusion bags continued to pose challenges for clinical staff, contributing to medication errors. Additionally, anaphylactoid reactions remained a concern.

### Two-Bag Regimen Development

A 2016 prospective observational study ([Isbister et al., 2016](#)) compared the traditional 3-bag NAC to a simplified 2-bag regimen. The revised dosing combined the 1st and 2nd bag into a single infusion of 200 mg/kg over 4 hours, followed by a maintenance dose of 100mg/kg over 16 hours, maintaining the same total cumulative dose of 300 mg/kg over 20 hours. The study demonstrated a lower incidence of adverse reactions with the 2-bag dosing regimen. Subsequent studies supported these findings ([McNulty et al., 2018](#); [Schmidt et al., 2018](#); [Pettie et al., 2019](#)). Wong et al. (2020) determined that the two-bag N-acetylcysteine regimen was non-inferior to the three-bag regimen with regards to efficacy in preventing acute liver injury for early presentations of acetaminophen overdose. These studies endorse the 2-bag regimen as a safe and effective alternative to the conventional 3-bag approach.

### Guideline Updates and Consensus Statements

A consensus statement was published in 2023 on behalf of four North American toxicology societies, synthesizing data from 84 acetaminophen treatment guidelines and 278 publications ([Dart et al., 2023](#)). The consensus recommended a minimum of 300 mg/kg of NAC (administered orally or intravenously) within the first 20-24 hours of treatment. However, no specific NAC regimen was endorsed as superior. In 2025, a comprehensive systematic review and meta-analysis with more than 7600 patients compared the 3-bag and 2-bag NAC regimens, concluding that there was no statistically significant difference in the relative risk of hepatotoxicity between the two regimens. However, the 2-bag regimen was associated with a significantly reduced incidence of NAARs and gastrointestinal adverse effects ([Nakatsu et al., 2025](#)).

### Critical Operational Steps for Transition from 3-Bag to 2-Bag NAC Regimen

#### Stakeholder Engagement:

- Involve key departments such as Pharmacy and Therapeutics Committee, pharmacy, emergency medicine, internal medicine, critical care, pediatrics, informatics, nursing and hepatology
- For tertiary or quaternary hospitals, ensure a clear plan with patients transferred in with 3-bag regimen and how to transition to a 2-bag regimen
- Clear communication strategy for roll out with education for involved departments about rationale, dosing, and administration for the new protocol

#### Informatics Updates:

- Update EMR build with standardized order set for the 2-bag protocol to ensure prescribing consistency and reduce medication errors
- Infusion pumps must be reprogrammed to support the revised dosing and timing of the 2-bag regimen, which should be verified by pharmacy and nursing teams

**2-Bag IV NAC**  
Total dose: 300 mg / kg over 20 hours  
200 mg / kg over 4 hours  
100 mg / kg over 16 hours

**3-Bag IV NAC**  
Total dose: 300 mg / kg over 21 hours  
150 mg / kg over 1 hour  
50 mg / kg over 4 hours  
100 mg / kg over 16 hours

### Clinical Recommendation

- In 2024, the 2-bag IV NAC regimen was approved by the US FDA and added to the NAC package insert
- It is frequently recommended by regional poison control centers and numerous institutions
- Specifically, both the Cincinnati Drug and Poison Information Center and the Central Ohio Poison Center endorse the 2-bag regimen, consisting of 200 mg/kg over 4 hours followed by 100 mg/kg over 16 hours
- Dose and duration modifications may be appropriate for select patient populations, particularly in cases involving high risk acetaminophen overdose

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