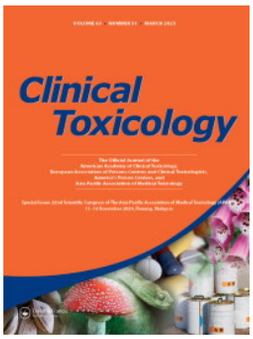

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REVIEW

Comparison of two-bag and three-bag acetylcysteine regimens in the treatment of paracetamol poisoning: a systematic review and meta-analysis

Larissa Nakatsu[a], Josh R. Lopez[b], Christian Mateo Garcia[a], Mathew Cherian[c], Jacob Nash[d], Davood Tofighi[e], Steven A. Seifert[a,f*], Susan Smolinske[f] and Brandon J. Warrick[a]

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ABSTRACT

Introduction: Worldwide, paracetamol poisoning is a common cause of acute liver failure and referral to transplant centers. Acetylcysteine has long been the mainstay of treatment, but recent literature suggests that a simplification of the "three-bag" method may decrease adverse effects. Our primary hypothesis is that a simplified dosing regimen (two-bag regimen) is non-inferior to the three-bag method in preventing liver injury. Our secondary hypothesis is that a simplified regimen will have lower rates of adverse effects.

Methods: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we searched Medline/PubMed, Google, Google Scholar, Cochrane Library, Embase and Toxnet on May 23, 2022. The Medical Subject Headings terms were NAC, acetaminophen toxicity, acetyl-cysteine, N-acetylcysteine, paracetamol, APAP, 2-bag, and 3-bag. The Embase terms were acetylcysteine, NAC, 2-bag, two bag, 3-bag, three bag, simplified dosing, acetaminophen, Tylenol®, paracetamol, APAP, drug overdose, poisoning, and overdose. Studies included both non-United States Food and Drug Administration-approved and United States Food and Drug Administration-approved acetylcysteine regimens. Case reports, review articles, and animal studies were excluded. Two authors independently reviewed each study using Rayyan QCRI to determine if the studies met search criteria while blinded to the selections of each other. The two authors discussed until reaching a consensus. We used a primary outcome of non-inferiority of hepatotoxicity. We used secondary outcomes of non-allergic anaphylactoid reactions and adverse events. We conducted a fixed-effect meta-analysis using R package meta. To visually summarize the meta-analysis results, we also produced forest plots. We used Cochran's Q test and I^2 statistical analysis to assess heterogeneity between the studies.

Results: Our search resulted in 657 total citations, which were reduced to unique citations. Of the 643 studies, 46 met the criteria for full text review, and eight met the study criteria. Of the eight studies investigating a simplified acetylcysteine regimen, four studies utilized some form of a modified two-bag infusion regimen, varying in duration or dosing of infusions, and four studies shared the same "common" two-bag treatment, a regimen that delivers acetylcysteine 200 mg/kg over 4 h, followed by 100 mg/kg acetylcysteine over 16 h. The six studies comparing a two-bag dosing regimen to the three-bag technique were utilized for our random effect model meta-analysis. We found no significant heterogeneity amongst the six studies for either hepatotoxicity ($Q(5) = 1.11$; $P=0.95$; $I^2 = 0\%$; 95% CI: 0%-74.6%) or non-allergic anaphylactoid reactions and adverse events ($Q(5) = 10.15$; $P=0.07$; $I^2 = 50.7\%$; 95% CI: 0%-80.4%). Compared to the traditional three-bag dosing regimen, the two-bag method did not demonstrate a difference in relative risk for hepatotoxicity (OR: 0.88; 95% CI: 0.72–1.08; $P=0.23$) but did demonstrate a significantly decreased likelihood of non-allergic anaphylactoid reactions and other adverse events (OR: 0.24; 95% CI: 0.17–0.35; $P<0.0001$).

Discussion: The two-bag method is a safe and effective treatment for acute paracetamol poisoning. The two-bag regimen is correlated with a significant reduction in non-allergic anaphylactoid reactions, compared to the three-bag method, and is non-inferior with respect to hepatotoxicity. While we feel this information is practice changing for many, further research in the form of a randomized control trial would be beneficial to compare even more abbreviated methods such as a "single bag method."

Conclusion: Two-bag acetylcysteine dosing regimens appear to be non-inferior to the three-bag method with respect to hepatotoxicity, and result in fewer anaphylactoid, cutaneous, and gastrointestinal reactions.

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Introduction

Worldwide, paracetamol poisoning is a common cause of acute liver failure and referral to transplant centers [1]. Acetylcysteine has been the mainstay of treatment to prevent and treat hepatotoxicity for decades [2]. In 1977, Prescott et al. [3] proposed a three-bag intravenous 20.25 h regimen to treat paracetamol poisoning; this regimen was subsequently modified in 2011 in the United Kingdom (UK) to a three-bag regimen over 21 h [4,5]. Both regimens administered a total dose of 300 mg/kg. The three bag 20.25 h/21 h intravenous regimens were widely adopted in Canada, Australia, and the United States [6,7]. Recently, several researchers from around the globe have tailored the duration of acetylcysteine to individual patients [8,9].

The three-bag intravenous acetylcysteine regimen involves the administration of acetylcysteine 150 mg/kg over 15 min to 60 min, 50 mg/kg over 4 h, and then 100 mg/kg over 16 h. Administration and medication errors range from 33–84%, depending on the country and region [10,11]. Recent literature has shown fewer non-allergic anaphylactoid reactions when simplified (two-bag) dosing regimens are used [9,11–14]. One study also showed reduced rates of medication and dosing errors [14].

Several two-bag acetylcysteine protocols exist. The most common version, among the studies included in this paper, delivers acetylcysteine 200 mg/kg over 4 h, followed by 100 mg/kg acetylcysteine over 16 h. We refer to this as the "common" two-bag dosing regimen. However, even further modified two-bag methods are now being studied. Although the "common" two-bag method has been formally adopted in a number of countries, the clinical practice guidelines for the US and Canada (published in August 2023 with representation from America's Poison Centers®, the American Academy of Clinical Toxicology, the American College of Medical Toxicology, and the Canadian Association of Poison Centers and Clinical Toxicology) do not recommend a specific acetylcysteine regimen, citing a lack of data on comparative effectiveness [15,16].

Our meta-analysis aims to compare the outcome frequencies of hepatotoxicity and adverse effects for the three-bag method and newer two-bag methods. We hypothesized that a simplified two-bag regimen is non-inferior to the three-bag method with respect to hepatotoxicity. Secondarily, we hypothesized that the simplified regimen has lower rates of adverse effects.

Methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, we performed a systematic review followed by a meta-analysis comparing two-bag acetylcysteine dosing to the three-bag acetylcysteine regimen. We utilized the Patient/Intervention/Comparison/Outcome (PICO) search strategy as follows. We were interested in humans who presented to the hospital with suspected or confirmed paracetamol poisoning and were treated with acetylcysteine therapy. Both acute and chronic poisoning were considered. We aimed to compare two-bag intravenous acetylcysteine dosing protocols (including the most common two-bag protocol as well as further modified two-bag protocols) to the three-bag protocol. Study outcomes were rates of hepatotoxicity and adverse events. We excluded articles without data on two-bag or three-bag methods or lacking data on adverse reactions. Case reports, review articles, and animal studies were also excluded. For articles other than English, we planned to obtain a translated version before excluding them from consideration. We had readily available translations for Spanish, French, Russian, Hindi, Indonesian, Malaysian, and German.

On May 23, 2022, we conducted a literature search for articles published in the last 14 years. The Medical Subject Headings terms were "NAC", "acetaminophen toxicity", "acetyl-cysteine", "N-acetylcysteine", "paracetamol", "APAP", "2-bag", and "3-bag". The Embase terms were "acetylcysteine", "NAC", "2-bag", "two bag", "3-bag", "three bag", "simplified dosing", "acetaminophen", "Tylenol®", "paracetamol", "APAP", "drug overdose", "poisoning", and "overdose". We searched Medline/PubMed, Google, Google Scholar, Cochrane Library, Embase and ToxNet. Dates included in the search were from September 1, 2008 to May 23, 2022. We selected this timeframe for timely relevance based on guidance from the contributing informatics researchers.

Two independent reviewers screened all citations for study eligibility. We utilized Rayyan software to blind both reviewers while working through the list. Disagreements were discussed until the two authors reached an agreement. Following screening, full manuscripts were obtained and underwent the same blinded review process. Again, disagreements were discussed until the two authors reached consensus.

For studies meeting inclusion criteria, we extracted data including study design, acetylcysteine dosing protocol, sample size, sex, age, alanine aminotransferase activity, aspartate aminotransferase activity, and adverse reactions. We defined the primary outcome, hepatotoxicity, as alanine aminotransferase activity >1,000 IU/L. The secondary outcomes were the presence of an adverse reaction, defined as hypotension, shortness of breath, angioedema, non-allergic anaphylactoid reaction, skin reactions (including rash, urticaria, wheals, flushing, and pruritus), gastrointestinal tract reactions (including nausea and vomiting, whether reflecting paracetamol toxicity or adverse reaction to acetylcysteine), and any other reports from authors.

We conducted a random-effects meta-analysis of the effect of two-bag versus three-bag treatment on hepatotoxicity, non-allergic anaphylactoid reactions, and other adverse reactions. We used the R package meta to conduct a random-effects meta-analysis [17]. Random-effects meta-analyses are recommended in medical decision-making contexts [18–20]. The software first computes the log odds ratio and its variance for individual studies. The summary log odds ratio is then computed as a weighted average of the log odds ratios, in which weights are the inverse of the estimated variances [21]. To visually summarize the meta-analysis results, we also produced forest plots. We used the Cochran Q test and I^2 statistics to test heterogeneity between the studies [22–24].

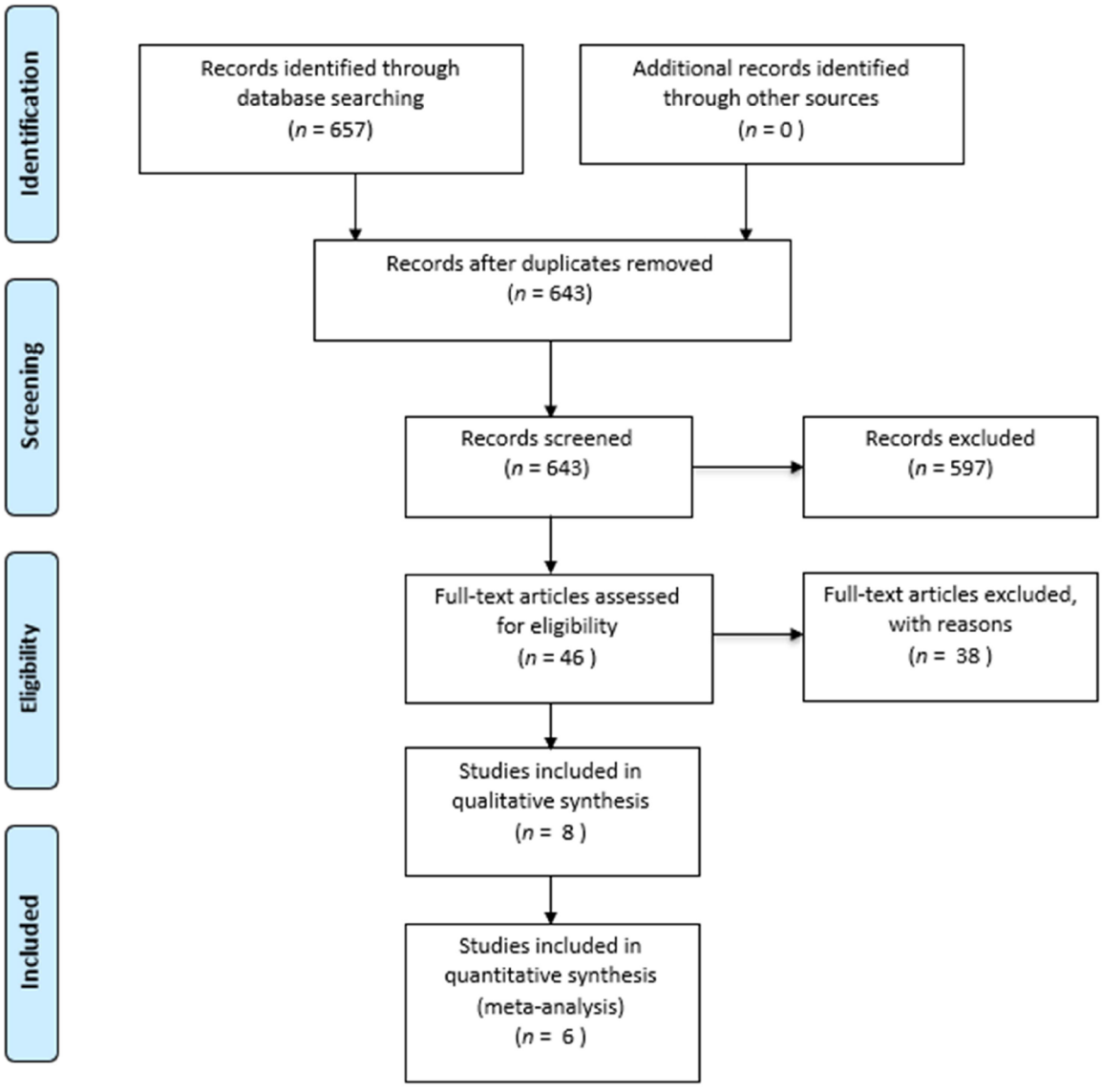

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

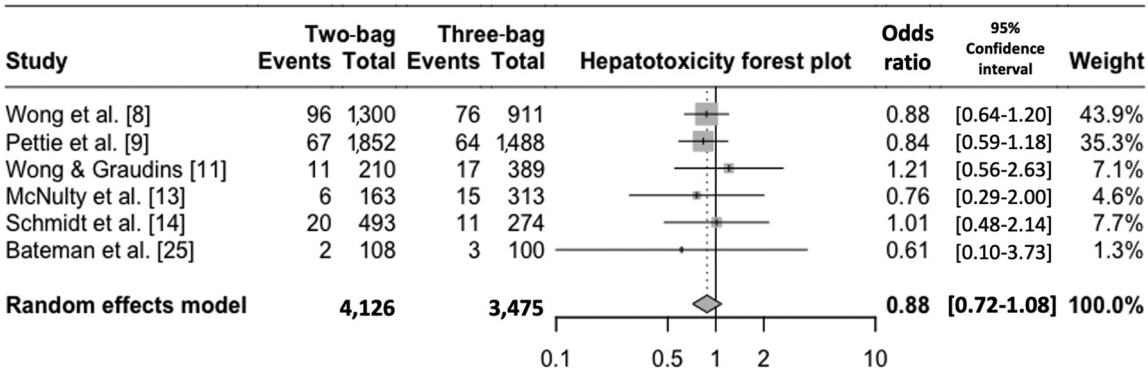

Figure 2. There was no significant heterogeneity found amongst the six studies included in the meta-analysis for hepatotoxicity (Q(5):1.11; $P = 0.95$; I^2=0%; 95% CI: 0–74.6%). compared to the traditional three-bag dosing regimen, the two-bag method did not demonstrate a difference in relative risk for hepatotoxicity (OR: 0.88; 95% CI: 0.72–1.08; $P = 0.23$).

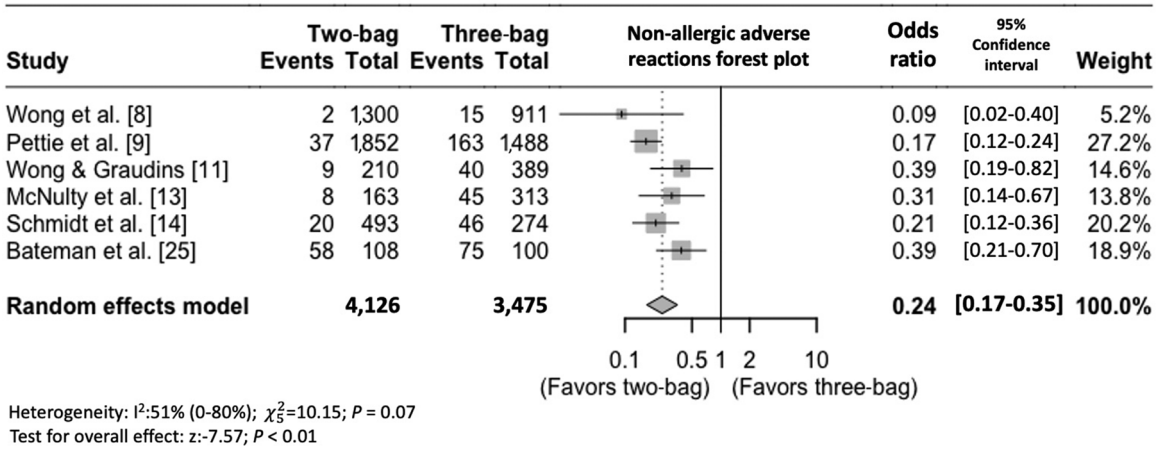

Figure 3. There was no significant heterogeneity found amongst the six studies for non-allergic anaphylactoid reactions and adverse events (Q(5): 10.15; $P=0.07$; $I^2 = 50.7\%$; 95% CI: 0–80.4%). compared to the traditional three-bag dosing regimen, the two-bag method significantly demonstrated a decreased likelihood of non-allergic anaphylactoid reactions and other adverse events (OR: 0.24; 95% CI: 0.17–0.35; $P<0.0001$).

Results

We identified 657 articles using the Medical Subject Headings (MeSH) and Embase terms above, which were reduced to 643 after deduplication. All studies were in English, and translation was not required. We identified 46 articles for a full text review based on the above-mentioned screening criteria. Of the 46 articles, four were excluded as review articles or treatment guidelines, 19 were excluded because they pertained only to oral acetylcysteine, 11 were excluded because they did not include data on adverse events or focused only on dosing errors or treatment delay, and four articles were excluded for reporting data only in non-human populations (Figure 1). The resulting eight studies were utilized for subsequent review and meta-analysis.

Of the eight studies, Pettie et al. [9], Wong and Graudins [11], Wong et al. [12], McNulty et al. [13], Schmidt et al. [14], and Bateman et al. [25] were highly similar in their comparison of two- and three-bag regimens and focus on hepatotoxicity and non-allergic anaphylactoid reactions. These studies are outlined in Table 1. The studies all compared the similar three-bag regimens (150 mg/kg for 0.25–1 h, followed by 50 mg/kg for 4 h and 100 mg/kg for 16 h) to a two-bag method. Wong and Graudins [11], Wong et al. [12], McNulty et al. [13], and Schmidt et al. [14] all used the same two-bag method (200 mg/kg for 4 h, followed by 100 mg/kg for 16 h), whereas Pettie et al. [9] and Bateman et al. [25] used a more abbreviated two-bag regimen (100 mg/kg over 2 h, followed by 200 mg/kg over 10 h). While the studies differ in some minor ways (minimum age of subjects, reporting of medication administration errors, and reporting of adverse reaction data), the overall similarity of these studies facilitates their inclusion in a meta-analysis to determine non-inferiority. The remaining studies by Wong et al. [8] and Isbister et al. [26] are not similar enough to be included in the meta-analysis, as they do not contain three-bag arms (Table 2).

Furthermore, of the eight studies, three included early termination arms or subgroups (Wong et al. [8], Pettie et al. [9], and Isbister et al. [26]).

Hepatotoxicity is not increased in patients receiving abbreviated protocols compared to the three-bag protocol

All eight studies report hepatotoxicity or liver injury markers as outcomes. The most common definition of hepatotoxicity is an alanine aminotransferase activity >1,000 IU/L. There were also slight variations in the time period (15 min to 60 min) over which the first bag in the three-bag protocol was administered. Wong and Graudins [11] and McNulty et al. [13] administered the initial bag over 15 min to 1 h, whereas Wong et al. [12] and Schmidt et al. [14] administered the bag over 1 h. Despite these slight variations, none of the six studies found a significant difference between rates of hepatotoxicity among patients receiving a three-bag protocol versus a two-bag protocol. Of the four studies examining the "common" two-bag protocol, Wong and Graudins [11] reported hepatotoxicity rates of 4.3% versus 5.2% ($P=0.68$), Wong et al. [12] reported rates of 8.3% versus 7.4% ($P=0.41$), McNulty et al. [13] reported rates of 4.8% versus 3.7% ($P=0.58$), and Schmidt et al. [14] reported rates of 4% versus 4% ($P=0.29$) for three-bag and "common" two-bag protocols, respectively. Comparing the three-bag protocol to their abbreviated two-bag protocol, Pettie et al. [9] and Bateman et al. [25] found hepatotoxicity (alanine aminotransferase activity >1,000 IU/L) rates of 4.3% versus 3.6% (absolute difference −0.7%; 95% CI: −2.1 to 0.6) and 3.0% versus 2.0% (95% CI and *P*-value not reported), respectively. For Wong and colleagues [8], neither the two-bag nor modified two-bag patient cohorts developed hepatotoxicity (OR: 1.0; 95% CI: 0.02–50).

We did not identify any significant heterogeneity amongst the six studies included in the meta-analysis for hepatotoxicity (Q(5) = 1.11; $P=0.95$; $I^2 = 0\%$; 95% CI: 0–74.6%). Compared to the traditional three-bag dosing regimen, the two-bag methods did not demonstrate a difference in relative risk for hepatotoxicity (OR: 0.88; 95% CI: 0.72–1.08; $P=0.23$). We calculated the overall effect as "no difference" between the two-bag and three-bag methods (z: -1.19; $P=0.23$). Across all studies, the simplified two-bag dosing regimens remained consistently non-inferior to the traditional three-bag method with respect to hepatotoxicity (Figure 2).

Table 1. Summary of common three-bag to two-bag regimen studies.

	Wong et al. [12]		Pettie et al. [9]		McNulty et al. [13]		Schmidt et al. [14]		Wong and Graudins [11]		Bateman et al. [25]			
Study type	Multicenter observational cohort study comparing groups receiving 21 h three-bag protocol (October 2009–May 2015) to patients receiving 20 h Two-bag protocol (February 2014–April 2019) following institutional changeover. Two-bag protocol patients prospectively recruited, but all data collected from retrospective chart review.		Prospective data collection (depending on site) comparing standard three-bag to abbreviated two-bag before and after change to SNAP protocol for patients meeting United Kingdom criteria for acetylcysteine treatment.		Cohort study comparing prospective data for two-bag cohort to retrospective data from historical three-bag control group (data collected prior to transition from three-bag to two-bag regimen).		Retrospective cohort analysis based on chart review after change from three-bag to two-bag protocol in 2012. In 2012, 100% of patients received three-bag; in 2013 21% three-bag/79% two-bag; in 2014 100% two-bag.		Comparison of retrospective data for three-bag regimen as control group (October 2009–2013) to retrospective data after transition to two-bag regimen (February 2014–June 2015). Two-bag protocol patients prospectively recruited, but all data collected from retrospective chart review.		Double-blind randomized factorial study comparing abbreviated modified two-bag to standard three-bag. Subgroup receiving pretreatment with ondansetron.			
Site	Nine Australian metropolitan hospitals		Three United Kingdom hospitals. Edinburgh (transitioned September 2015); London (transitioned June 2016); Newcastle (transitioned 2016)		Toxicology service in western Sydney, Australia (August 2010–September 2016)		Three Denmark university hospitals		Three emergency departments in the Monash Health system in Victoria, Australia		Three United Kingdom hospitals (September 6, 2010–December 31, 2012)			
Regimens compared	Three-bag: 150 mg/kg over 1 h →50 mg/kg over 4 h → 100 mg/kg for 16 h Two-bag: 200 mg/kg over 4 h → 100 mg/kg over 16 h		Three-bag: 150 mg/kg over 1 h → 50 mg/kg over 4 h → 100 mg/kg over 16 h Modified two-bag: 100 mg/kg over 2 h → 200 mg/kg over 10 h		Three-bag: 150 mg/kg over 15 min-1 h→ 50 mg/kg for 4 h → 100 mg/kg over 16 h Two-bag: 200 mg/kg over 4 h → 100 mg/kg over 16 h		Three-bag: 150 mg/kg over 15 min → 50 mg/kg over 4 h → 100 mg/kg for 16 h Two-bag: 200 mg/kg over 4 h → 100 mg/kg over 16 h		Three-bag: 150 mg/kg over 15 min-1 h → 50 mg/kg over 4 h → 100 mg/kg over 16 h Two-bag: 200 mg/kg over 4 h → 100 mg/kg over 16 h		Three-bag: 150 mg/kg over 15 min → 50 mg/kg over 4 h → 100 mg/kg over 16 h Modified two-bag: 100 mg/kg over 2 h → 200 mg/kg over 10 h → then 5% dextrose over 8–13 h			
	Three-bag	Two-bag	Three-bag	Modified two-bag (SNAP)	Three-bag	Two-bag	Three-bag	Two-bag	Three-bag	Two-bag	Three-bag	Three-bag + ondansetron	Modified two-bag	Modified two-bag + ondansetron
Number	911	1,300	1,488	1,852	313	163	274	493	389	210	56	56	55	55
Female, *n* (%)	729 (80%)	949 (73%)	992	1,231	245 (78%)	116 (71%)	211	354	305	168	33	34	33	31
Weight (kg), mean (± SD)	–	–	–	–	69.8 (18.8)	71.4 (16.3)	75 (25)	75 (24)	–	–	–	–	–	–
Weight (kg), median (IQR)	–	–	–	–	–	–	–	–	64 (55–80)	64 (55–80)	70 (60–80)	68 (60–81)	70 (63–83)	70 (55–86)
Age (y), median (IQR)	26 (19–38)	27 (19–43)	Royal Infirmary of Edinburgh: 32 (21–44) St. Thomas' Hospital (London)/ Royal Victoria Infirmary (Newcastle): 30 (22–45)	Royal Infirmary of Edinburgh: 33 (22–45) St. Thomas' Hospital (London)/ Royal Victoria Infirmary (Newcastle): 32 (23–48)	25 (19–36)	31 (22–46)	26	27	22 (17–35)	27 (18–42)	33 (27–46)	32 (22–45)	36 (25–49)	29 (20–24)

(*Continued*)

Table 1. Continued.

	Three-bag	Two-bag	Three-bag	Modified two-bag (SNAP)	Three-bag	Two-bag	Three-bag	Two-bag	Three-bag	Two-bag	Three-bag	Three-bag + ondansetron	Modified two-bag	Modified two-bag + ondansetron
Age <16 years, *n* (%)	–	–	–	–	17 (5)	4 (2)	–	–	–	–	–	–	–	–
Age <18 years, *n*	–	–	–	–	–	–	41	38	107	50	–	–	–	–
Co-ingestion, *n* (%)	*Ethanol: 113 (15) *Opioids: 138 (18)	*Ethanol: 138 (14) *Opioids: 172 (17)	–	–	186 (59)	95 (58)	–	–	370 (95)	177 (84)	–	–	–	–
Deliberate self-poisoning, single ingestion, *n* (%)	*759	*1,003	462	446	262 (84)	129 (79)	218 (80)	406 (82)	276	88	–	–	–	–
Repeated supratherapeutic ingestion, *n* (%)	32 (3)	124 (7)	325	321	50 (16)	34 (21)	51 (19)	77 (16)	–	–	–	–	–	–
Paracetamol single ingestion dose (mg/kg), median (IQR)	*250 (185–380)	*250 (177–357)	Royal Infirmary of Edinburgh: 212 (148–294) St. Thomas' Hospital (London)/ Royal Victoria Infirmary (Newcastle): 250 (175–370)	Royal Infirmary of Edinburgh: 217 (151–314) St. Thomas' Hospital (London)/ Royal Victoria Infirmary (Newcastle): 229 (159–333)	245	235	286	284	–	–	264 (182–417)	233 (184–312)	233 (169–318)	224 (168–333)
Paracetamol single ingestion dose, median (mg/kg)	–	–	–	–	–	–	–	–	320	275	–	–	–	–
Time to first paracetamol concentration (h), median (IQR)	–	–	–	–	6 (4–10)	5 (4–9)	5.53	6.75	5 (4–8)	6 (4–11)	–	–	–	–
Acetylcysteine dose, median (g)	300	300	–	–	20.7	21	19.5	20.9	19.5	19.5	–	–	–	–
Acetylcysteine duration (h), range (h)	*21 (21–21)	*20 (20–20)	–	–	21 (10–21)	20 (8–20)	20.5	20	21 (1–133)	20(1–100)	–	–	–	–
Time to acetylcysteine initiation post-single ingestion (h), median (IQR)	*7 (5–10)	*7 (6–12)	–	–	8 (6–12)	8 (6–12)	–	–	–	–	–	–	–	–
Hospital length of stay (days), median (IQR)	*1.3 (1–2)	*1 (1–1.5)	–	–	2 (1–4)	2 (1–3)	2	1	3 (2–4)	2 (2–3.25)	–	–	–	–
Alanine aminotransferase activity >1,000 IU/L, *n* (%)	76 (8.3)	96 (7.4)	64 (4.3)	67 (3.6)	15 (4.8)	6 (3.7)	11 (4.0)	20 (4.1)	17 (4.3)	11 (5.2)	2 (3.8)	1 (2.0)	0	2 (3.9)
Medication errors, *n*	–	–	–	–	–	–	1	8	3	2	–	–	–	–
Non-allergic anaphylactoid reactions, *n* (%)	15 (1.6)	3 (0.02)	163 (11)	37 (2.0)	45 (14)	8 (5)	46 (17)	20 (4)	40 (10)	9 (4.3)	75/100 (75)		58/108 (54)	
Time to reaction (h), (IQR)	–	–	–	–	2 (1–3)	1 (1–4)	–	–	–	–	–	–	–	–

(*Continued*)

Table 1. Continued.

	Three-bag	Two-bag	Three-bag	Modified two-bag (SNAP)	Three-bag	Two-bag	Three-bag	Two-bag	Three-bag	Two-bag	Three-bag	Three-bag + ondansetron	Modified two-bag	Modified two-bag + ondansetron
Severe reaction-hypotension, shortness of breath, edema; *n* (%)	15 (1.6%)	3 (0.02)	–	–	25 (8)	3 (2)	10 (4)	3 (0.6)	7 (2.5)	1 (0.5)	31/109 (28.4%)		5/108 (4.6%)	
Skin reaction only, *n* (%)	58 (6.3%)	14 (1.1)	–	–	20 (6)	5 (3)	38 (14)	12 (2)	33 (8.4)	8 (3.8)	–	–	–	–
Gastrointestinal reaction, *n* (%)	279 (31%)	245 (19)	–	–	116 (37)	51 (31)	3 (1)	0	150 (39)	87 (41)	71/109 (65.1%)		39/108 (36.1%)	
Vomiting only, *n* (%)	–	–	–	–	97 (31)	43 (26)	–	–	–	–	–	–	–	–
Nausea only, *n* (%)	–	–	–	–	–	–	–	–	28 (7)	32 (15)	–	–	–	–
Nausea and vomiting, *n* (%)	–	–	–	–	–	–	3 (1)	0	122 (32)	55 (26)	–	–	–	–
Reaction treated with antihistamine, *n* (%)	–	–	163 (11.0)	37 (2.0)	33 (11)	6 (4)	–	–	–	–	31/100 (31%)		5/108 (4.6%)	
Gastrointestinal tract symptoms requiring antiemetic rescue within 12 h of acetylcysteine initiation, *n* (%)	–	–	–	–	–	–	–	–	–	–	36/54 (67%)	19/55 (35%)	22/55 (40%)	14/54 (26%)
Non-allergic anaphylactoid reactions requiring antihistamine rescue or acetylcysteine interruption within 12 h of acetylcysteine initiation, *n* (%)	–	–	163 (11)	37 (2.0)	–	–	–	–	–	–	17/54 (31%)	15/55 (27%)	5/55 (9.1%)	4/54 (7.4%)

*Data from 4–24 h initial blood group.

Table 2. Summary of modified two-bag studies.

	Wong et al. [8]	Isbister et al. [26]			
Study type	Multicenter, cluster-controlled, open-label trial comparing standard two-bag method to a modified two bag method which terminated acetylcysteine infusion after 12 h in low-risk patients. Low-risk patients defined as normal alanine aminotransferase activity and creatinine concentration on admission and normal alanine aminotransferase activity, creatinine concentration, and paracetamol concentration at 12 h.	Prospective observational study comparing a modified two-bag dosing regimen to previous historical study data with primary focus on rate of non-allergic anaphylactoid reactions and rate of initial acetylcysteine infusion.			
Site	Six Australian metropolitan hospitals (February 2016–February 2018)	Two tertiary Australian referral hospitals with toxicological services: Princess Alexandra Hospital and Calvary Mater Newcastle			
Regimens compared	Two-bag: 200 mg/kg over 4 h → 100 mg/kg over 16 h Modified two-bag: 200 mg/kg over 4 h → 50 mg/kg over 8 h → Ringer lactate 1 L over 8 h	Two-bag: 200 mg/kg over 11 h → 100 mg/kg over 16 h Early discontinuation: acetylcysteine discontinued at 4 h for low-risk patients (below 150 mg/L nomogram line)			
	Two-bag (20 h regimen):	Modified two-bag	Modified two-bag (total)	Full two-bag	Early discontinuation two-bag
Number	50	50	654	231	420
Female, *n*	40	37	453	–	–
Age, median (years)	–	–	29	–	–
Age <16 years, *n*	–	–	0	–	–
Age <18 years, *n*	–	–	–	–	–
Co-ingestion, *n*	16	24	–	–	–
Deliberate self-poisoning, single ingestion, *n*	46	49	576	–	–
Repeated supratherapeutic ingestion, *n*	4	1	78	–	–
Paracetamol single ingestion dose (mg/kg), median (IQR)	269 (198–346)	250 (180–385)	–	–	–
Acetylcysteine dose (g)	300	250	–	–	–
Acetylcysteine duration hours (h), median (IQR)	20 (20–20)	13 (13–13.5)	–	–	–
Time to acetylcysteine initiation post-single ingestion (h), median (IQR)	7 (6–10)	7 (6–12)	–	–	–
Hospital length of stay (days), median (IQR)	1	1	–	–	–
Alanine aminotransferase activity >1,000 IU/L, *n*	0	0	16	–	–
Medication errors, *n*	–	–	4	–	–
Non-allergic anaphylactoid reactions, *n* (%)	1 (2.0)	0	229 (35)	111 (48)	116 (28)
Time to reaction (h), median (IQR)	2 (2–2)	–	–	–	–
Severe reaction – hypotension, shortness of breath, edema, *n* (%)	1 (2.0)	0	3	1	2
Skin reaction only, *n* (%)	0	0	50 (8)	26 (11)	29 (7)
Gastrointestinal reaction, *n* (%)	12 (24)	14 (28)	173 (30)	105 (45)	104 (25)
Vomiting only, *n* (%)	7 (14)	5 (10)	–	–	–
Nausea only, *n* (%)	3 (6)	7 (14)	–	–	–
Nausea and vomiting, *n* (%)	2 (4)	2 (4)	–	–	–
Non-allergic anaphylactoid reactions requiring antihistamine rescue or acetylcysteine interruption within 12 h of acetylcysteine initiation, *n*	1	0	–	–	–

A two-bag regimen consistently results in fewer adverse events and decreased likelihood of non-allergic anaphylactoid reactions

The studies included in this analysis variably reported adverse events, including non-allergic anaphylactoid reactions, skin reactions, and gastrointestinal side effects. Seven studies directly reported occurrences of non-allergic anaphylactoid reactions [8, 11–14, 25, 26], and one (by Pettie and colleagues [9]) reported only the number of patients requiring medication for management of their non-allergic anaphylactoid reactions. For the purpose of our analysis, we used medication administration as a proxy measure of non-allergic anaphylactoid reactions for their study.

All six studies comparing two-bag and three-bag regimens found lower rates of non-allergic anaphylactoid reactions in patients receiving the two-bag regimen. This difference was

significant in five studies (Pettie et al. [9], Wong and Graudins [11], Wong et al. [12], McNulty et al. [13], and Schmidt et al. [14]). Bateman and colleagues [25] noted a lower rate of non-allergic anaphylactoid reactions among patients receiving the two-bag regimen (54% versus 75%) but did not report statistical significance.

Of the studies comparing modified two-bag methods, both noted lower rates of non-allergic anaphylactoid reactions in patients receiving the more abbreviated regimens [8, 26]. This difference was significant in Isbister et al. [26], but Wong et al. [8] did not comment on the statistical significance of their findings.

Five studies reported rates of cutaneous reactions (rash, flushing, urticaria, wheals, and pruritus) with either of two similar regimens [11–14,26]. Cutaneous reactions were less frequent in patients receiving a two-bag regimen compared to the three-bag method (historical controls) in two studies (Wong and Graudins [11] (3.8% versus 8.4%; $P=0.04$) and Schmidt et al. [14] (2% versus 14%; $P<0.001$); but non-significant in McNulty et al. [13] (3% versus 6%; $P=0.12$). Wong and colleagues [12] did not state the significance of the difference demonstrated in their study (0.23% versus 1.6%). While the study conducted by Isbister et al. [26] did not incorporate a three-bag regimen, fewer cutaneous reactions were observed in patients receiving their modified two-bag regimen compared to their "full" (acetylcysteine 200 mg/kg given over [11 h minus time since ingestion] followed by acetylcysteine 100 mg/kg over 16 h) two-bag regimen (7% versus 11%).

Gastrointestinal adverse events were examined in the four studies using the "common" two-bag method, as well as three of the modified two-bag studies (Wong et al. [8], Bateman et al. [25], and Isbister et al. [26]). As most studies did not specify when the patients developed nausea or vomiting relative to acetylcysteine administration, these gastrointestinal effects likely reflect a combination of symptomatic paracetamol poisoning and acetylcysteine intolerance. Regardless of etiology, lower rates of nausea and vomiting likely reflect improved patient wellbeing. The respective authors found no significant difference in the incidence of gastrointestinal symptoms between patients in the two-bag versus three-bag groups in Wong et al. [8] (28% versus 24%; $P=0.64$), Wong and Graudins [11] (41% versus 39%; $P=0.38$), and McNulty et al. [13] (31% versus 37%). Wong and colleagues [12] noted significantly fewer gastrointestinal symptoms in patients receiving the two-bag versus three-bag regimens (19% versus 31%; $P<0.0001$). Similarly, Isbister et al. [26] noted a significantly lower incidence of gastrointestinal reactions in patients receiving a shortened version of their modified two-bag regimen compared to the "full" two-bag regimen (25% versus 45%), suggesting that rates of gastrointestinal effects in two-bag regimens could be even further reduced in shorter regimens.

Bateman and colleagues [25] uniquely analyzed the effects of pretreating or rescuing with antiemetics, finding that 9.6% of patients assigned to their modified two-bag protocol reported gastrointestinal symptoms or required antiemetic therapy compared to 65% in the three-bag arm ($P<0.0001$). Significantly fewer patients pretreated with ondansetron reported gastrointestinal symptoms or required rescue compared to patients receiving placebo, with 41.0% of patients who received ondansetron compared with 60.2% of patients in the placebo cohort developing gastrointestinal symptoms or requiring rescue ($P=0.003$) [25].

In the meta-analysis, we did not identify any significant heterogeneity among the six studies for non-allergic anaphylactoid reactions and adverse events (Q(5): 10.15; $P=0.07$; $I^2 = 50.7\%$; 95% CI: 0%-80.4%). Compared to the traditional three-bag dosing regimen, the two-bag methods significantly demonstrated a decreased likelihood of non-allergic anaphylactoid reactions and other adverse events (OR: 0.24; 95% CI: 0.17–0.35; $P<0.0001$). We calculated the overall effect as significantly favoring the two-bag methods over the three-bag method (z: 7.57; $P<0.001$). Compared to the three-bag dosing regimen, the two-bag dosing regimens consistently resulted in a decreased likelihood of non-allergic anaphylactoid reactions and adverse event occurrences across studies (Figure 3).

Shortened two-bag regimens appear promising in low-risk patients

Three of the studies examined the safety and tolerability of abbreviated versions of the common two-bag method in patients deemed "low-risk." Each study used its own criteria to define low-risk and used a unique truncated protocol. Wong and colleagues [8] defined "low-risk" patients as those with normal alanine aminotransferase activities and creatinine concentrations on admission and at 12 h into acetylcysteine treatment, as well as a therapeutic paracetamol concentration at 12 h. These "low-risk" patients had their acetylcysteine infusion terminated after 12 h of treatment. Pettie et al. [9] also used a 12 h regimen but defined "low-risk" as an international normalized ratio ≤1.3, alanine aminotransferase activity <100 IU/L and less than double the initial alanine aminotransferase activity, and paracetamol concentration <20 mg/L after 10 h into the initial 12 h infusion. Isbister and colleagues [26] defined "low-risk" patients as having a serum paracetamol concentration below the 150 mg/L nomogram line at 4 h and stopped acetylcysteine infusions for these patients after 4 h. However, early initiation of acetylcysteine in the study of Isbister et al. [26] (starting the infusion before 4 h paracetamol concentrations were available) resulted in the inclusion of patients with ingestions who might not otherwise have met treatment criteria, confounding the findings of their shortened protocol. In each of these studies, the authors concluded that their modified two-bag protocols were non-inferior to the full-length protocols with respect to hepatotoxicity [8, 9]. Isbister and colleagues [26] also found the modified two-bag regimen to be associated with lower rates of adverse events.

Discussion

The six studies included in the meta-analysis clearly showed a significant reduction in non-allergic anaphylactoid reactions in two-bag regimens compared to the three-bag method.

Furthermore, the simplification of treatment regimens is known to result in fewer treatment delays and medication errors when compared to the three-bag regimen. While only the Wong et al. [8] study was powered for non-inferiority, our meta-analysis with outcomes of hepatotoxicity and non-allergic anaphylactoid reactions confirms the reduction in non-allergic anaphylactoid reactions, while also demonstrating non-inferiority between the two-bag and three-bag regimens.

These studies support, at a minimum, that a two-bag method is a safe and effective treatment for acute paracetamol overdoses. They also support early termination of acetylcysteine therapy based on "low-risk" features such as unchanged alanine aminotransferase activity at 12 h and paracetamol concentrations below the nomogram. While the latter four studies differed in their modalities and primary and secondary outcomes, the areas of overlap suggest that early termination of even further simplified two-bag dosing regimens may be sufficient and safe in reducing hepatotoxicity in paracetamol overdose. As an example, when the three-bag regimen was first introduced, the first infusion was given as a bolus over 15 min. However, due to a high rate of non-allergic anaphylactoid reaction, the infusion was subsequently slowed to one hour. We suspect the reduction of non-allergic anaphylactoid reactions in a two-bag method results from even further slowing of the acetylcysteine infusion rate.

Limitations include the paucity of prospective, double-blinded, randomized, controlled trials comparing different regimens. The inherent difficulty of controlling the time to first acetylcysteine administration makes it extremely challenging to power a study for outcomes such as hepatotoxicity or liver transplant, which are more strongly influenced by time to administration rather than regimen. Further, the threshold for administration of acetylcysteine differs between countries. For example, the threshold to treat with acetylcysteine in Denmark (where rapid paracetamol concentration testing is not widely available) is based on a history of ingestion of at least paracetamol 6 g rather than a serum paracetamol concentration. However, among countries that rely upon a paracetamol concentration, some (such as the US and Canada) use a threshold of 150 mg/L at 4 h, while others (such as the UK) use a threshold of 100 mg/L at 4 h. In addition, the threshold for treating the adverse effects of acetylcysteine varies, so the administration of antihistamines or antiemetics will not precisely correlate to the rate of adverse effects (as had to be assumed in Pettie et al. [9]). This lack of standardization complicates data aggregation and analysis. Moreover, conducting such studies poses significant challenges, and such studies may be of limited benefit in light of the evidence discussed above.

Growing evidence supports further abbreviated regimens, including the effective use of a one-bag method [27]. While most two-bag regimens are composed of weight-based, individualized preparations unique to each patient, one-bag methods use a uniform concentration for all patients. Further research is likely to produce evidence that this simplification will result in lower incidences of medication administration errors, and delays in care.

Conclusion

Two-bag acetylcysteine dosing regimens appear to be non-inferior to the three-bag method with respect to hepatotoxicity, while resulting in fewer non-allergic anaphylactoid, cutaneous, and gastrointestinal reactions.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Editorial note

On 9 December 2024, the United States Food and Drug Administration approved a new dosing regimen for acetylcysteine that combines the first two bags of the standard intravenous regimen into a single, slower infusion to deliver 200 mg/kg over 4 h.

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