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N-acetylcysteine for sepsis and systemic inflammatory response in adults (Review)

Szakmany T, Hauser B, Radermacher P

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[Intervention Review]

N-acetylcysteine for sepsis and systemic inflammatory response in adults

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ABSTRACT

Background

Death is common in systemic inflammatory response syndrome (SIRS) or sepsis-induced multisystem organ failure and it has been thought that antioxidants such as N-acetylcysteine could be beneficial.

Objectives

We assessed the clinical effectiveness of intravenous N-acetylcysteine for the treatment of patients with SIRS or sepsis.

Search methods

We searched the following databases: Cochrane Central Register of Clinical Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 12); MEDLINE (January 1950 to January 2012); EMBASE (January 1980 to January 2012); CINAHL (1982 to January 2012); the NHS Trusts Clinical Trials Register and Current Controlled Trials (www.controlled-trials.com); LILACS; KoreaMED; MEDCARIB; INDMED; PANTELEIMON; Ingenta; ISI Web of Knowledge and the National Trials Register to identify all relevant randomized controlled trials available for review.

Selection criteria

We included only randomized controlled trials (RCTs) in the meta-analysis.

Data collection and analysis

We independently performed study selection, quality assessment and data extraction. We estimated risk ratios (RR) for dichotomous outcomes. We measured statistical heterogeneity using the I^2 statistic.

Main results

We included 41 fully published studies (2768 patients). Mortality was similar in the N-acetylcysteine group and the placebo group (RR 1.06, 95% CI 0.79 to 1.42; I^2 = 0%). Neither did N-acetylcysteine show any significant effect on length of stay, duration of mechanical ventilation or incidence of new organ failure. Early application of N-acetylcysteine to prevent the development of an oxidato-inflammatory response did not affect the outcome, nor did late application that is after 24 hours of developing symptoms. Late application was associated with cardiovascular instability.

Authors' conclusions

Overall, this meta-analysis puts doubt on the safety and utility of intravenous N-acetylcysteine as an adjuvant therapy in SIRS and sepsis. At best, N-acetylcysteine is ineffective in reducing mortality and complications in this patient population. At worst, it can be harmful, especially when administered later than 24 hours after the onset of symptoms, by causing cardiovascular depression. Unless future RCTs provide evidence of treatment effect, clinicians should not routinely use intravenous N-acetylcysteine in SIRS or sepsis and academics should not promote its use.

PLAIN LANGUAGE SUMMARY

Intravenous N-acetylcysteine compared to placebo for treatment of systemic inflammatory response syndrome and sepsis in seriously ill adults

Systemic inflammatory response syndrome (SIRS) is a complex response to an insult such as major surgery or trauma. It is called sepsis syndrome, or simply sepsis, when infection is present. The generalized inflammatory reaction involves activation of leukocytes and endothelial cells and the release of inflammatory mediators and toxic oxygen free radicals. Diffuse microthrombosis can result in localized tissue perfusion abnormalities and low oxygenation (hypoxia). Both SIRS and sepsis can be difficult to treat and are major causes of multiple organ failure and the death of patients in the intensive care unit. SIRS and sepsis both lead to a drop in the level of antioxidants normally present in the body.

N-acetylcysteine is an antioxidant with strong anti-inflammatory effects that is used in treating endotoxaemia and overdoses of acetaminophen. This Cochrane review of 41 randomized controlled trials with 2768 critically ill adult patients found no evidence to support the theory that N-acetylcysteine might reduce the risk of death in adults with SIRS or sepsis. Intravenous N-acetylcysteine did not affect the length of stay in the intensive care unit, duration of mechanical ventilation, duration of support for the cardiovascular system or incidence of new organ failure. There is currently insufficient evidence to support the use of N-acetylcysteine in SIRS or sepsis. We also found that when N-acetylcysteine was administered more than 24 hours after the development of clinical signs of SIRS or sepsis it may even be harmful, by causing cardiovascular depression.

Twenty of the trials used N-acetylcysteine in patients around the time of surgery, including cardiac, vascular and major abdominal surgery, and liver transplantation. Eight studies evaluated N-acetylcysteine in patients with severe sepsis or septic shock associated with the medical conditions acute respiratory distress syndrome (ARDS), multiple organ failure, liver failure, malaria or burns. The dosing of N-acetylcysteine, timing and duration of treatment, from a single intravenous dose to infusions up to seven days, varied. Twenty papers had a low risk of bias.

Summary of findings for the main comparison.

N-acetylcysteine compared with placebo for SIRS or sepsis

Patient or population: Adult patients with SIRS or sepsis

Settings: Intensive care unit

Intervention: N-acetylcysteine

Comparison: Placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	N-acetylcysetine				
Mortality 30-day	136 per 1000	144 per 1000 (100 to 185)	RR 1.07 (0.80 to 1.43)	930 (11)	+++O moderate	
Length of stay on the intensive care unit (days)	The mean **Length of stay on the intensive care unit** ranged across control groups from 1 to 33 days	The mean difference (95%CI) **Length of stay on the intensive care unit** in the intervention groups was -0.22 (-0.86 to 0.43)		1309 (19)	+++O moderate	
Duration of mechanical ventilation (days)	The mean Duration of mechanical ventilation ranged across control groups from 1 to 25 days	The mean difference (95% CI) Duration of mechanical ventilation in the intervention groups was -0.00 (-0.04 to 0.04)		423 (9)	+++O moderate	
Incidence of new organ failure	158 per 1000	165 per 1000 (123 to 241)	RR 1.01 (0.80 to 1.27)	1224 (12)	+++O moderate	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; GRADE: GRADE Working Group grades of evidence (see explanations)

GRADE Working Group grades of evidence

High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality (+++O): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality (++OO): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality (+OOO): We are very uncertain about the estimate.

BACKGROUND

There is an increasing incidence of systemic inflammatory response syndrome (SIRS) and sepsis, and consequent multiple organ failure, especially in the developed world. Despite recent advances in antibacterial and other therapies the mortality rate only shows a slow decline (Engel 2007).

Description of the condition

Since the discovery of oxygen free radicals about 30 years ago there has been a growing interest in their role in inflammatory diseases (Crimi 2006). Although the pathophysiology of systemic inflammatory response syndrome (SIRS) and sepsis is complex, and only partially understood, it has been proposed that following an insult, such as trauma, systemic infection or major surgery, the development of multiple organ failure is due to a generalized inflammatory reaction involving activation of leukocytes and endothelial cells and the release of inflammatory mediators and toxic oxygen free radicals of both intracellular and extracellular origin (Pinsky 2003). Another important mechanism of sepsis-induced organ failure is diffuse microthrombosis, resulting in locoregional abnormalities of tissue perfusion and tissue hypoxia. In patients affected by mild-to-moderate organ dysfunction there is an imbalance between oxidant and antioxidant forces, and it has been suggested that in multiple organ failure there is an overwhelming production of oxygen free radicals that results in tissue destruction (Goode 1995). Several studies have demonstrated decreased concentrations of plasma antioxidants in septic patients and those in multiple organ failure as they try to combat the increased production of free radicals (Cowley 1996; Goode 1995; Ogilvie 1991).

Description of the intervention

Similar protection against free radical mediated injury to the endogenous mechanisms might be achieved by using exogenous agents such as N-acetylcysteine, which has been used clinically for nearly 40 years. Historically it has been administered for chronic bronchitis, cystic fibrosis and paracetamol intoxication (Kiefer 2000; Pinsky 2003).

How the intervention might work

N-acetylcysteine acts as a powerful oxygen free radical scavenger and also replenishes depleted glutathione stores, enhancing the endogenous antioxidant defence (Aruoma 1989; Repine 1992). It also has a powerful anti-inflammatory effect when given as a pre- and post-treatment in endotoxaemia (Schmidt 1997; Schmidt 1998). In experimental animal studies N-acetylcysteine was administered before induction of sepsis with endotoxin infusion (Hsu 2004; Zhang 1994a). These studies suggested that timing of the treatment was important. In previous in vitro and in vivo studies N-acetylcysteine treatment attenuated TNF and IL-8 production and enhanced oxygen extraction in septic shock, severe multiple organ failure and acute respiratory distress syndrome (ARDS) (Paterson 2003; Peristeris 1992; Spapen 1998). Many authors have proposed the use of exogenous agents such as N-acetylcysteine to prevent oxygen free radical damage in patients suffering from septic shock (Spies 1994; Zhang 1994b). Despite the theoretical advantages, the benefit of N-acetylcysteine remains controversial in critically ill patients (Henderson 1994; Pinsky 2003). Molnar found that early treatment with N-acetylcysteine (within 24 hours of hospital admission) may improve mortality in a subgroup of patients from a heterogeneous intensive care population (Molnar 1999). On the other hand, recent randomized placebo-controlled studies in patients with ARDS and early septic shock or SIRS found no significant differences in gas exchange, development of ARDS, inflammatory response and mortality in patients treated with N-acetylcysteine or placebo (Domenighetti 1997; Spapen 2005; Szakmany 2003). Furthermore, several papers reported conflicting and undesirable effects of N-acetylcysteine administration. Depressed cardiac performance was found in septic patients and impaired bacterial killing due to augmented neutrophil phagocytosis was reported in animals and humans (Heller 2001; Koch 1996; Peake 1996). Late administration of N-acetylcysteine was associated with an adverse outcome in experimental and clinical sepsis (Molnar 1999; Vassilev 2004).

Why it is important to do this review

Although many clinical trials have investigated its effect, the value of N-acetylcysteine administration in the critically ill has not been assessed in a systematic review.

OBJECTIVES

Our aim was to critically appraise and summarize all randomized clinical trials involving intravenous N-acetylcysteine administration in adult patients suffering from sepsis and SIRS.

We wanted to answer the question: does N-acetylcysteine influence the outcome in sepsis or SIRS?

Our primary objective was to investigate whether intravenous N-acetylcysteine has any effect on the 30-day all-cause mortality.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs) in the meta-analysis. No cross-over or quasi-randomization designs were allowed.

Types of participants

We included trials involving participants with SIRS and sepsis according to the Bone criteria (Bone 1992), regardless of the underlying cause. If the authors of the study did not specify that they used the Bone criteria, we have assessed the study to determine if the inclusion criteria were in line with the published SIRS or sepsis definition.

We only included trials conducted in adult patient populations. There are at least three important differences between adult and paediatric sepsis, which would make grouping of the data confusing. First, the causes of sepsis may be substantially different, with viral infections contributing a large proportion of the sepsis cases. Second, the risk for paediatric sepsis is almost exclusively in children with chronic comorbid medical conditions, such as chronic lung disease. Third, case-fatality rates are substantially lower in children than in adults, although the risk of death is similar between children and young adults.

Types of interventions

We included studies where one of the groups was treated with intravenous N-acetylcysteine in bolus intravenous doses or as a continuous infusion, or a combination of the two. We included studies if intravenous N-acetylcysteine was compared with placebo or standard treatment. Placebo was considered if a similar composition and volume of fluid was administered without the active ingredient; standard treatment was considered if the patient received standard care without the administration of N-acetylcysteine.

Types of outcome measures

Primary outcomes

1. Our principal outcome measure was 30-day all-cause mortality.
2. Overall mortality: we used the longest follow-up data from each trial regardless of the period of follow up.

Secondary outcomes

1. Length of stay in the critical care unit.
2. Duration of mechanical ventilation.
3. Duration of inotropic support.
4. Incidence of new organ failures, such as:
a) acute renal failure;
b) ARDS;
c) liver failure;
d) circulatory failure;
5. quality of life;
6. cost.

Search methods for identification of studies

We used several techniques to identify published and ongoing studies for this review. We included all relevant published studies regardless of the language.

Electronic searches

We searched the following databases: Cochrane Central Register of Clinical Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 12); MEDLINE (January 1950 to January 2012); EMBASE (January 1980 to January 2012); CINAHL (1982 to January 2012); the NHS Trusts Clinical Trials Register and Current Controlled Trials (www.controlled-trials.com); LILACS; KoreaMED; MEDCARIB; INDMED; PANTELEIMON; Ingenta; ISI Web of Knowledge and the National Trials Register to identify all relevant randomized controlled trials available for review. We used the SilverPlatter MEDLINE and the Ovid version of all other databases.

We searched MEDLINE using the strategy detailed in Appendix 1. We modified this search strategy as necessary and applied it to the CENTRAL (Appendix 2), CINAHL (Appendix 3) and EMBASE databases as well. We applied the search strategy detailed in Appendix 1 to the LILACS, KoreaMED, MEDCARIB, INDMED, PANTELEIMON, CCT, Ingenta, ISI Web of Knowledge and National Trials Register databases.

We utilized the Cochrane highly sensitive RCT filter for MEDLINE from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We identified relevant studies initially by title then by abstract and finally by full text. Two authors (TSZ and BH) independently performed the electronic searches.

Searching other resources

We searched the bibliographies of reports of randomized trials and any identified reviews.

We also searched for abstracts from conference proceedings published from 1994 to December 2011 in the *American Journal of Respiratory and Critical Care Medicine*, *Chest*, *Critical Care Medicine* and *Intensive Care Medicine*.

We contacted the authors of all identified trials to ask them about any other published or unpublished trials that may have been conducted.

Data collection and analysis

Selection of studies

Selection of trials

Two authors (BH, TSZ) independently reviewed the titles and abstracts identified from the searches. We obtained full copies of potentially relevant trials and assessed all full copies according to the parameters outlined in 'Criteria for considering studies for this review'. Only eligible trials were considered for inclusion in the meta-analysis. The authors resolved any discrepancies by discussion, if necessary.

Data extraction and management

Data collection

Two authors (BH, TSZ) independently extracted data using a form modified from one developed by the Cochrane Anaesthesia Review Group. We (as far as possible) extracted data on the basis of an intention-to-treat analysis. Two authors (BH and TSZ) entered all data independently into Review Manager (RevMan 5.1) after checking for differences.

Assessment of risk of bias in included studies

Assessment of methodological quality

We evaluated the validity and design characteristics of each trial. To draw conclusions about the overall risk of bias for an outcome it was necessary to evaluate the trials for major sources of bias, also defined as domains (random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias). The Cochrane Collaboration's recommended tool for assessing risk of bias is neither a scale nor a checklist, but rather the domain-based evaluation. Any assessment of the overall risk of bias involves consideration of the relative importance of the different domains (Higgins 2011).

We assessed the methodological quality of the included studies according to the Cochrane Collaboration's tool for assessing risk of bias.

We assessed the studies for bias based on the following criteria:

- random sequence generation;
- allocation concealment;

- blinding of participants, personnel and outcome assessors;
- incomplete outcome data;
- selective reporting;
- other bias.

We have generated a risk of bias tables for each included trial (Characteristics of included studies).

We defined the trials as having low risk of bias only if they adequately fulfilled the criteria listed in the *Cochrane Handbook for Systematic Reviews of Interventions*. We performed summary assessments of the risk of bias for each important outcome (across domains) within and across studies. We applied a 'Risk of bias' graph (Figure 1) and a 'Risk of bias' summary figure (Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

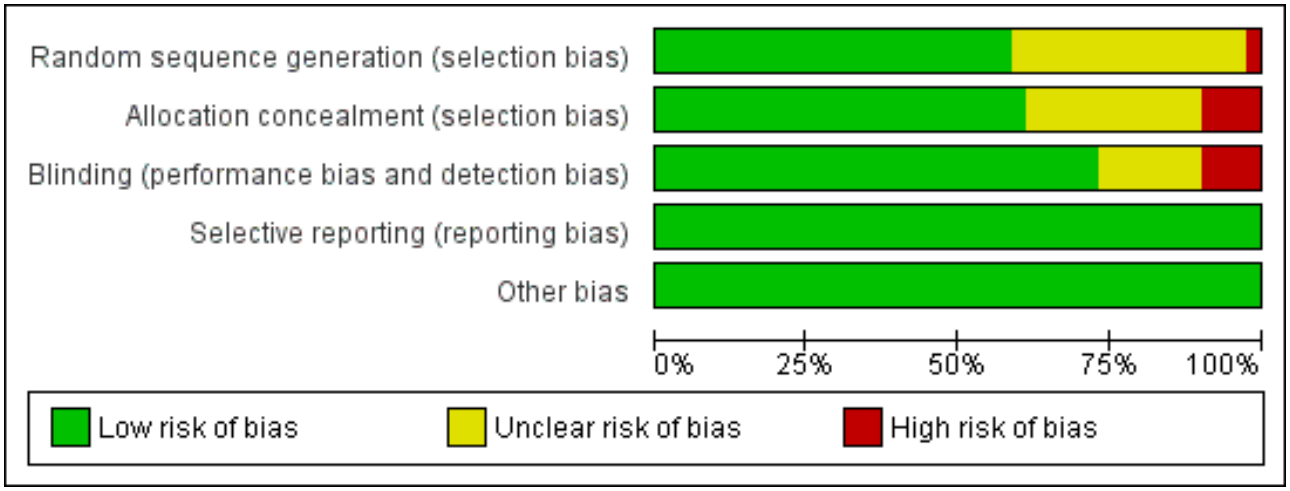


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study. +: yes, -: no, ?: unclear

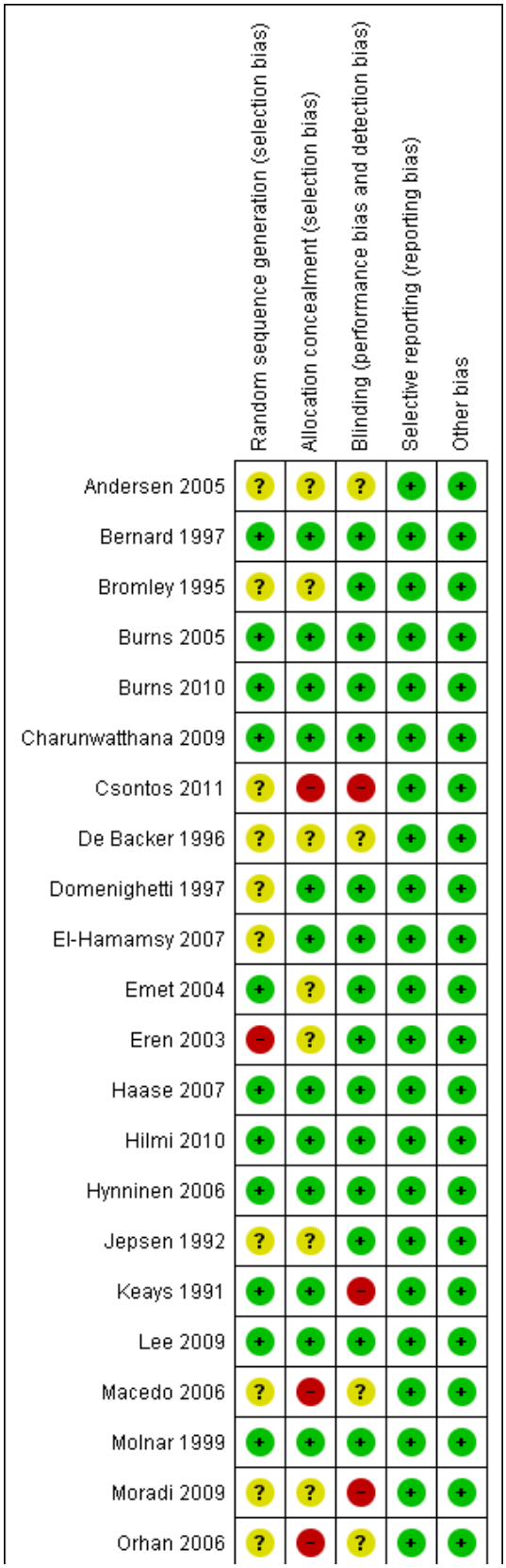
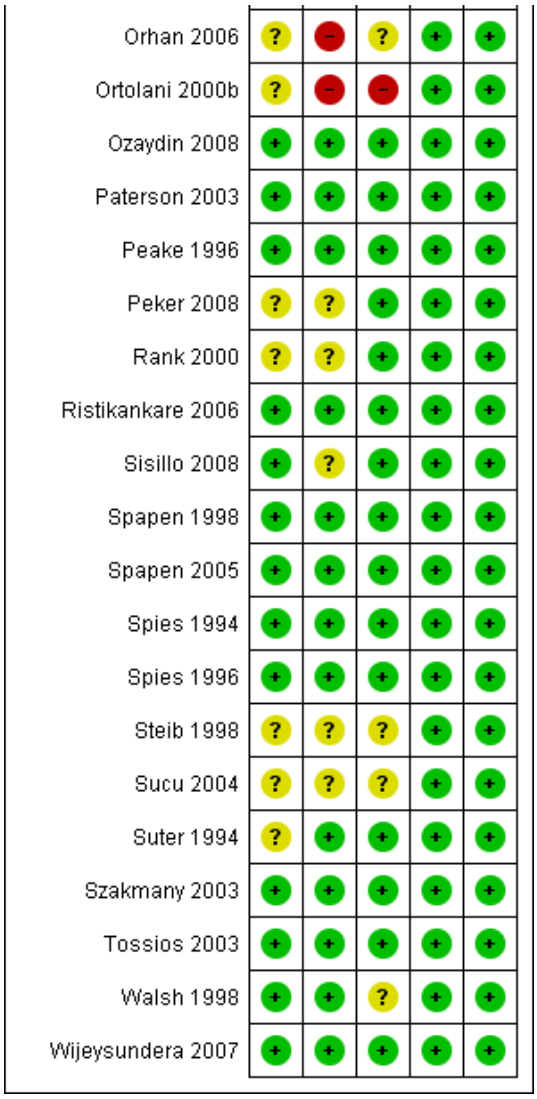


Figure 2. (Continued)



Measures of treatment effect

Dichotomous data

We summarized dichotomous data using risks ratio (RR) as the summary estimate of treatment effect with 95% confidence interval (CI).

Continuous data

We summarized continuous outcomes using the mean difference (MD). For data reported using different scales which cannot be converted to a uniform scale, we used the standardized mean difference (SMD). If the mean and SD of the continuous outcomes were not reported in the studies, we assigned the median as the mean if sample size was greater than 25 and estimated the SD from the range (that is, SD range 0.95/4 or interquartile range/1.35) as suggested by Hozo et al (Hozo 2005). If sample size was less than 25 we used formulaes suggested by Hozo et al to calculate the mean (Hozo 2005). If we could not calculate the mean and SD from the available data, we excluded the study from the analysis.

Unit of analysis issues

In trials where more than two treatment arms were present, using a different dosage of N-acetylcysteine, we divided the control group into several parts so that the total numbers add up to the original size of the group.

Dealing with missing data

We contacted all the first authors and contact persons of the trials with missing data in order to retrieve the relevant data.

Intention-to-treat analysis is recommended in order to minimize bias in design, follow up, and analysis of the efficacy of randomized clinical trials. It gives a pragmatic estimate of the benefit of a change in treatment policy rather than of the potential benefit in patients who receive treatment exactly as planned (Hollis 1999). Full application of intention to treat is possible only when complete outcome data are available for all randomized participants. Despite the fact that about half of all published reports of randomized controlled trials state that Intention-to-treat analysis is used,

handling of deviations from randomized allocation varies widely and many trials have missing data for the primary outcome variable. Methods used to deal with this are generally inadequate, potentially leading to bias (Hollis 1999).

Performing an Intention-to-treat analysis in a systematic review is not straightforward in practice since review authors must decide how to handle outcome data that are missing in the contributing trials. No consensus exists about how missing data should be handled in intention-to-treat analyses, and different approaches may be appropriate in different situations (Higgins 2011; Hollis 1999). In the case of missing data we chose 'complete-case analysis' for our primary outcomes, which simply excludes from the analysis all participants with the outcome missing.

Selective outcome reporting occurs when non-significant results are selectively withheld from publication. It is defined as selection on the basis of the results of a subset of the original variables recorded for inclusion in the publication of trials. The most important types of selective outcome reporting are: selective omission of outcomes from reports; selective choice of data for an outcome; selective reporting of analyses using the same data; selective reporting of subsets of the data; and selective under-reporting of data (Higgins 2011). Statistical methods to detect within-study selective reporting are still in their infant stage. We chose to explore selective outcome reporting by comparing publications with their protocols, if the latter were available.

Assessment of heterogeneity

Clinical heterogeneity

We used the term 'clinical heterogeneity' to describe clinical differences in the studies to do with the participants, interventions and outcomes. We based the decision to pool studies on the absence of clinical heterogeneity. We assessed clinical heterogeneity by judgment. We based these judgments on patient demographics, clinical circumstances and the comparability of the interventions applied.

Assessment of reporting biases

If sufficient studies were identified we constructed funnel plots (trial effect versus standard error) to assess for possible publication bias, expressed by asymmetry (Egger 1997). In the case of asymmetry we chose to apply the Arcsine-Thompsen test, as proposed by Rücker (Rücker 2008).

Data synthesis

Patients admitted to the intensive care unit (ICU) are a heterogenous group in terms of admitting diagnosis, prognosis and resource use. This heterogeneity not only exist between individual patients in a single critical care unit but also in the case-mix of patients admitted to different units. Whilst acknowledging this heterogeneity we decided to pool all studies together and perform individual sensitivity analyses to evaluate if there was any difference between the groups.

We pooled data using either the random-effects model (REM) or fixed-effect model (FEM) depending on the presence or absence of statistical heterogeneity. Risk ratios (RR) were pooled using the Mantel-Hansen (M-H) method. If there were many ‘zeros’ the Peto method was considered. The mean difference (MD) for continuous data was analysed using the inverse variance method. We used RevMan 5.1 for all analyses.

Subgroup analysis and investigation of heterogeneity

We performed stratified meta-analyses, using all available mortality data only, to investigate the influence of:
1. sepsis versus SIRS;
2. aetiology of critical illness (medical versus surgical studies);
3. delay of administration of N-acetylcysteine (less than 24 hours versus more than 24 hours from the first documented signs of SIRS or sepsis).

Conduct of the proposed subgroup analyses, defined a priori, was 'hypothesis generating'. We expected that all subgroup analyses would be underpowered and we viewed these as exploratory given their propensity to generate misleading conclusions (Oxman 1992).

Statistical heterogeneity

We conducted an evaluation of the heterogeneity of the data using the I^2 statistic (Higgins 2002), which is a statistic that describes the proportion of variation in point estimates that is attributable to heterogeneity as opposed to sampling error. We decided a priori that in the case where the assumption of homogeneity was rejected for any endpoint ($I^2 > 50\%$) a random-effects model would be applied to estimate the variance component associated with between-study variation for that endpoint. According to this method, the variance for each individual study in the meta-analysis is the sum of within- and between-study components of the variance. We also decided a priori not to pool the data if the I^2 statistic indicated significant heterogeneity ($I^2 > 80\%$).

Sensitivity analysis

1. Comparing estimates of the pooled intervention effect in trials with low risk of bias to estimates from trials with high risk of bias (i.e. trials having at least one inadequate risk of bias component).

2. Comparing estimates of the pooled intervention effect in trials based on the different components of risk of bias (random sequence generation, allocation concealment, blinding).

We calculated RR with 95% CI, if possible, for our sensitivity and subgroup analyses based on our primary outcome measure (mortality).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies

We identified 6983 potential studies in the initial electronic search. One potential study was identified during a Google search. No additional studies were identified by contacting experts in the field or relevant pharmaceutical companies, or by searching personal reference databases of the authors or steering group. No additional studies were identified following screening of reference lists of potentially eligible studies and previously published systematic reviews (snowballing). See Figure 3 for our search results.

Figure 3. Study flow diagram.

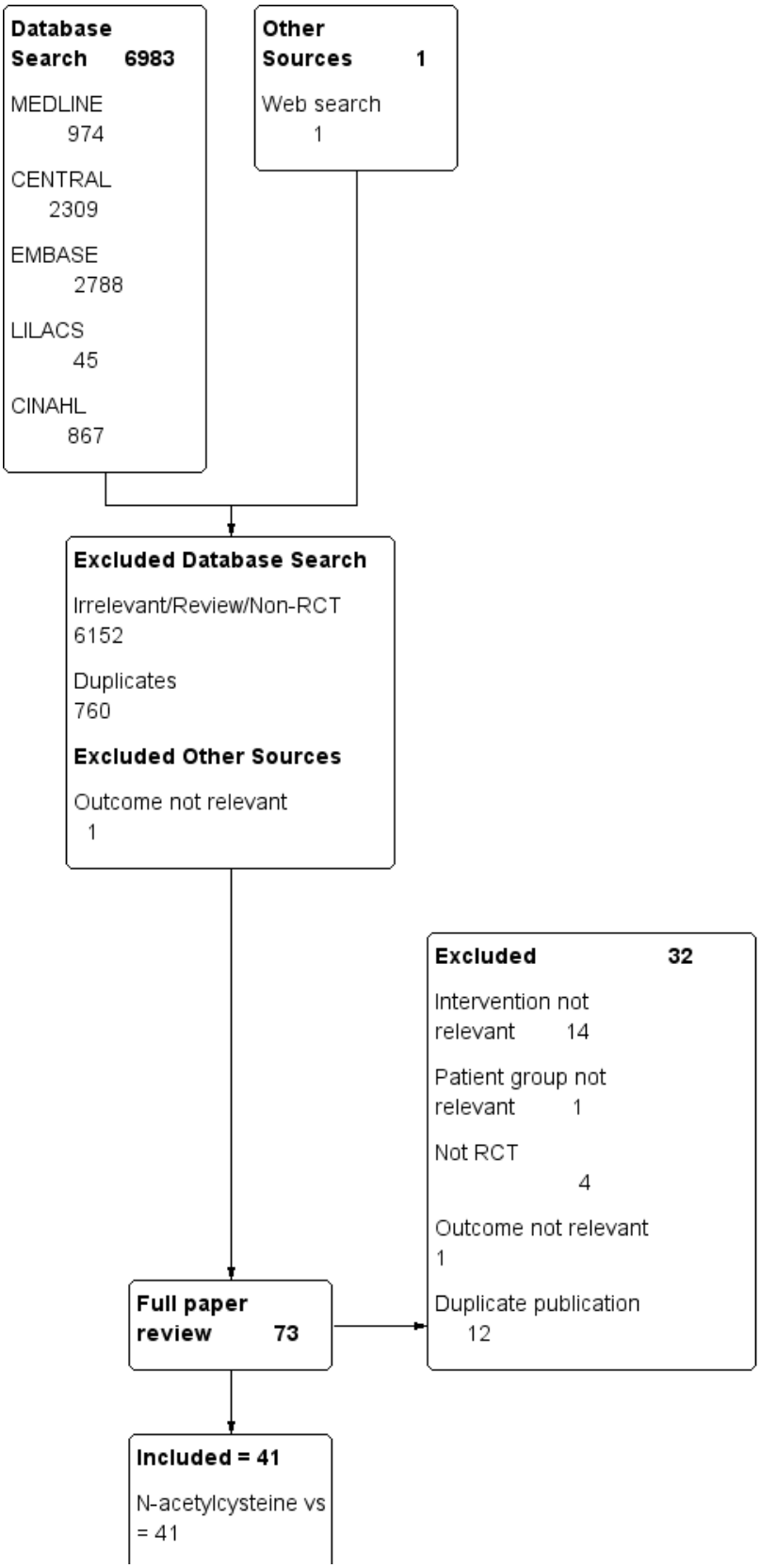
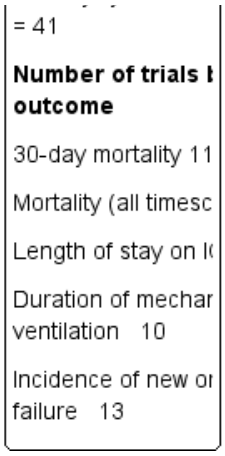


Figure 3. (Continued)



Results of the search

We identified 73 potentially eligible studies following screening of abstracts of potential studies (BH, TSZ). We found no ongoing trials. The two review authors (BH, TSZ) completely agreed on the selection of included studies. We obtained no additional information from the primary authors.

Included studies

We included 41 fully published studies (including 2768 patients). A detailed summary of each included study, including patient characteristics and the N-acetylcysteine dosing regimens used, can be found in Characteristics of included studies. The included studies were conducted between 1991 and 2009.

All studies used intravenous N-acetylcysteine but two studies used oral N-acetylcysteine preoperatively then intravenous N-acetylcysteine intraoperatively (El-Hamamsy 2007; Macedo 2006). Twenty studies evaluated the use of N-acetylcysteine perioperatively, 15 during cardiac surgery (Andersen 2005; Burns 2005; De Backer 1996; El-Hamamsy 2007; Eren 2003; Haase 2007; Orhan 2006; Ozaydin 2008; Peker 2008; Ristikankare 2006; Sisillo 2008; Spies 1996; Sucu 2004; Tossios 2003; Wijeysundera 2007); three during liver transplantation (Bromley 1995; Hilmi 2010; Steib 1998; Hilmi 2010); two in vascular surgery (Hynninen 2006; Macedo 2006) and one after major abdominal surgery (Szakmany 2003). Eight studies used N-acetylcysteine in patients with severe sepsis or septic shock (Emet 2004; Ortolani 2000b; Paterson 2003; Peake 1996; Rank 2000; Spapen 1998; Spapen 2005; Spies 1994); five in ARDS (Bernard 1997; Domenighetti 1997; Jepsen 1992; Moradi 2009; Suter 1994); two in multiple organ failure (Burns 2010; Molnar 1999); three in fulminant liver failure (Keays 1991; Lee 2009; Walsh 1998), one in malaria (Charunwatthana 2009) and one in burns (Csontos 2011). There was a wide variety in the N-acetylcysteine dose regime used, which ranged from 25 mg/kg to 150 mg/kg. Timing and duration of N-acetylcysteine treatment varied considerably, from single bolus dose to infusions up to seven days. In one trial (Ortolani 2000b) N-acetylcysteine was compared to rutin and placebo. We only report the data for the N-acetylcysteine and placebo groups from this trial. Three trials compared N-acetylcysteine with no treatment (Csontos 2011; Macedo 2006; Orhan 2006). Other clinical outcome variables in line with our defined primary and secondary outcomes were inconsistently reported.

Excluded studies

We excluded 32 potentially relevant publications (Adabag 2008; Agusti 1997; Barr 2008; Csontos 2011; Csontos 2011b; De Rosa 2000; Devlin 1997; Fischer 2005; Fraga 2011; Haase 2008; Heller 2001; Jepsen 1989; Koksal 2008; Komisarof 2007; Koramaz 2006; Kurian 2010; Laurent 1996; Lawlor 2007; Milewski 2006; Molnar 1998; Molnar 2003; Najafi 2009; Niemi 2006; Ortolani 2000a; Reinhart 1995; Sahib 2010; Saricaoglu 2005; Siriwardena 2007; Soltan-Sharifi 2007; Spies 1993; Szakmany 2002; Wijeysundera 2009; Zingg 2007). The reasons for their exclusion are summarized in Characteristics of excluded studies.

Risk of bias in included studies

We have identified 20 papers with low risk of bias. For a more detailed description of individual trial qualities, see the table Characteristics of included studies. The various bias domains are presented in the 'Risk of bias' graph and a 'Risk of bias' summary figure (Figure 1; Figure 2).

Allocation

Random sequence generation was adequately reported in 24 trials (Bernard 1997; Burns 2005; Burns 2010; Charunwatthana 2009; Emet 2004; Haase 2007; Hilmi 2010; Hynninen 2006; Keays 1991; Lee 2009; Molnar 1999; Ozaydin 2008; Paterson 2003; Peake 1996; Ristikankare 2006; Sisillo 2008; Spapen 1998; Spapen 2005; Spies 1994; Spies 1996; Szakmany 2003; Tossios 2003; Walsh 1998; Wijeysundera 2007). Allocation concealment was adequately reported in 25 studies (Bernard 1997; Burns 2005; Burns 2010; Charunwatthana 2009; Domenighetti 1997; El-Hamamsy 2007; Emet 2004; Haase 2007; Hilmi 2010; Hynninen 2006; Keays 1991; Lee 2009; Molnar 1999; Ozaydin 2008; Paterson 2003; Peake 1996; Ristikankare 2006; Spapen 1998; Spapen 2005; Spies 1994; Spies 1996; Suter 1994; Szakmany 2003; Tossios 2003; Walsh 1998; Wijeysundera 2007).

Blinding

Thirty trials provided sufficient data to be categorized as double blinded (Bernard 1997; Bromley 1995; Burns 2005; Burns 2010; Charunwatthana 2009; Domenighetti 1997; El-Hamamsy 2007; Emet 2004; Eren 2003; Haase 2007; Hilmi 2010; Hynninen 2006; Jepsen 1992; Lee 2009; Molnar 1999; Ozaydin 2008; Paterson 2003; Peake 1996; Peker 2008; Rank 2000; Ristikankare 2006; Sisillo 2008;

Spapen 1998; Spapen 2005; Spies 1994; Spies 1996; Suter 1994; Szakmany 2003; Tossios 2003; Wijeysundera 2007). The remaining 11 trials were either open label or did not provided sufficient information about how double blinding was achieved (Andersen 2005; Csontos 2011; De Backer 1996; Keays 1991; Macedo 2006; Moradi 2009; Orhan 2006; Ortolani 2000b; Steib 1998; Sucu 2004; Walsh 1998).

Incomplete outcome data

There was complete follow up in all trials except four for the primary outcome (De Backer 1996; Spapen 2005; Spies 1996; Walsh 1998). In these four trials the authors did not provide data on mortality nor on the length of follow up.

Selective reporting

In one study we found evidence of the possibility of selective reporting. In this study the number of patients recruited to the treatment (17 patients) and placebo (10 patients) groups was very different. Furthermore three patients in the N-acetylcysteine group were excluded from the analysis, without reasonable explanation (Moradi 2009). We were unable to retrieve the original protocols of the trials and thus were unable to examine selective outcome reporting, as described above. However, all but four trials provided data on our primary outcome of mortality (De Backer 1996; Spapen 2005; Spies 1996; Walsh 1998).

Other potential sources of bias

The funnel plot of standard error versus risk ratio for 30-day mortality (Figure 4) and the funnel plot for all reported mortality (Figure 5) showed a symmetrical distribution that indicated no bias or publication bias. Since there was no asymmetry or heterogeneity in the funnel plot, we found no need to apply the Arcsine-Thompson test as proposed by Rücker (Rücker 2008).

Figure 4. Funnel plot of comparison: 1 N-acetylcysteine versus placebo, outcome: 1.1 30-day all-cause mortality.

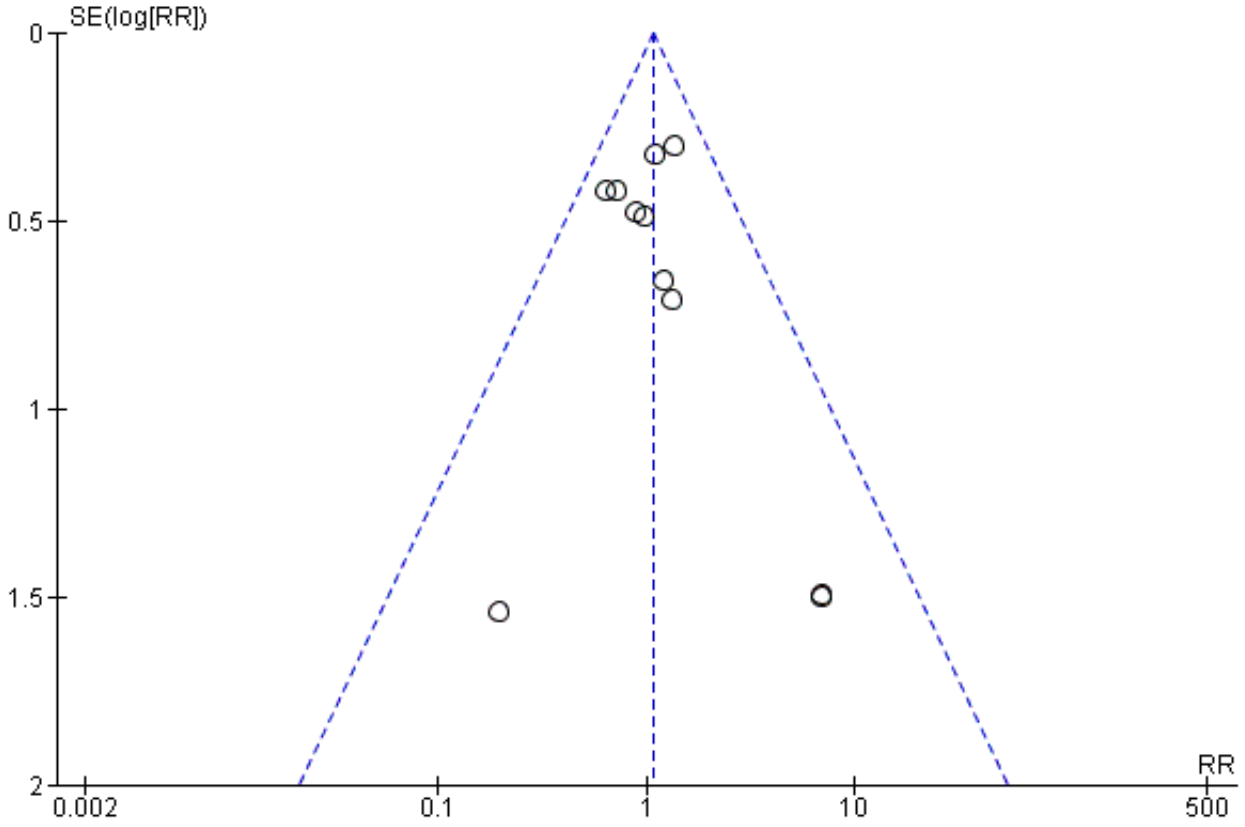
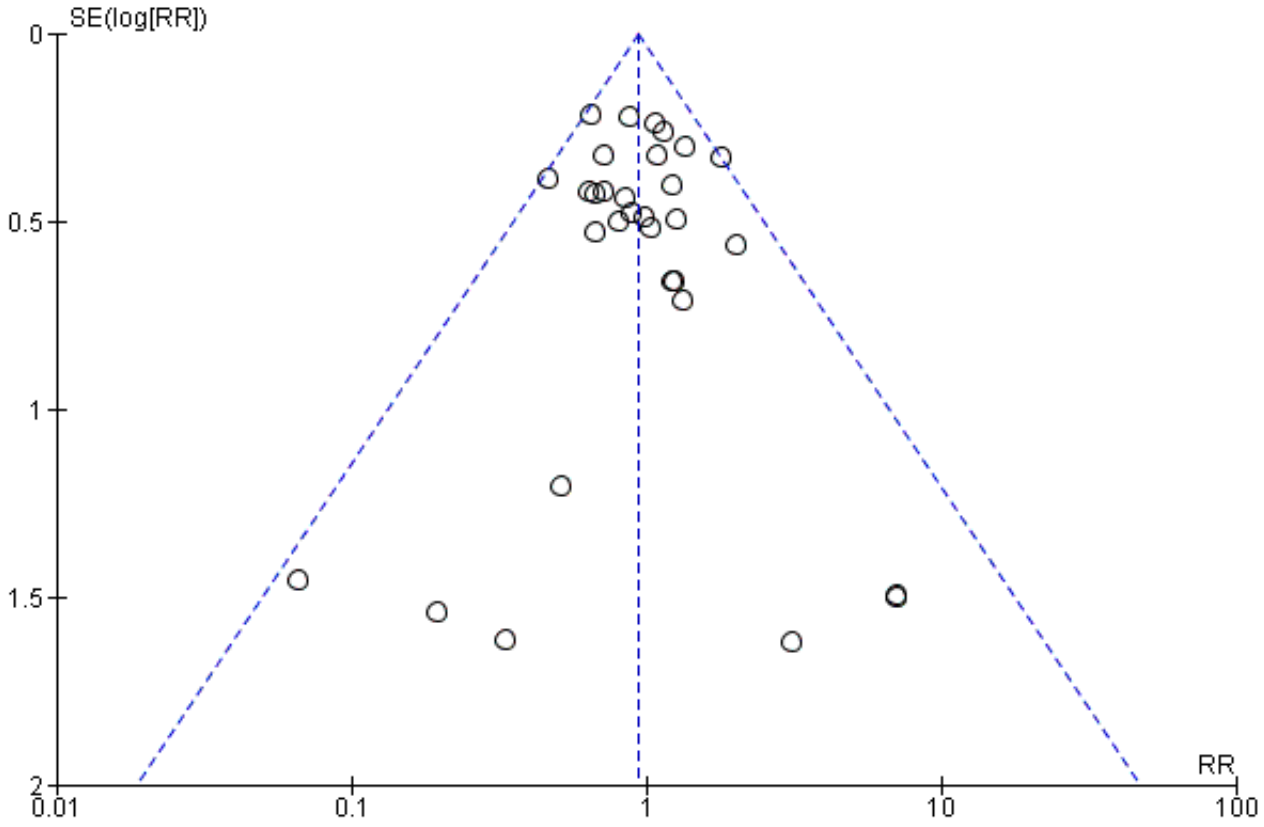


Figure 5. Funnel plot of comparison: 2 N-acetylcysteine versus placebo - subgroup analysis, outcome: 2.1 Mortality (all reported time scales).



Effects of interventions

See: **Summary of findings for the main comparison**

Eleven trials reported the primary outcome. Combining the data from these studies and applying complete-case analysis showed no statistically significant effect of N-acetylcysteine on 30-day all-cause mortality: 67/467 (14.35%) deaths in the N-acetylcysteine group compared with 63/463 (13.60%) deaths in the control group (RR 1.07, 95% CI 0.80 to 1.43; I^2 = 0%) (Analysis 1.1). In combining the data from the 37 studies reporting mortality, using the longest reported follow-up data, mortality was similar: 223/1228 (18.16%) in the N-acetylcysteine group and 241/1233 (19.55%) in the placebo group (RR 0.94, 95% CI 0.81 to 1.09; I^2 = 0%) (Analysis 2.1).

Sensitivity analysis - analysis of bias

Comparing estimates of the pooled intervention effect based on the overall risk of bias (Analysis 2.2) (high risk of bias: 12 studies, 919 patients; low risk of bias: 17 studies, 1524 patients); on random sequence generation (Analysis 2.3) (adequate sequence generation: 20 studies, 1899 patients; inadequate or unclear sequence generation: 12 studies, 602 patients); on allocation concealment (Analysis 2.4) (adequate allocation concealment: 22 studies, 1835 patients; inadequate or unclear allocation concealment: 11 studies, 706 patients) or on blinding (Analysis 2.5) (adequate blinding: 25 studies, 2228 patients; inadequate or unclear blinding: 6 studies, 233 patients) did not result in any statistically significant finding in any of the subgroups examined.

Sensitivity analysis - analysis of follow-up time

As the studies reported variable follow-up times we have pooled the trials in two groups, one reporting short follow-up time scales (less than 30 days) and one with a long follow-up time scale. We could not find any significant difference in reported mortality between patients in the N-acetylcysteine and placebo arms in any of these subgroups (Analysis 2.6) (short time scale: 14 studies, 1524 patients; long time scale: 18 studies, 957 patients).

Subgroup analysis - sepsis versus SIRS and medical versus surgical aetiology

None of the stratified meta-analyses revealed any significant effect of N-acetylcysteine. It did not affect mortality in patients admitted to the ICU with sepsis or SIRS (Analysis 2.7) (sepsis: eight studies, 369 patients; SIRS: nine studies, 527 patients), nor did it show any significant effect when we analysed the aetiology of the critical illness (Analysis 2.8) (medical background: 16 studies, 926 patients; surgical background: 13 studies, 1478 patients).

Subgroup analysis - early versus late administration

Application of N-acetylcysteine early to prevent the development of an oxidato-inflammatory response did not affect outcome, nor did late application that is after 24 hours of developing symptoms (Analysis 2.9) (early administration: 24 studies, 2075 patients; late administration: eight studies, 362 patients). Three trials compared N-acetylcysteine to no treatment and there was no significant difference between these two groups (10 deaths/43 patients versus

10 deaths/49 patients, respectively) (Csontos 2011; Macedo 2006; Orhan 2006).

Secondary outcomes

N-acetylcysteine did not show any significant effect on length of ICU stay, duration of mechanical ventilation or incidence of new organ failure (Analysis 3.1; Analysis 4.1; Analysis 5.1). When analysing length of stay there was significant heterogeneity that was not otherwise explained (I^2 = 83%, P < 0.0001), therefore a summary estimate must be interpreted with great caution. Only five trials compared the duration of inotropic support, they reported that the difference was not significant between the N-acetylcysteine and control groups (Burns 2005; Haase 2007; Hynninen 2006; Molnar 1999; Szakmany 2003). None of the trials reported healthcare costs and quality of life data.

DISCUSSION

In this systematic review of 41 trials with 2768 patients with sepsis and SIRS we found no benefits of N-acetylcysteine on survival (See Summary of findings for the main comparison). The analysis on mortality showed no heterogeneity and was robust when performing different subgroup and sensitivity analyses. The sparse data on mortality are not promising but are not evidence of the absence of a beneficial effect; the data suggest that a potentially beneficial effect of N-acetylcysteine must be very modest and the actual point estimate on the 30-day all-cause mortality suggests harm (Analysis 1.1; Analysis 2.1).

As the included studies reported the mortality over variable time periods, there was the possibility of over- or underestimating the mortality when pooling studies with long and short follow-up times. Therefore we have performed a subgroup analysis, which showed no significant difference between short-term, that is less than 30 days, and long-term, that is more than 30 days up to one year, reported mortality (Analysis 2.6).

Despite the well-defined inclusion criteria, there is considerable heterogeneity amongst the trials in terms of patient population, timing and dosage of N-acetylcysteine. We included 20 studies in which N-acetylcysteine was used to prevent the evolution of the oxido-inflammatory response, where patients developed SIRS during the operation. We also identified 21 studies where patients were treated with N-acetylcysteine after they had already developed symptoms of SIRS or sepsis. To address this heterogeneity we completed an a priory defined subgroup analysis. However, the analysis did not show any effect on mortality when patients with sepsis or with an established systemic inflammatory response were studied (Analysis 2.7).

To assess the impact of N-acetycysteine on the various primary aetiologies, we have conducted subgroup analyses in patients admitted to the ICU with a 'medical' condition (16 studies of patients with conditions ranging from sepsis, multiorgan failure and ARDS to acute fulminant liver failure and burns) as opposed to a distinct surgical insult (13 studies, including patients undergoing cardiac, vascular and major abdominal surgery). None of these yielded significant results (Analysis 2.8).

Early or late administration of N-acetylcysteine did not affect the outcome (Analysis 2.9). Although all of the methodologically sound trials involving this patient population observed that late administration might be harmful (Molnar 1999; Peake 1996; Spies 1994), our sensitivity analysis could not confirm this (Analysis 2.9) (eight studies, 362 patients). Peake and colleagues (Peake 1996) and later Spapen et al (Spapen 2005) also demonstrated that late administration of N-acetylcysteine in patients with septic shock caused depression of cardiovascular performance, as indicated by a decrease in cardiac output and the mean arterial pressure. The possibility for excess mortality was attributed to depressed cardiovascular function with a higher need of vasopressors. This finding was corroborated by reports showing that delayed administration also failed to improve tissue oxygenation and partial pressure of arterial oxygen over fraction of inspired oxygen (PaO_2/FiO_2) ratio (Agusti 1997; Spapen 2005). This could not be confirmed when analysing the secondary outcome measures, mainly because of the lack of reported data on length of inotropic support. However, it has been mentioned in various trials that the infusion of N-acetylcysteine caused temporary haemodynamic instability, but this was not quantified further (Emet 2004; Molnar 1999; Peake 1996; Rank 2000; Spapen 2005; Spies 1996).

Perhaps the failure to find a clinical role for therapies aimed at the reduction of oxygen free radicals is because the studies are based on the limited paradigm that oxygen free radicals only cause injury. An alternative view is that although oxygen free radicals are potentially highly toxic, redox reactions are also part of the basic chemical processes of life. Oxygen free radicals are an essential part of many metabolic pathways; they are part of the frameworkof basic energy producing processes. Organisms have had to evolve elaborate mechanisms to live with these reactive molecules and seem also to have evolved to use the reactive nature of these molecules for intracellular signal transduction (Magder 2006). Based on these results a key concept in dealing with oxygen free radicals must be to regulate but not eradicate them.

Early administration, on the other hand, whilst not showing a statistically significant effect did indicate a possible benefit (23 studies) (Analysis 2.9). Similar signal was detected when only the high quality trials were analysed (data not shown). Early administration of N-acetylcysteine could beneficially affect the lipid peroxidation of cell membranes. It is becoming increasingly apparent that redox-sensitive signalling pathways, known to be important in initiating inflammatory-immune activation pathways, influence a broad array of cell signalling and gene pathways in the context of the transition metal milieu (Cross 2006). These can relate to antimicrobial host defence and to reparative and adaptive processes, sometimes involving production of anti-inflammatory cytokines and wound healing (Cross 2006).

The dose of N-acetylcysteine in the included trials showed great variability, from a single bolus of 50 mg/kg to continuous infusions delivering N-acetylcysteine in doses in the region of 15,000 to 20,000 mg/day. The rationale for the different regimens in different studies has not been clarified and so their clinical relevance is questionable. It is possible that the applied dose was either excessive or inadequate in some of the studies. The majority of the studies based their dosing regimens on the protocol for patients receiving treatment for acetaminophen poisoning (150 mg/kg). It has been suggested that the initial concentration of 150 mg/kg N-acetylcysteine should be modified since liver damage in acetaminophen poisoning was prevented just as effectively by the lowest as well as at the highest plasma concentrations of the drug (Prescott 1989). The possible disadvantage of excessive doses

could be the formation of toxic intermediate molecules during N-acetylcysteine metabolism, such as thiol and glutathionyl free radicals, glutathione disulfide and cysteine (Harman 1984).

The studies showed a great variability regarding the length of treatment, from one single bolus to six days of continuous treatment, with no evidence to support any of the applied methods. Interestingly, the most recent experimental data indicates that prolonged N-acetylcysteine was deleterious even in acetaminophen intoxication, for which N-acetylcysteine is normally the antidote (Yang 2009). Based on our data, we could not find any correlation between the dosage of N-acetylcysteine and outcome in this patient population.

Summary of main results

In summary, we found that N-acetylcysteine is ineffective in reducing mortality and morbidity in SIRS and sepsis.

Overall completeness and applicability of evidence

Our study pools data on the effect of intravenous N-acetylcysteine from 41 studies involving 2768 patients. The trials were identified following a detailed systematic search of the literature. Study inclusion criteria were tightly defined and the meta-analysis was rigorously conducted according to a predefined analysis plan addressing specific hypotheses. The meta-analysis combined data from a group of predominantly underpowered single centre studies. However, the included studies reflect international practice, from North America to the Middle East and Australasia, although the majority of included studies are from major teaching centres.

Although there was minimal heterogeneity among trial results on mortality, we are aware that we pooled clinical trials that are typical of critical care and perioperative medicine in terms of age, patients, settings, and treatment regimens. Thus, the validity of our meta-analysis may be criticized. However, all trials included critically ill patients where a common systemic inflammatory pathway was activated. Therefore, we think that there is a good biologic reason to perform a broad meta-analysis, which also considerably increases the generalizability and usefulness of the review (Goetzsche 2000).

Quality of the evidence

The quality of the included studies varied and it was apparent from the result of the sensitivity analysis that internal flaws in the study design could result in significant bias. Only 20 out of 41 trials were scored as high quality and according to our power calculation the sample size of 1524 patients that was included in these trials is not enough to exclude malevolence. To ascertain the presence of a 2% relative risk reduction, according to our calculations 8548 patients would be needed in a well-designed, transparently reported multicentre trial to clear the doubts about the use of N-acetylcysteine in the critically ill.

Potential biases in the review process

Several possible sources of bias arise in this meta-analysis. First, selection bias is possible with every review. To avoid this, we searched for studies from several databases without language restrictions. Second, the possibility of publication bias cannot be excluded. Visual inspection of the Funnel plot also suggested that publication bias is unlikely. Third, flaws in the original study designs are a significant potential source of bias. The studies included in this review are typical of studies in critical care research in general in that the vast majority of studies are underpowered and single centre. The meta-analysis includes 2768 patients but the unit of analysis is the study (or study subgroup) and the sample size (41 studies) is relatively small. Although defined a priori, our stratified analysis (subgroup analysis) should be seen as hypothesis generating only. Fourth, while studies utilized different N-acetylcysteine doses and schedules, we were unable to assess this heterogeneity on outcomes, thus we cannot discern the optimal N-acetylcysteine dosing from our meta-analysis.

Agreements and disagreements with other studies or reviews

This review represents the best up-to-date summary of the literature. We framed a tightly defined question and used explicit inclusion criteria for studies and a predefined analysis plan. Our primary result agrees with from those of recent reviews in this area, which have raised questions about the efficacy of N-acetylcysteine in preventing renal dysfunction, other morbidity or death in the perioperative period (Adabag 2009; Baker 2009; Ho 2009; Naughton 2008; Nigwekar 2009).

Clinical application of N-acetylcysteine in sepsis has been questioned in two recent editorials in leading journals (Molnar 2008; Spapen 2004). These voiced similar concerns to ours regarding the efficacy and safety of the drug.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, this meta-analysis puts doubt on the safety and utility of intravenous N-acetylcysteine as an adjuvant therapy in SIRS and sepsis. At best, N-acetylcysteine is ineffective in reducing mortality and complications in this patient population. At worst, it can be harmful, especially when administered later than 24 hours after the onset of symptoms, by causing cardiovascular depression. Unless future RCTs provide evidence of treatment effect, clinicians should not routinely use intravenous N-acetylcysteine in SIRS and sepsis and academics should not promote its use.

Implications for research

Many issues regarding the use of N-acetylcysteine in patients with SIRS and sepsis have received remarkably poor attention or remain unresolved. The pharmacokinetics and pharmacodynamics of the drug are virtually unknown. It remains to be determined whether and how N-acetylcysteine influences basic cellular processes such as bacterial clearance, neutrophil-endothelial cell interplay and apoptosis. More information is needed about possible drug interactions and toxic effects of N-acetylcysteine or its metabolites. Until we have a better understanding of these questions, intravenous N-acetylcysteine should only be used in adequately powered (and preferably multicentre) studies testing an explicitly framed hypothesis. These should be methodologically rigorous and blinded.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andersen 2005

Methods	Randomized, placebo-controlled trial
Participants	Cardiac surgery, high risk
Interventions	iv N-acetylcysteine 100mg/kg bolus on induction then 20mg/kg/hr during surgery versus placebo (not specified)
Outcomes	Inflammatory response, mortality
Notes	No side effects

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation to treatment group not clearly stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of treatment: not stated. Blinding of assessor: not stated. Blinding of data analysis: not stated.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Bernard 1997

Methods	Randomized, double blinded, placebo-controlled trial
Participants	ARDS
Interventions	iv N-acetylcysteine 210 mg daily for 10 days versus placebo (5% dextrose)
Outcomes	30-day mortality
Notes	

Bernard 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer permuted block generation.
Allocation concealment (selection bias)	Low risk	Ready made concealed bags supplied by pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, medical and nursing team and patients were blinded.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Bromley 1995

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Orthotopic liver transplantation
Interventions	iv N-acetylcysteine 150 mg/kg bolus then 12.5mg/kg/hr for 4 hrs then 6.25 mg/kg/hr until the end of surgery versus placebo (not specified)
Outcomes	haemodynamic variables, 30-day mortality, morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only stated "randomized".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated: "double-blind".
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Burns 2005

Methods	Randomized, quadruple blinded, placebo-controlled trial
Participants	Cardiac surgery
Interventions	iv N-acetylcysteine 4 times 600mg in 24 hours, two intraoperatively two postoperatively versus placebo (5% dextrose)
Outcomes	renal function, mortality, morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated permuted blocks strategy.
Allocation concealment (selection bias)	Low risk	Centrally prepared premixed and preprepared bags.
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated in manuscript: Patients, health care clinicians, and individuals participating in the data collection and data analysis were blinded to treatment assignment.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Burns 2010

Methods	Randomised controlled trial
Participants	Critically ill patients undergoing contrast enhanced CT
Interventions	iv N-acetylcysteine 5000mg before CT, 2500mg 6 hours and 12 hours after CT versus placebo (dextrose 5%)
Outcomes	increase in creatinine by 50 micromol/L by day 5, ICU length of stay
Notes	No adverse reactions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number tables.
Allocation concealment (selection bias)	Low risk	Study medication centrally prepared and supplied in identical bags.
Blinding (performance bias and detection bias)	Low risk	Patients, medical and nursing staff were blinded to the intervention.

Burns 2010 *(Continued)*

All outcomes	
Selective reporting (reporting bias)	Low risk
Other bias	Low risk

Charunwatthana 2009

Methods	Randomized double blinded trial
Participants	Severe malaria
Interventions	iv N-acetylcysteine 150mg/kg bolus, 50mg/kg for 4 hrs then 100mg/kg for 16 hrs versus placebo (dextrose 5%)
Outcomes	lactate clearance, mortality, morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer allocated blocks.
Allocation concealment (selection bias)	Low risk	Identical ampoules supplied centrally.
Blinding (performance bias and detection bias) All outcomes	Low risk	Doctors, nurses and patients were masked for the treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Csontos 2011

Methods	Randomised controlled trial
Participants	Patients with severe burns
Interventions	N-acetylcysteine 150mg/kg bolus and 12mg/kg/hr for 5 days versus standard treatment (no placebo)
Outcomes	oxidative stress, inflammatory markers, oedema formation
Notes	

Risk of bias

Csontos 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states randomised controlled trial, but no method given for randomization.
Allocation concealment (selection bias)	High risk	N-acetylcysteine was compared to standard treatment (no placebo).
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

De Backer 1996

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery, low risk
Interventions	iv N-acetylcysteine 72mg/kg bolus preoperatively then 72 mg/kg for 12 hrs versus placebo (0.9% NaCl)
Outcomes	inflammatory mediators in BAL
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only stated: "randomized".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Only stated: "double-blinded fashion".
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Domenighetti 1997

Methods	Randomized, double blinded, placebo-controlled trial

Domenighetti 1997 *(Continued)*

Participants	ARDS
Interventions	iv N-acetylcysteine 190 mg/kg/day for 3 days versus placebo (not specified)
Outcomes	mortality, morbidity, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states: "randomized".
Allocation concealment (selection bias)	Low risk	Similar vials.
Blinding (performance bias and detection bias) All outcomes	Low risk	Researchers, medical, nursing staff and patients blinded.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

El-Hamamsy 2007

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery
Interventions	N-acetylcysteine oral 600 mg preoperatively then 150 mg/kg iv bolus on incision versus placebo (5% dextrose)
Outcomes	mortality, organ dysfunction
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states: "randomized".
Allocation concealment (selection bias)	Low risk	Similar preparation for N-acetylcysteine and placebo.
Blinding (performance bias and detection bias) All outcomes	Low risk	States: "double-blinded".

El-Hamamsy 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk
Other bias	Low risk

Emet 2004

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Severe sepsis
Interventions	iv N-acetylcysteine 150 mg/kg bolus then 12 mg/kg/hr for 6 hrs versus placebo (dextrose 5%)
Outcomes	Gastric tonometry, inflammatory response, mortality, length of mechanical ventilation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated blocks.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Drug solution and infusion was administered to all patients by a nurse without any knowledge about the study protocol. Patients and medical staff was blinded to the treatment.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Eren 2003

Methods	Randomized, placebo-controlled trial
Participants	Cardiac surgery (low risk)
Interventions	iv N-acetylcysteine 100 mg/kg bolus on induction and 40 mg/kg/day for 24 hrs versus placebo (0.9% NaCl)
Outcomes	haemodynamics, oxygenation, time for extubation, lipid peroxidation, mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Eren 2003 *(Continued)*

Random sequence generation (selection bias)	High risk	States: The decision of which procedure should be performed was made independently by the surgeon.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Medical, nursing staff and patients.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Haase 2007

Methods	Randomized, multi blind, placebo-controlled trial
Participants	Cardiac surgery (high risk for postoperative renal failure)
Interventions	iv N-acetylcysteine 150mg/kg bolus on induction, 50mg/kg for 4 hrs then 100mg/kg for 16 hrs versus placebo (dextrose 5%)
Outcomes	Absolute change in serum creatinine from baseline, morbidity, LOS, mortality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer random number generator with permuted blocks.
Allocation concealment (selection bias)	Low risk	Central randomization, premixed bags were used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and all staff were blinded to the treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Hilmi 2010

Methods	Randomised controlled double blinded clinical trial
Participants	Patients undergoing orthotopic liver transplantation

Hilmi 2010 *(Continued)*

Interventions	N-acetylcysteine 140mg/kg bolus at the start of surgery, 70mg/kg every 4 hours for a total of 12 doses versus placebo (5% dextrose)
Outcomes	incidence of post-transplantation acute kidney injury, liver graft performance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation in blocks.
Allocation concealment (selection bias)	Low risk	Central randomization, premixed bags were used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and all staff were blinded to the treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Hynninen 2006

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Vascular surgery
Interventions	iv N-acetylcysteine 150 mg/kg bolus on induction then 150 mg/kg for 24 hrs versus placebo (dextrose 5%)
Outcomes	renal dysfunction
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation in blocks.
Allocation concealment (selection bias)	Low risk	Central randomization, premixed bags.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and staff.
Selective reporting (reporting bias)	Low risk	

Hynninen 2006 *(Continued)*

Other bias	Low risk

Jepsen 1992

Methods	Randomized, double blinded, placebo-controlled trial
Participants	ARDS
Interventions	iv N-acetylcysteine 150 mg/kg bolus and 20 mg/kg/hr for 7 days versus placebo (not stated)
Outcomes	resolution of ARDS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only stated: patients were randomized.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and staff were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Keays 1991

Methods	Randomized, placebo-controlled trial
Participants	Patients with fulminant liver failure
Interventions	iv N-acetylcysteine 150mg/kg bolus on induction, 50mg/kg for 4 hrs then 100mg/kg for 16 hrs versus placebo (dextrose 5%) until recovery from encephalopathy or death
Outcomes	mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation.

Keays 1991 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of treatment: no. Blinding of assessor: not stated. Blinding of data analysis: not stated.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Lee 2009

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Liver failure patients waiting for liver transplantation
Interventions	iv N-acetylcysteine 150 mg/kg/h over 1 hour, followed by 12.5 mg/kg/h for 4 hours, then continuous infusions of 6.25 mg/kg N-acetylcysteine for the remaining 67 hours versus placebo (5% dextrose)
Outcomes	21-day mortality, transplant-free survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.
Allocation concealment (selection bias)	Low risk	Central allocation, premixed bags prepared by pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, staff and investigators blinded for treatment intervention.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Macedo 2006

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Vascular surgery patients
Interventions	N-acetylcysteine 2400 mg oral before surgery then 1200 mg iv for 48 hrs postop versus no treatment

Macedo 2006 *(Continued)*

Outcomes	occurrence of acute renal failure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	High risk	N-acetylcysteine versus no treatment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated "double-blinded" but compared N-acetylcysteine versus no treatment.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Molnar 1999

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Ventilated patients with two or more organ failures
Interventions	iv N-acetylcysteine 150 mg/kg bolus then 12 mg/kg/hr for 3 to 5 days versus placebo (dextrose 5%)
Outcomes	mortality, resolution of organ dysfunction
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, medical and nursing staff were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Moradi 2009

Methods	Randomized, single blinded, placebo-controlled trial
Participants	ARDS
Interventions	iv N-acetylcysteine 150 mg/kg bolus then 50 mg/kg/day for 3 days versus placebo (dextrose 5%)
Outcomes	mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only stated; "simple randomization".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of treatment: patients only. Blinding of assessor: no. Blinding of data analysis: not stated.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Orhan 2006

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery (low risk)
Interventions	iv N-acetylcysteine 50 mg/kg bolus on induction vs no treatment
Outcomes	oxidative stress levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	High risk	Method of allocation to treatment group not clearly stated.
Blinding (performance bias and detection bias)	Unclear risk	Stated double blind, but investigated N-acetylcysteine versus no treatment.

Orhan 2006 *(Continued)*

All outcomes	
Selective reporting (reporting bias)	Low risk
Other bias	Low risk

Ortolani 2000b

Methods	Randomised controlled trial
Participants	ARDS patients
Interventions	iv N-acetylcysteine 50 mg/kg bolus 8 hourly for 9 days versus placebo (5% dextrose). Third group received 50 mg/kg N-acetylcysteine plus rutin 5mg/kg, but this data is not included
Outcomes	lipid peroxidation, glutathione levels
Notes	Only iv N-acetylcysteine and placebo group data are analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	States "patients were randomly assigned" but no method described.
Allocation concealment (selection bias)	High risk	No data.
Blinding (performance bias and detection bias) All outcomes	High risk	Non-blinded trial.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ozaydin 2008

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery
Interventions	N-acetylcysteine 50 mg/kg bolus preoperatively then 50 mg/kg/day for 48 hrs versus placebo (0.9% NaCl)
Outcomes	incidence of postoperative AF
Notes	

Risk of bias

Ozaydin 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for treatment assignment.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Paterson 2003

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Patients with sepsis
Interventions	N-acetylcysteine 150mg/kg bolus then, 50mg/kg for 4 hrs then 50mg/kg for 16 hrs versus placebo (0.9% NaCl) for 72 hrs
Outcomes	NF-kB activation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Sealed envelope, premixed infusion.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for the treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Peake 1996

Methods	Randomized, double blinded, placebo-controlled trial

Peake 1996 *(Continued)*

Participants	Septic shock patients
Interventions	N-acetylcysteine 150mg/kg bolus then 50mg/kg for 4 hrs then 100mg/kg for 44 hrs versus placebo (dextrose 5%)
Outcomes	improvement in haemodynamic variables, resolution of organ failure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation.
Allocation concealment (selection bias)	Low risk	Sealed envelope, premixed bag of infusion by pharmacist.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Peker 2008

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery
Interventions	N-acetylcysteine 50 mg/kg bolus preoperatively then 50 mg/kg/day for 48 hrs versus placebo (0.9% NaCl)
Outcomes	markers of myocardial injury
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only stated: patients were randomized.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, medical staff and investigators blinded for treatment allocation.

Peker 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk
Other bias	Low risk

Rank 2000

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Septic shock
Interventions	N-acetylcysteine 150 mg/kg bolus then 12.5 mg/kg/hr versus placebo (dextrose 5%) for 90 minutes
Outcomes	liver blood flow and liver function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states: "patients were randomly assigned".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ristikankare 2006

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery
Interventions	N-acetylcysteine 150mg/kg bolus on induction, 50mg/kg for 4 hrs then 100mg/kg for 16 hrs versus placebo (0.9% NaCl)
Outcomes	renal function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Ristikankare 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number generation.
Allocation concealment (selection bias)	Low risk	Hospital pharmacy prepared the study infusions.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, staff and investigators were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Sisillo 2008

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery
Interventions	N-acetylcysteine 1200 mg bolus before induction then 1200 mg 12 hourly for 36 hrs versus placebo (0.9% NaCl)
Outcomes	occurrence of acute renal failure
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for treatment allocations.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Spapen 1998

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Septic shock patients

Spapen 1998 *(Continued)*

Interventions	N-acetylcysteine 150 mg/kg bolus then 50 mg/kg over 4 hours versus placebo (dextrose 5%)
Outcomes	haemodynamic and oxygen transport variables, inflammatory markers
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated permuted blocks.
Allocation concealment (selection bias)	Low risk	Infusions prepared by hospital pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for treatment allocations.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Spapen 2005

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Severe sepsis
Interventions	N-acetylcysteine50 mg/kg/4 hrs followed by 100 mg/kg/24 hrs for 44 hrs versus placebo (5% dextrose)
Outcomes	microalbuminuria, organ dysfunction scores
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated permuted blocks.
Allocation concealment (selection bias)	Low risk	Infusions prepared by hospital pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for treatment allocations.
Selective reporting (reporting bias)	Low risk	

Spapen 2005 *(Continued)*

Other bias	Low risk

Spies 1994

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Septic shock patients
Interventions	N-acetylcysteine 150 mg/kg bolus then 12.5 mg/kg/hr for 90 minutes versus placebo (dextrose 5%)
Outcomes	oxygen consumption, haemodynamic variables
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Spies 1996

Methods	Randomized, double blinded, placebo-controlled trial
Participants	High risk cardiac surgery patients
Interventions	N-acetylcysteine 150 mg/kg bolus versus placebo (dextrose 5%)
Outcomes	VO_2, tissue oxygenation
Notes	No mortality or other clinical outcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.

Spies 1996 *(Continued)*

Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Steib 1998

Methods	Randomized, placebo-controlled trial
Participants	Liver transplant patients
Interventions	N-acetylcysteine 150mg/kg bolus then, 50mg/kg for 4 hrs then 100mg/kg for 16 hrs versus placebo (dextrose 5%)
Outcomes	intraoperative haemodynamics and postoperative graft function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not-stated, only says "(patients) were allocated randomly to be administered either NAC or, ... placebo".
Allocation concealment (selection bias)	Unclear risk	Method of allocation to treatment group not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of treatment: not stated. Blinding of assessor: not stated. Blinding of data analysis: not stated. Probably not, as no indication of blinding in the manuscript.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Sucu 2004

Methods	Randomized placebo-controlled trial
Participants	Cardiac surgery
Interventions	N-acetylcysteine 50 mg/kg on induction than daily for 3 days versus placebo (0.9% saline)

Sucu 2004 *(Continued)*

Outcomes	Antioxidant capacity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of allocation sequence generation not stated.
Allocation concealment (selection bias)	Unclear risk	Method of allocation to treatment group not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding of treatment: not stated. Blinding of assessor: not stated. Blinding of data analysis: not stated.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Suter 1994

Methods	Randomized, double blinded, placebo-controlled trial
Participants	ALI/ARDS
Interventions	N-acetylcysteine 40 mg/kg/day for 3 days versus placebo (not stated)
Outcomes	development of ARDS, mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states: "patients were randomized".
Allocation concealment (selection bias)	Low risk	Similar vials for treatment and placebo.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients and investigators were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Szakmany 2003

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Major abdominal surgery
Interventions	N-acetylcysteine 150 mg/kg bolus on induction then 12 mg/kg/hr intraoperatively versus placebo (dextrose 5%)
Outcomes	organ dysfunction, mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.
Allocation concealment (selection bias)	Low risk	Sealed envelopes, pre-prepared infusions.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, staff and investigators were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Tossios 2003

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery
Interventions	N-acetylcysteine 100 mg/kg bolus on induction then 12 mg/kg/hr intraoperatively versus placebo (0.9% NaCl)
Outcomes	antioxidant levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.
Allocation concealment (selection bias)	Low risk	Identical appearance glass vials, supplied by pharmacy.

Tossios 2003 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, staff and investigators were blinded for treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Walsh 1998

Methods	Randomized controlled trial
Participants	Fulminant liver failure patients
Interventions	iv N-acetycysteine 150 mg/kg body over 15 minutes, followed by 50 mg/kg over 4 hours, followed by 100mg/kg over 16 hours versus placebo (5% dextrose)
Outcomes	haemodynamic variables, N-acetycysteine levels
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generation.
Allocation concealment (selection bias)	Low risk	Sealed envelopes, matching infusion bags.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Wijeysundera 2007

Methods	Randomized, double blinded, placebo-controlled trial
Participants	Cardiac surgery with moderate renal insufficiency
Interventions	N-acetylcysteine 100 mg/kg on induction then 20 mg/kg/hr for 4 hrs versus placebo (dextrose 5%)
Outcomes	renal impairment
Notes	

Wijeysundera 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random tables.
Allocation concealment (selection bias)	Low risk	Central randomization and preparation of drugs by independent pharmacist.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, clinicians and data-collectors were blinded to treatment allocation.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adabag 2008	Oral N-acetylcysteine
Agusti 1997	Cross-over design
Barr 2008	Oral N-acetylcysteine
Csontos 2011b	Duplicate publication
De Rosa 2000	Oral N-acetylcysteine
Devlin 1997	Non-RCT
Fischer 2005	Duplicate publication
Fraga 2011	i.v. N-acetylcysteine and deferoxamine combination
Haase 2008	Duplicate publication
Heller 2001	i.v. N-acetylcysteine regime versus different N-acetylcysteine regime (not placebo)
Jepsen 1989	Oral N-acetylcysteine
Koksal 2008	Non-intravenous N-acetylcysteine
Komisarof 2007	Oral N-acetylcysteine
Koramaz 2006	Oral N-acetylcysteine
Kurian 2010	Non-intravenous N-acetylcysteine
Laurent 1996	Duplicate publication

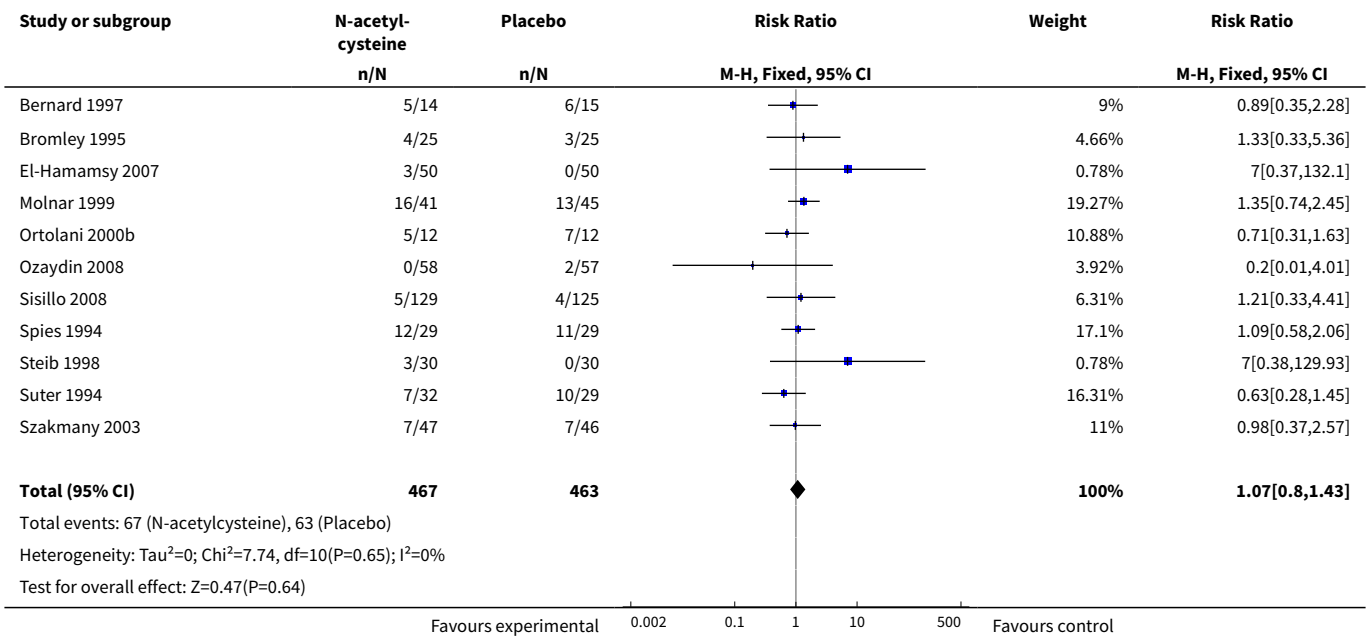
Study	Reason for exclusion
Lawlor 2007	Oral N-acetylcysteine
Milewski 2006	Oral N-acetylcysteine
Molnar 1998	Duplicate publication
Molnar 2003	Duplicate publication
Najafi 2009	Duplicate publication
Niemi 2006	Duplicate publication
Ortolani 2000a	N-acetylcysteine and glutathione (GSH) in treatment arm
Reinhart 1995	Duplicate publication
Sahib 2010	Non-randomized trial, oral N-acetylcysteine
Saricaoglu 2005	No clinical outcome data
Siriwardena 2007	N-acetylcysteine, selenium and vitamin C in treatment arm
Soltan-Sharifi 2007	Duplicate publication
Spies 1993	Duplicate publication
Szakmany 2002	Duplicate publication
Wijeysundera 2009	Duplicate publication
Zingg 2007	Non-randomized trial (before-after design)

DATA AND ANALYSES

Comparison 1. N-acetylcysteine versus placebo - primary outcome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 30-day all-cause Mortality	11	930	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.80, 1.43]

Analysis 1.1. Comparison 1 N-acetylcysteine versus placebo - primary outcome, Outcome 1 30-day all-cause Mortality.



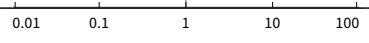
Comparison 2. N-acetylcysteine versus placebo - sensitivity and subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (all reported timescales)	31	2461	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
2 Mortality - Overall risk of bias	31	2461	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
2.1 High risk of bias	14	919	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.72, 1.10]
2.2 Low risk of bias	17	1542	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.80, 1.19]
3 Mortality - adequate sequence generation	32	2501	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
3.1 Adequate sequence generation	20	1899	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.12]
3.2 Inadequate or unclear sequence generation	12	602	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.21]
4 Mortality - Allocation concealment	33	2541	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
4.1 Adequate allocation concealment	22	1835	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.13]
4.2 Inadequate or unclear allocation concealment	11	706	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.71, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Mortality - Blinding	31	2461	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
5.1 Adequate blinding	25	2228	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.15]
5.2 Inadequate or unclear blinding	6	233	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.07]
6 Mortality - short and long timescales	31	2481	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.10]
6.1 Short timescale	14	1524	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.72, 1.09]
6.2 Long term timescale	18	957	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.83, 1.24]
7 Mortality - sepsis or other critical illness (SIRS)	16	896	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.12]
7.1 Mortality in sepsis	8	369	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.84, 1.41]
7.2 Mortality in other critical illness (SIRS)	9	527	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.71, 1.08]
8 Mortality - medical or surgical patients	29	2404	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.10]
8.1 Mortality in medical patients	17	956	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
8.2 Mortality in surgical patients	12	1448	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.68, 1.52]
9 Mortality - early or late administration	31	2461	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.81, 1.08]
9.1 Mortality in early administration	24	2099	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.04]
9.2 Mortality in late administration	8	362	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.86, 1.38]

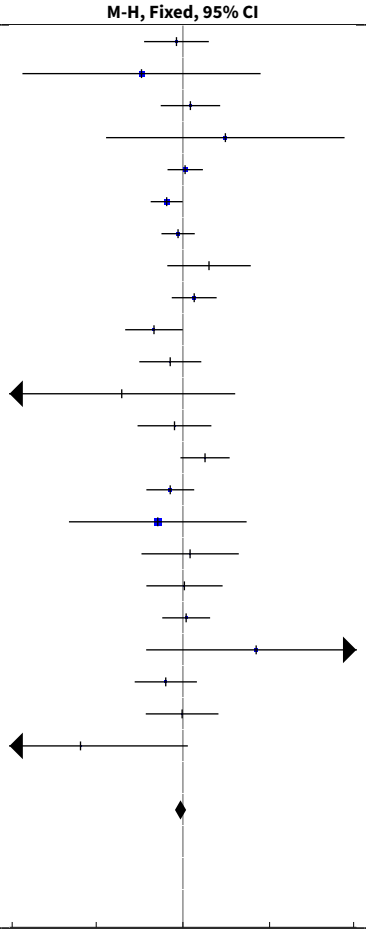
Analysis 2.1. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 1 Mortality (all reported timescales).

Study or subgroup	N-acetylcysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bernard 1997	5/14	6/15		2.39%	0.89[0.35,2.28]
Bromley 1995	4/25	3/25		1.24%	1.33[0.33,5.36]
Burns 2005	5/148	4/147		1.65%	1.24[0.34,4.53]
Burns 2010	6/21	9/21		3.71%	0.67[0.29,1.54]
Charunwatthana 2009	21/56	17/52		7.27%	1.15[0.68,1.92]
Csontos 2011	4/15	6/15		2.47%	0.67[0.23,1.89]
Domenighetti 1997	7/22	5/20		2.16%	1.27[0.48,3.37]
El-Hamamsy 2007	3/50	0/50		0.21%	7[0.37,132.1]



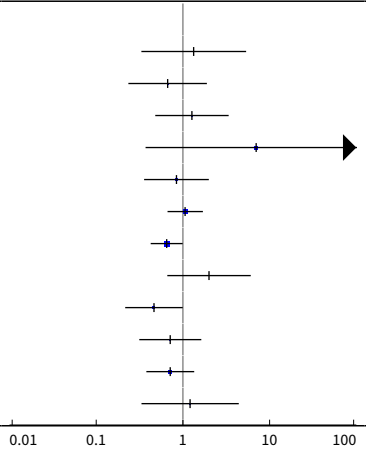
Favours experimental — Favours control

Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Emet 2004	7/27	8/26		3.36%	0.84[0.36,1.99]
Haase 2007	0/30	1/30		0.62%	0.33[0.01,7.87]
Hilmi 2010	11/50	9/50		3.71%	1.22[0.56,2.69]
Hynninen 2006	1/34	0/35		0.2%	3.09[0.13,73.21]
Jepsen 1992	17/32	17/34		6.8%	1.06[0.67,1.7]
Keays 1991	13/25	20/25		8.25%	0.65[0.43,0.99]
Lee 2009	24/81	31/92		11.97%	0.88[0.57,1.37]
Macedo 2006	6/18	4/24		1.41%	2[0.66,6.06]
Molnar 1999	16/41	13/45		5.11%	1.35[0.74,2.45]
Moradi 2009	5/14	10/13		4.28%	0.46[0.22,1]
Ortolani 2000b	5/12	7/12		2.89%	0.71[0.31,1.63]
Ozaydin 2008	0/58	2/57		1.04%	0.2[0.01,4.01]
Paterson 2003	4/10	5/10		2.06%	0.8[0.3,2.13]
Peake 1996	9/10	5/10		2.06%	1.8[0.94,3.46]
Rank 2000	10/30	14/30		5.77%	0.71[0.38,1.35]
Ristikankare 2006	1/38	2/39		0.81%	0.51[0.05,5.43]
Sisillo 2008	5/129	4/125		1.68%	1.21[0.33,4.41]
Spapen 1998	5/12	4/10		1.8%	1.04[0.38,2.87]
Spies 1994	12/29	11/29		4.54%	1.09[0.58,2.06]
Steib 1998	3/30	0/30		0.21%	7[0.38,129.93]
Suter 1994	7/32	10/29		4.33%	0.63[0.28,1.45]
Szakmany 2003	7/47	7/46		2.92%	0.98[0.37,2.57]
Wijeysundera 2007	0/88	7/87		3.11%	0.07[0,1.14]
Total (95% CI)	**1228**	**1233**		**100%**	**0.94[0.81,1.09]**
Total events: 223 (N-acetylcysteine), 241 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=28.18, df=30(P=0.56); I^2=0%					
Test for overall effect: Z=0.86(P=0.39)					

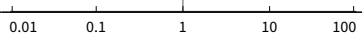


Analysis 2.2. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 2 Mortality - Overall risk of bias.

Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 High risk of bias					
Bromley 1995	4/25	3/25		1.24%	1.33[0.33,5.36]
Csontos 2011	4/15	6/15		2.47%	0.67[0.23,1.89]
Domenighetti 1997	7/22	5/20		2.16%	1.27[0.48,3.37]
El-Hamamsy 2007	3/50	0/50		0.21%	7[0.37,132.1]
Emet 2004	7/27	8/26		3.36%	0.84[0.36,1.99]
Jepsen 1992	17/32	17/34		6.8%	1.06[0.67,1.7]
Keays 1991	13/25	20/25		8.25%	0.65[0.43,0.99]
Macedo 2006	6/18	4/24		1.41%	2[0.66,6.06]
Moradi 2009	5/14	10/13		4.28%	0.46[0.22,1]
Ortolani 2000b	5/12	7/12		2.89%	0.71[0.31,1.63]
Rank 2000	10/30	14/30		5.77%	0.71[0.38,1.35]
Sisillo 2008	5/129	4/125		1.68%	1.21[0.33,4.41]

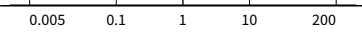


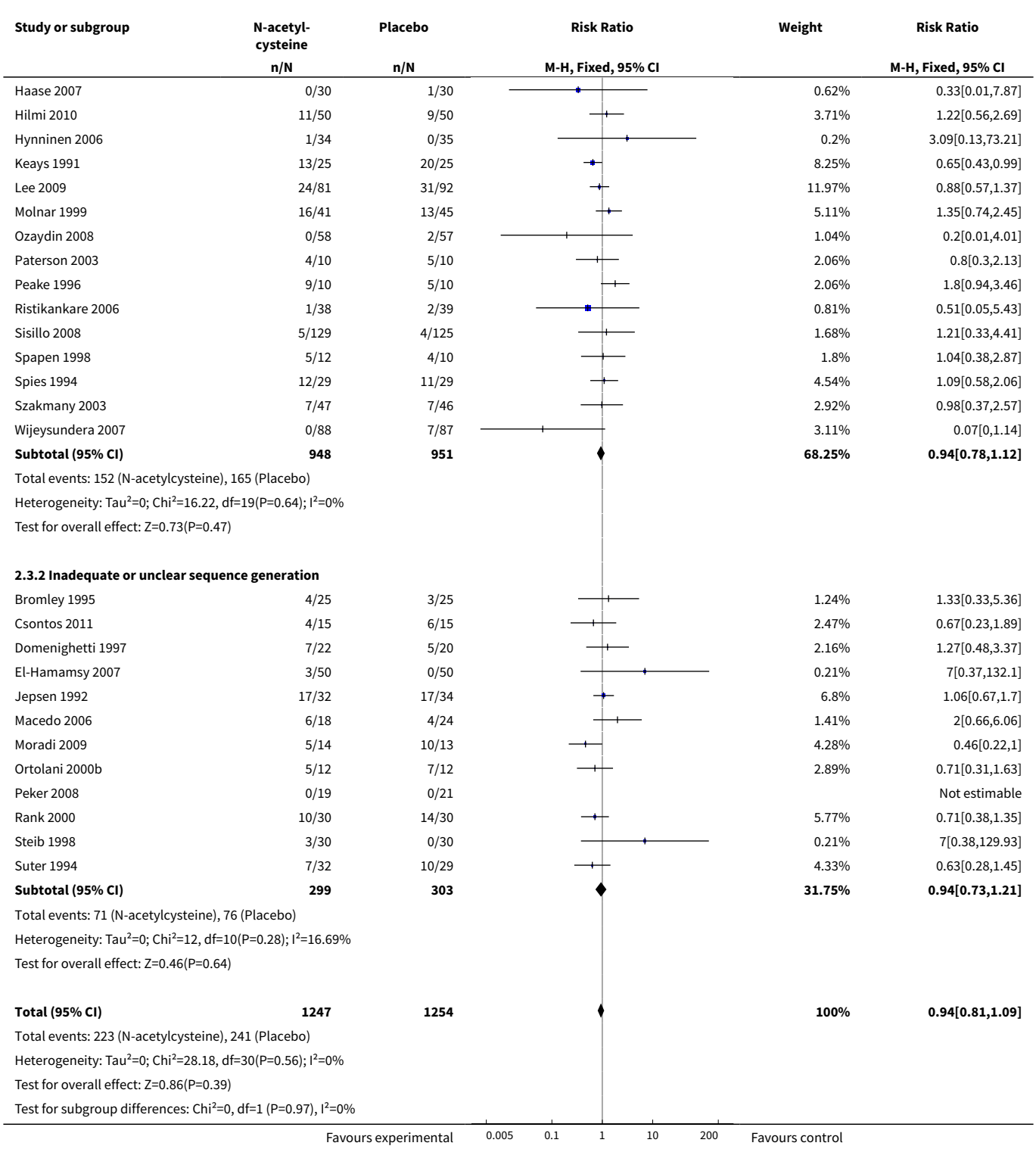
Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Steib 1998	3/30	0/30		0.21%	7[0.38,129.93]
Suter 1994	7/32	10/29		4.33%	0.63[0.28,1.45]
Subtotal (95% CI)	**461**	**458**		**45.03%**	**0.89[0.72,1.1]**
Total events: 96 (N-acetylcysteine), 108 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=14.08, df=13(P=0.37); I^2=7.64%					
Test for overall effect: Z=1.06(P=0.29)					
2.2.2 Low risk of bias					
Bernard 1997	5/14	6/15		2.39%	0.89[0.35,2.28]
Burns 2005	5/148	4/147		1.65%	1.24[0.34,4.53]
Burns 2010	6/21	9/21		3.71%	0.67[0.29,1.54]
Charunwatthana 2009	21/56	17/52		7.27%	1.15[0.68,1.92]
Haase 2007	0/30	1/30		0.62%	0.33[0.01,7.87]
Hilmi 2010	11/50	9/50		3.71%	1.22[0.56,2.69]
Hynninen 2006	1/34	0/35		0.2%	3.09[0.13,73.21]
Lee 2009	24/81	31/92		11.97%	0.88[0.57,1.37]
Molnar 1999	16/41	13/45		5.11%	1.35[0.74,2.45]
Ozaydin 2008	0/58	2/57		1.04%	0.2[0.01,4.01]
Paterson 2003	4/10	5/10		2.06%	0.8[0.3,2.13]
Peake 1996	9/10	5/10		2.06%	1.8[0.94,3.46]
Ristikankare 2006	1/38	2/39		0.81%	0.51[0.05,5.43]
Spapen 1998	5/12	4/10		1.8%	1.04[0.38,2.87]
Spies 1994	12/29	11/29		4.54%	1.09[0.58,2.06]
Szakmany 2003	7/47	7/46		2.92%	0.98[0.37,2.57]
Wijeysundera 2007	0/88	7/87		3.11%	0.07[0,1.14]
Subtotal (95% CI)	**767**	**775**		**54.97%**	**0.98[0.8,1.19]**
Total events: 127 (N-acetylcysteine), 133 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=12.43, df=16(P=0.71); I^2=0%					
Test for overall effect: Z=0.24(P=0.81)					
Total (95% CI)	**1228**	**1233**		**100%**	**0.94[0.81,1.09]**
Total events: 223 (N-acetylcysteine), 241 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=28.18, df=30(P=0.56); I^2=0%					
Test for overall effect: Z=0.86(P=0.39)					
Test for subgroup differences: Chi^2=0.38, df=1 (P=0.54), I^2=0%					



Analysis 2.3. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 3 Mortality - adequate sequence generation.

Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Adequate sequence generation					
Bernard 1997	5/14	6/15		2.39%	0.89[0.35,2.28]
Burns 2005	5/148	4/147		1.65%	1.24[0.34,4.53]
Burns 2010	6/21	9/21		3.71%	0.67[0.29,1.54]
Charunwatthana 2009	21/56	17/52		7.27%	1.15[0.68,1.92]
Emet 2004	7/27	8/26		3.36%	0.84[0.36,1.99]

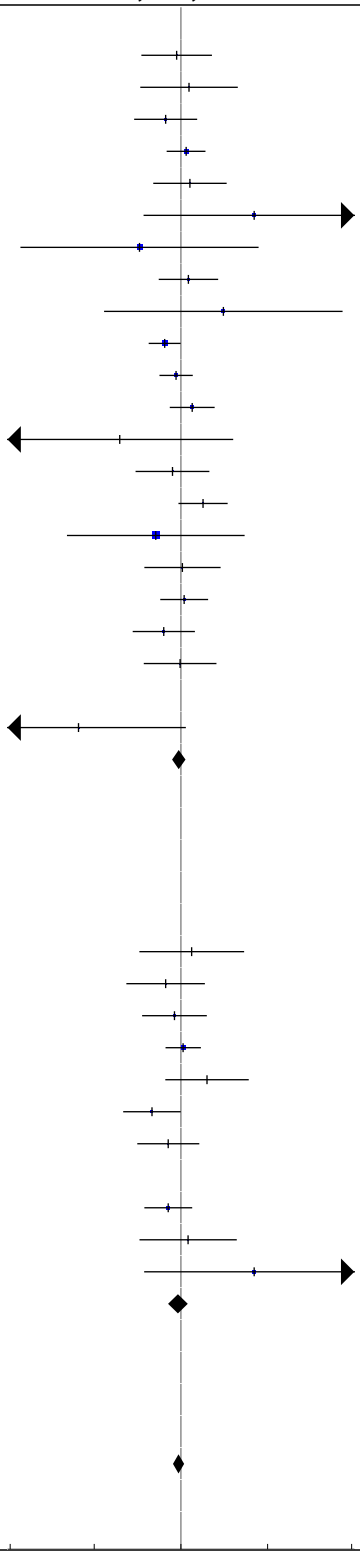




Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Haase 2007	0/30	1/30		0.62%	0.33[0.01,7.87]
Hilmi 2010	11/50	9/50		3.71%	1.22[0.56,2.69]
Hynninen 2006	1/34	0/35		0.2%	3.09[0.13,73.21]
Keays 1991	13/25	20/25		8.25%	0.65[0.43,0.99]
Lee 2009	24/81	31/92		11.97%	0.88[0.57,1.37]
Molnar 1999	16/41	13/45		5.11%	1.35[0.74,2.45]
Ozaydin 2008	0/58	2/57		1.04%	0.2[0.01,4.01]
Paterson 2003	4/10	5/10		2.06%	0.8[0.3,2.13]
Peake 1996	9/10	5/10		2.06%	1.8[0.94,3.46]
Ristikankare 2006	1/38	2/39		0.81%	0.51[0.05,5.43]
Sisillo 2008	5/129	4/125		1.68%	1.21[0.33,4.41]
Spapen 1998	5/12	4/10		1.8%	1.04[0.38,2.87]
Spies 1994	12/29	11/29		4.54%	1.09[0.58,2.06]
Szakmany 2003	7/47	7/46		2.92%	0.98[0.37,2.57]
Wijeysundera 2007	0/88	7/87		3.11%	0.07[0,1.14]
Subtotal (95% CI)	**948**	**951**		**68.25%**	**0.94[0.78,1.12]**
Total events: 152 (N-acetylcysteine), 165 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=16.22, df=19(P=0.64); I^2=0%					
Test for overall effect: Z=0.73(P=0.47)					
2.3.2 Inadequate or unclear sequence generation					
Bromley 1995	4/25	3/25		1.24%	1.33[0.33,5.36]
Csontos 2011	4/15	6/15		2.47%	0.67[0.23,1.89]
Domenighetti 1997	7/22	5/20		2.16%	1.27[0.48,3.37]
El-Hamamsy 2007	3/50	0/50		0.21%	7[0.37,132.1]
Jepsen 1992	17/32	17/34		6.8%	1.06[0.67,1.7]
Macedo 2006	6/18	4/24		1.41%	2[0.66,6.06]
Moradi 2009	5/14	10/13		4.28%	0.46[0.22,1]
Ortolani 2000b	5/12	7/12		2.89%	0.71[0.31,1.63]
Peker 2008	0/19	0/21			Not estimable
Rank 2000	10/30	14/30		5.77%	0.71[0.38,1.35]
Steib 1998	3/30	0/30		0.21%	7[0.38,129.93]
Suter 1994	7/32	10/29		4.33%	0.63[0.28,1.45]
Subtotal (95% CI)	**299**	**303**		**31.75%**	**0.94[0.73,1.21]**
Total events: 71 (N-acetylcysteine), 76 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=12, df=10(P=0.28); I^2=16.69%					
Test for overall effect: Z=0.46(P=0.64)					
Total (95% CI)	**1247**	**1254**		**100%**	**0.94[0.81,1.09]**
Total events: 223 (N-acetylcysteine), 241 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=28.18, df=30(P=0.56); I^2=0%					
Test for overall effect: Z=0.86(P=0.39)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.97), I^2=0%					

Analysis 2.4. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 4 Mortality - Allocation concealment.

Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Adequate allocation concealment					
Bernard 1997	5/14	6/15		2.39%	0.89[0.35,2.28]
Burns 2005	5/148	4/147		1.65%	1.24[0.34,4.53]
Burns 2010	6/21	9/21		3.71%	0.67[0.29,1.54]
Charunwatthana 2009	21/56	17/52		7.27%	1.15[0.68,1.92]
Domenighetti 1997	7/22	5/20		2.16%	1.27[0.48,3.37]
El-Hamamsy 2007	3/50	0/50		0.21%	7[0.37,132.1]
Haase 2007	0/30	1/30		0.62%	0.33[0.01,7.87]
Hilmi 2010	11/50	9/50		3.71%	1.22[0.56,2.69]
Hynninen 2006	1/34	0/35		0.2%	3.09[0.13,73.21]
Keays 1991	13/25	20/25		8.25%	0.65[0.43,0.99]
Lee 2009	24/81	31/92		11.97%	0.88[0.57,1.37]
Molnar 1999	16/41	13/45		5.11%	1.35[0.74,2.45]
Ozaydin 2008	0/58	2/57		1.04%	0.2[0.01,4.01]
Paterson 2003	4/10	5/10		2.06%	0.8[0.3,2.13]
Peake 1996	9/10	5/10		2.06%	1.8[0.94,3.46]
Ristikankare 2006	1/38	2/39		0.81%	0.51[0.05,5.43]
Spapen 1998	5/12	4/10		1.8%	1.04[0.38,2.87]
Spies 1994	12/29	11/29		4.54%	1.09[0.58,2.06]
Suter 1994	7/32	10/29		4.33%	0.63[0.28,1.45]
Szakmany 2003	7/47	7/46		2.92%	0.98[0.37,2.57]
Tossios 2003	0/20	0/20			Not estimable
Wijeysundera 2007	0/88	7/87		3.11%	0.07[0,1.14]
Subtotal (95% CI)	**916**	**919**		**69.91%**	**0.94[0.79,1.13]**
Total events: 157 (N-acetylcysteine), 168 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=19.01, df=20(P=0.52); I^2=0%					
Test for overall effect: Z=0.65(P=0.52)					
2.4.2 Inadequate or unclear allocation concealment					
Bromley 1995	4/25	3/25		1.24%	1.33[0.33,5.36]
Csontos 2011	4/15	6/15		2.47%	0.67[0.23,1.89]
Emet 2004	7/27	8/26		3.36%	0.84[0.36,1.99]
Jepsen 1992	17/32	17/34		6.8%	1.06[0.67,1.7]
Macedo 2006	6/18	4/24		1.41%	2[0.66,6.06]
Moradi 2009	5/14	10/13		4.28%	0.46[0.22,1]
Ortolani 2000b	5/12	7/12		2.89%	0.71[0.31,1.63]
Peker 2008	0/19	0/21			Not estimable
Rank 2000	10/30	14/30		5.77%	0.71[0.38,1.35]
Sisillo 2008	5/129	4/125		1.68%	1.21[0.33,4.41]
Steib 1998	3/30	0/30		0.21%	7[0.38,129.93]
Subtotal (95% CI)	**351**	**355**		**30.09%**	**0.92[0.71,1.2]**
Total events: 66 (N-acetylcysteine), 73 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.05, df=9(P=0.43); I^2=0.5%					
Test for overall effect: Z=0.59(P=0.56)					
Total (95% CI)	**1267**	**1274**		**100%**	**0.94[0.81,1.09]**
Total events: 223 (N-acetylcysteine), 241 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=28.18, df=30(P=0.56); I^2=0%					



Study or subgroup	N-acetyl-cysteine	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Test for overall effect: Z=0.86(P=0.39)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.9), I^2=0%					

Favours experimental 0.01 0.1 1 10 100 Favours control

Analysis 2.5. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 5 Mortality - Blinding.

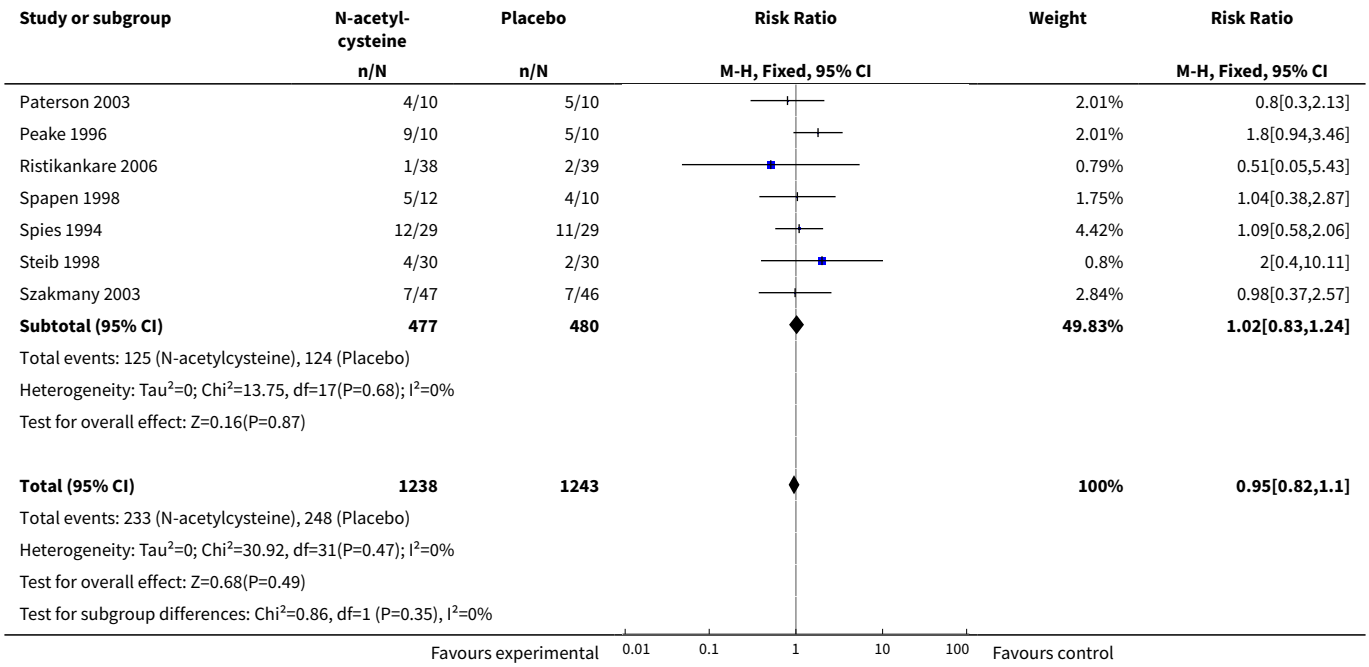
Study or subgroup	N-acetyl-cysteine	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
2.5.1 Adequate blinding					
Bernard 1997	5/14	6/15		2.39%	0.89[0.35,2.28]
Bromley 1995	4/25	3/25		1.24%	1.33[0.33,5.36]
Burns 2005	5/148	4/147		1.65%	1.24[0.34,4.53]
Burns 2010	6/21	9/21		3.71%	0.67[0.29,1.54]
Charunwatthana 2009	21/56	17/52		7.27%	1.15[0.68,1.92]
Domenighetti 1997	7/22	5/20		2.16%	1.27[0.48,3.37]
El-Hamamsy 2007	3/50	0/50		0.21%	7[0.37,132.1]
Emet 2004	7/27	8/26		3.36%	0.84[0.36,1.99]
Haase 2007	0/30	1/30		0.62%	0.33[0.01,7.87]
Hilmi 2010	11/50	9/50		3.71%	1.22[0.56,2.69]
Hynninen 2006	1/34	0/35		0.2%	3.09[0.13,73.21]
Jepsen 1992	17/32	17/34		6.8%	1.06[0.67,1.7]
Lee 2009	24/81	31/92		11.97%	0.88[0.57,1.37]
Molnar 1999	16/41	13/45		5.11%	1.35[0.74,2.45]
Ozaydin 2008	0/58	2/57		1.04%	0.2[0.01,4.01]
Paterson 2003	4/10	5/10		2.06%	0.8[0.3,2.13]
Peake 1996	9/10	5/10		2.06%	1.8[0.94,3.46]
Rank 2000	10/30	14/30		5.77%	0.71[0.38,1.35]
Ristikankare 2006	1/38	2/39		0.81%	0.51[0.05,5.43]
Sisillo 2008	5/129	4/125		1.68%	1.21[0.33,4.41]
Spapen 1998	5/12	4/10		1.8%	1.04[0.38,2.87]
Spies 1994	12/29	11/29		4.54%	1.09[0.58,2.06]
Suter 1994	7/32	10/29		4.33%	0.63[0.28,1.45]
Szakmany 2003	7/47	7/46		2.92%	0.98[0.37,2.57]
Wijeysundera 2007	0/88	7/87		3.11%	0.07[0,1.14]
Subtotal (95% CI)	**1114**	**1114**		**80.5%**	**0.97[0.83,1.15]**
Total events: 187 (N-acetylcysteine), 194 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=16.98, df=24(P=0.85); I^2=0%					
Test for overall effect: Z=0.31(P=0.76)					
2.5.2 Inadequate or unclear blinding					
Csontos 2011	4/15	6/15		2.47%	0.67[0.23,1.89]
Keays 1991	13/25	20/25		8.25%	0.65[0.43,0.99]
Macedo 2006	6/18	4/24		1.41%	2[0.66,6.06]
Moradi 2009	5/14	10/13		4.28%	0.46[0.22,1]
Ortolani 2000b	5/12	7/12		2.89%	0.71[0.31,1.63]
Steib 1998	3/30	0/30		0.21%	7[0.38,129.93]
Subtotal (95% CI)	**114**	**119**		**19.5%**	**0.79[0.58,1.07]**

Favours experimental 0.01 0.1 1 10 100 Favours control

Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 36 (N-acetylcysteine), 47 (Placebo)					
Heterogeneity: Tau²=0; Chi²=7.63, df=5(P=0.18); I²=34.44%					
Test for overall effect: Z=1.52(P=0.13)					
Total (95% CI)	**1228**	**1233**		**100%**	**0.94[0.81,1.09]**
Total events: 223 (N-acetylcysteine), 241 (Placebo)					
Heterogeneity: Tau²=0; Chi²=28.18, df=30(P=0.56); I²=0%					
Test for overall effect: Z=0.86(P=0.39)					
Test for subgroup differences: Chi²=1.44, df=1 (P=0.23), I²=30.4%					

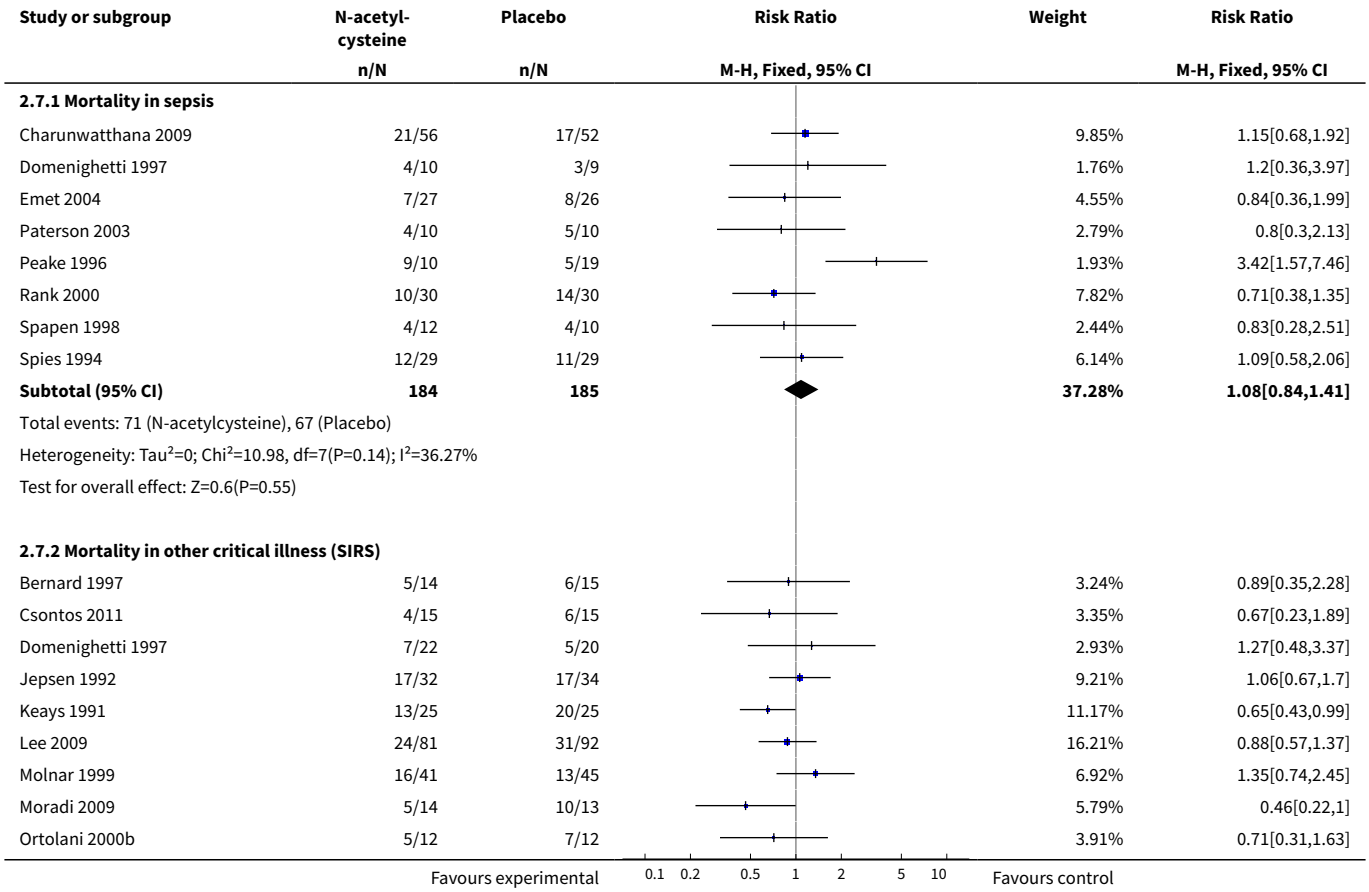
Analysis 2.6. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 6 Mortality - short and long timescales.

Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Short timescale					
Burns 2005	5/148	4/147		1.61%	1.24[0.34,4.53]
Charunwatthana 2009	21/56	17/52		7.08%	1.15[0.68,1.92]
Domenighetti 1997	7/22	5/20		2.1%	1.27[0.48,3.37]
Haase 2007	0/30	1/30		0.6%	0.33[0.01,7.87]
Hynninen 2006	1/34	0/35		0.2%	3.09[0.13,73.21]
Keays 1991	13/25	20/25		8.03%	0.65[0.43,0.99]
Lee 2009	24/81	31/92		11.66%	0.88[0.57,1.37]
Macedo 2006	6/18	4/24		1.38%	2[0.66,6.06]
Ozaydin 2008	0/58	2/57		1.01%	0.2[0.01,4.01]
Peake 1996	9/10	5/10		2.01%	1.8[0.94,3.46]
Rank 2000	10/30	14/30		5.62%	0.71[0.38,1.35]
Sisillo 2008	5/129	4/125		1.63%	1.21[0.33,4.41]
Suter 1994	7/32	10/29		4.21%	0.63[0.28,1.45]
Wijeysundera 2007	0/88	7/87		3.03%	0.07[0,1.14]
Subtotal (95% CI)	**761**	**763**		**50.17%**	**0.89[0.72,1.09]**
Total events: 108 (N-acetylcysteine), 124 (Placebo)					
Heterogeneity: Tau²=0; Chi²=16.81, df=13(P=0.21); I²=22.65%					
Test for overall effect: Z=1.13(P=0.26)					
2.6.2 Long term timescale					
Bernard 1997	5/14	6/15		2.33%	0.89[0.35,2.28]
Bromley 1995	4/25	3/25		1.2%	1.33[0.33,5.36]
Burns 2010	6/21	9/21		3.61%	0.67[0.29,1.54]
Csontos 2011	4/15	6/15		2.41%	0.67[0.23,1.89]
El-Hamamsy 2007	3/50	0/50		0.2%	7[0.37,132.1]
Emet 2004	7/27	8/26		3.27%	0.84[0.36,1.99]
Hilmi 2010	11/50	9/50		3.61%	1.22[0.56,2.69]
Jepsen 1992	17/32	17/34		6.62%	1.06[0.67,1.7]
Molnar 1999	16/41	13/45		4.98%	1.35[0.74,2.45]
Moradi 2009	5/14	10/13		4.16%	0.46[0.22,1]
Ortolani 2000b	5/12	7/12		2.81%	0.71[0.31,1.63]



Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Paterson 2003	4/10	5/10		2.01%	0.8[0.3,2.13]
Peake 1996	9/10	5/10		2.01%	1.8[0.94,3.46]
Ristikankare 2006	1/38	2/39		0.79%	0.51[0.05,5.43]
Spapen 1998	5/12	4/10		1.75%	1.04[0.38,2.87]
Spies 1994	12/29	11/29		4.42%	1.09[0.58,2.06]
Steib 1998	4/30	2/30		0.8%	2[0.4,10.11]
Szakmany 2003	7/47	7/46		2.84%	0.98[0.37,2.57]
Subtotal (95% CI)	**477**	**480**		**49.83%**	**1.02[0.83,1.24]**
Total events: 125 (N-acetylcysteine), 124 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=13.75, df=17(P=0.68); I^2=0%					
Test for overall effect: Z=0.16(P=0.87)					
Total (95% CI)	**1238**	**1243**		**100%**	**0.95[0.82,1.1]**
Total events: 233 (N-acetylcysteine), 248 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=30.92, df=31(P=0.47); I^2=0%					
Test for overall effect: Z=0.68(P=0.49)					
Test for subgroup differences: Chi^2=0.86, df=1 (P=0.35), I^2=0%					

Analysis 2.7. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 7 Mortality - sepsis or other critical illness (SIRS).



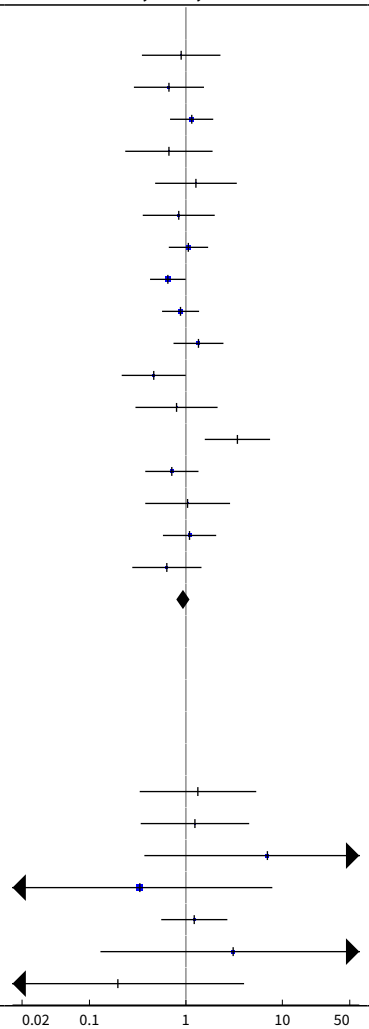
Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 Mortality in sepsis					
Charunwatthana 2009	21/56	17/52		9.85%	1.15[0.68,1.92]
Domenighetti 1997	4/10	3/9		1.76%	1.2[0.36,3.97]
Emet 2004	7/27	8/26		4.55%	0.84[0.36,1.99]
Paterson 2003	4/10	5/10		2.79%	0.8[0.3,2.13]
Peake 1996	9/10	5/19		1.93%	3.42[1.57,7.46]
Rank 2000	10/30	14/30		7.82%	0.71[0.38,1.35]
Spapen 1998	4/12	4/10		2.44%	0.83[0.28,2.51]
Spies 1994	12/29	11/29		6.14%	1.09[0.58,2.06]
Subtotal (95% CI)	**184**	**185**		**37.28%**	**1.08[0.84,1.41]**
Total events: 71 (N-acetylcysteine), 67 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=10.98, df=7(P=0.14); I^2=36.27%					
Test for overall effect: Z=0.6(P=0.55)					
2.7.2 Mortality in other critical illness (SIRS)					
Bernard 1997	5/14	6/15		3.24%	0.89[0.35,2.28]
Csontos 2011	4/15	6/15		3.35%	0.67[0.23,1.89]
Domenighetti 1997	7/22	5/20		2.93%	1.27[0.48,3.37]
Jepsen 1992	17/32	17/34		9.21%	1.06[0.67,1.7]
Keays 1991	13/25	20/25		11.17%	0.65[0.43,0.99]
Lee 2009	24/81	31/92		16.21%	0.88[0.57,1.37]
Molnar 1999	16/41	13/45		6.92%	1.35[0.74,2.45]
Moradi 2009	5/14	10/13		5.79%	0.46[0.22,1]
Ortolani 2000b	5/12	7/12		3.91%	0.71[0.31,1.63]

Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Subtotal (95% CI)	**256**	**271**		**62.72%**	**0.88[0.71,1.08]**
Total events: 96 (N-acetylcysteine), 115 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.3, df=8(P=0.4); I^2=3.6%					
Test for overall effect: Z=1.26(P=0.21)					
Total (95% CI)	**440**	**456**		**100%**	**0.95[0.81,1.12]**
Total events: 167 (N-acetylcysteine), 182 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=21.63, df=16(P=0.16); I^2=26.01%					
Test for overall effect: Z=0.58(P=0.56)					
Test for subgroup differences: Chi^2=1.57, df=1 (P=0.21), I^2=36.26%					

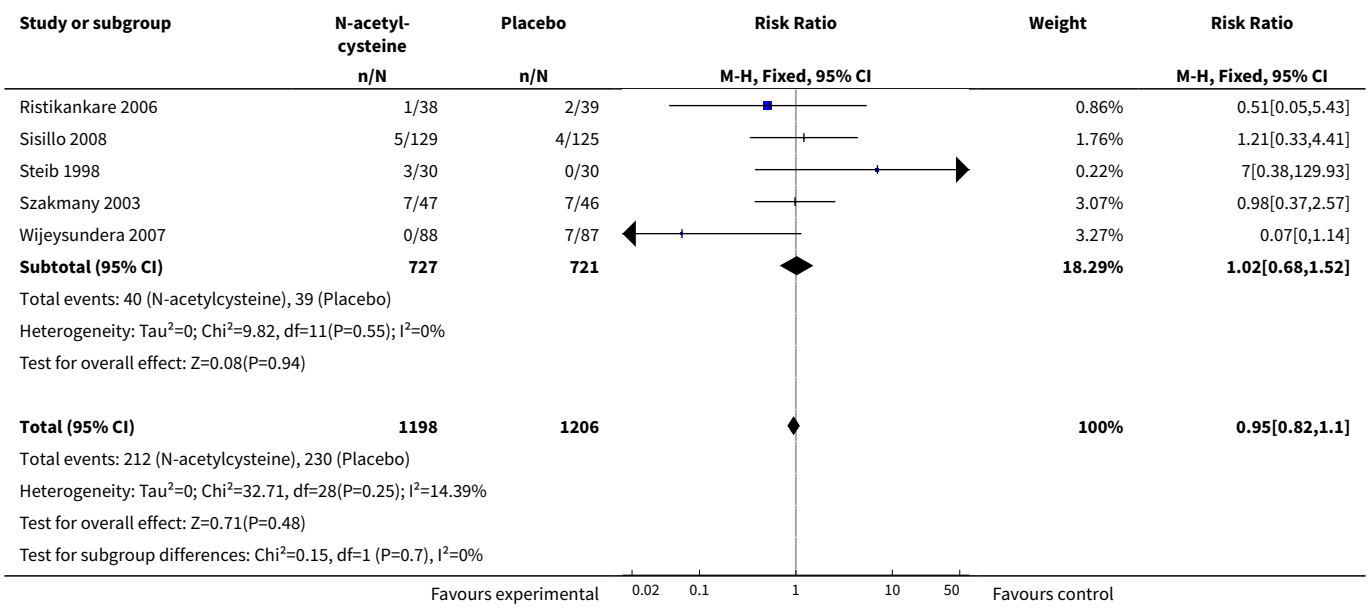
Favours experimental — Favours control

Analysis 2.8. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 8 Mortality - medical or surgical patients.

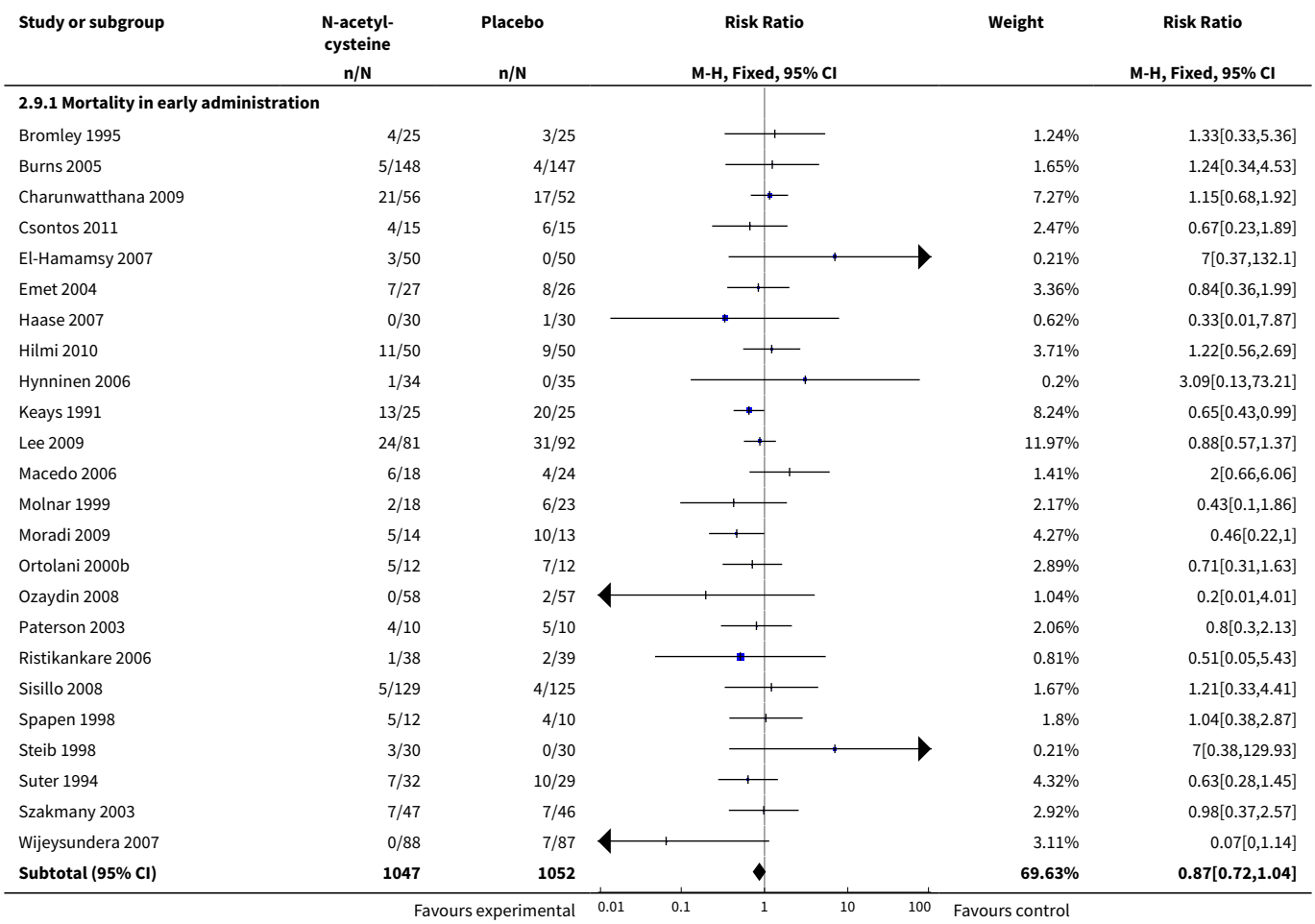
Study or subgroup	N-acetyl-cysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.8.1 Mortality in medical patients					
Bernard 1997	5/14	6/15		2.51%	0.89[0.35,2.28]
Burns 2010	6/21	9/21		3.9%	0.67[0.29,1.54]
Charunwatthana 2009	21/56	17/52		7.65%	1.15[0.68,1.92]
Csontos 2011	4/15	6/15		2.6%	0.67[0.23,1.89]
Domenighetti 1997	7/22	5/20		2.27%	1.27[0.48,3.37]
Emet 2004	7/27	8/26		3.54%	0.84[0.36,1.99]
Jepsen 1992	17/32	17/34		7.15%	1.06[0.67,1.7]
Keays 1991	13/25	20/25		8.67%	0.65[0.43,0.99]
Lee 2009	24/81	31/92		12.59%	0.88[0.57,1.37]
Molnar 1999	16/41	13/45		5.38%	1.35[0.74,2.45]
Moradi 2009	5/14	10/13		4.5%	0.46[0.22,1]
Paterson 2003	4/10	5/10		2.17%	0.8[0.3,2.13]
Peake 1996	9/10	5/19		1.5%	3.42[1.57,7.46]
Rank 2000	10/30	14/30		6.07%	0.71[0.38,1.35]
Spapen 1998	5/12	4/10		1.89%	1.04[0.38,2.87]
Spies 1994	12/29	11/29		4.77%	1.09[0.58,2.06]
Suter 1994	7/32	10/29		4.55%	0.63[0.28,1.45]
Subtotal (95% CI)	**471**	**485**		**81.71%**	**0.93[0.79,1.09]**
Total events: 172 (N-acetylcysteine), 191 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=22.46, df=16(P=0.13); I^2=28.76%					
Test for overall effect: Z=0.87(P=0.38)					
2.8.2 Mortality in surgical patients					
Bromley 1995	4/25	3/25		1.3%	1.33[0.33,5.36]
Burns 2005	5/148	4/147		1.74%	1.24[0.34,4.53]
El-Hamamsy 2007	3/50	0/50		0.22%	7[0.37,132.1]
Haase 2007	0/30	1/30		0.65%	0.33[0.01,7.87]
Hilmi 2010	11/50	9/50		3.9%	1.22[0.56,2.69]
Hynninen 2006	1/34	0/35		0.21%	3.09[0.13,73.21]
Ozaydin 2008	0/58	2/57		1.09%	0.2[0.01,4.01]

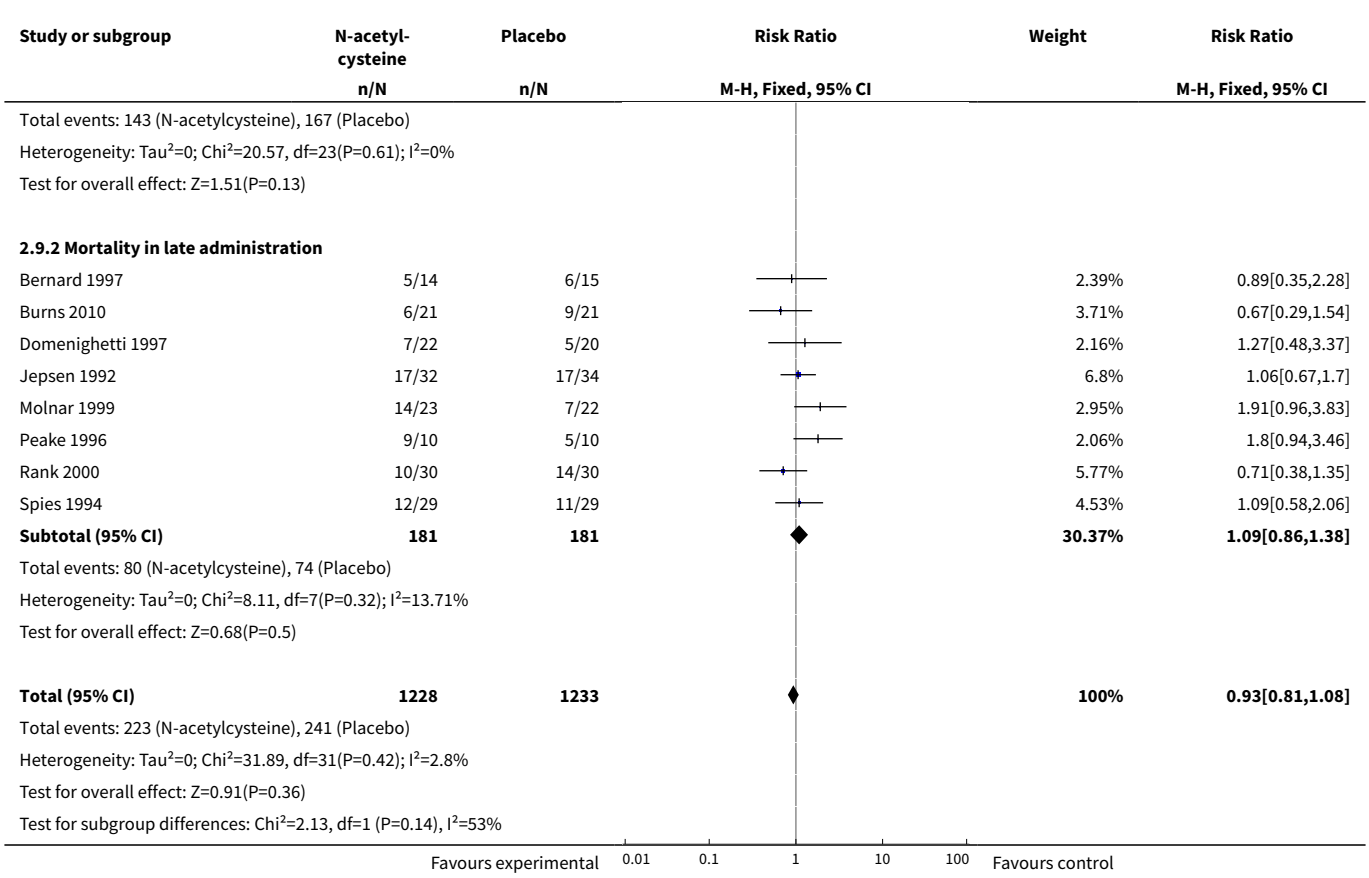


Favours experimental — Favours control



Analysis 2.9. Comparison 2 N-acetylcysteine versus placebo - sensitivity and subgroup analysis, Outcome 9 Mortality - early or late administration.

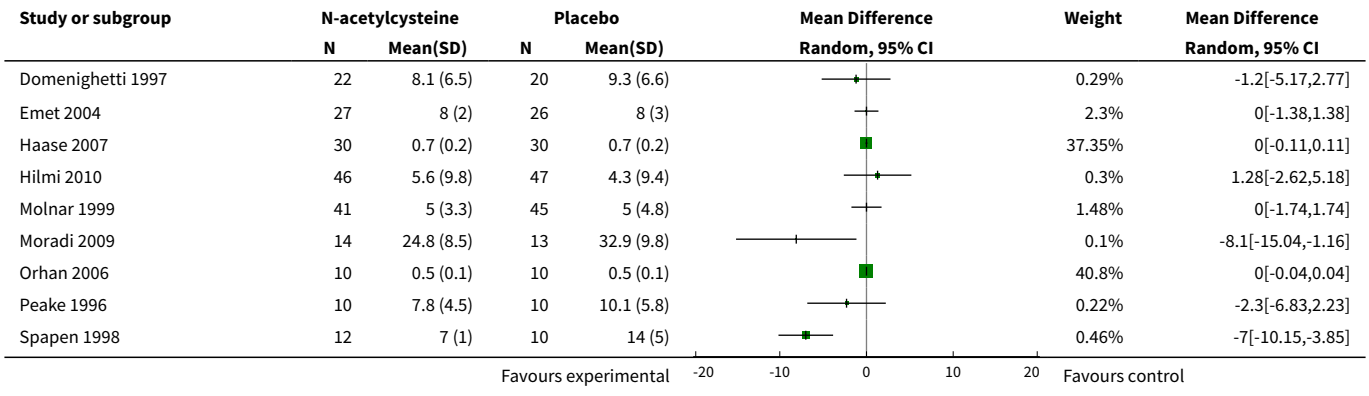


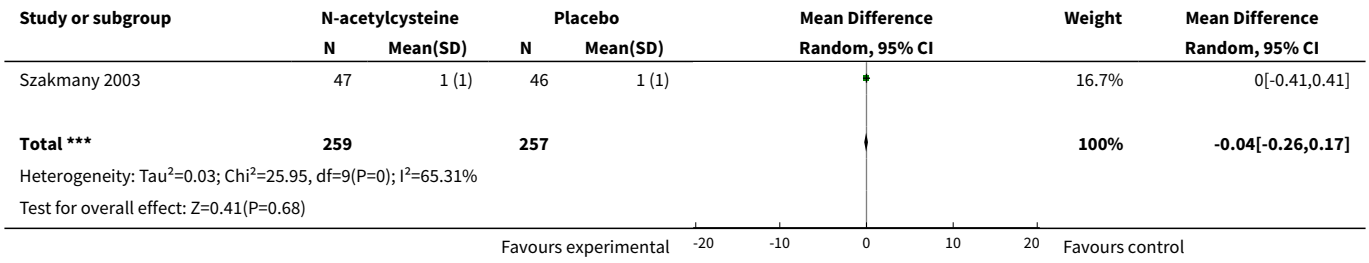


Comparison 3. N-acetylcysteine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of mechanical ventilation	10	516	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.26, 0.17]

Analysis 3.1. Comparison 3 N-acetylcysteine versus placebo, Outcome 1 Duration of mechanical ventilation.



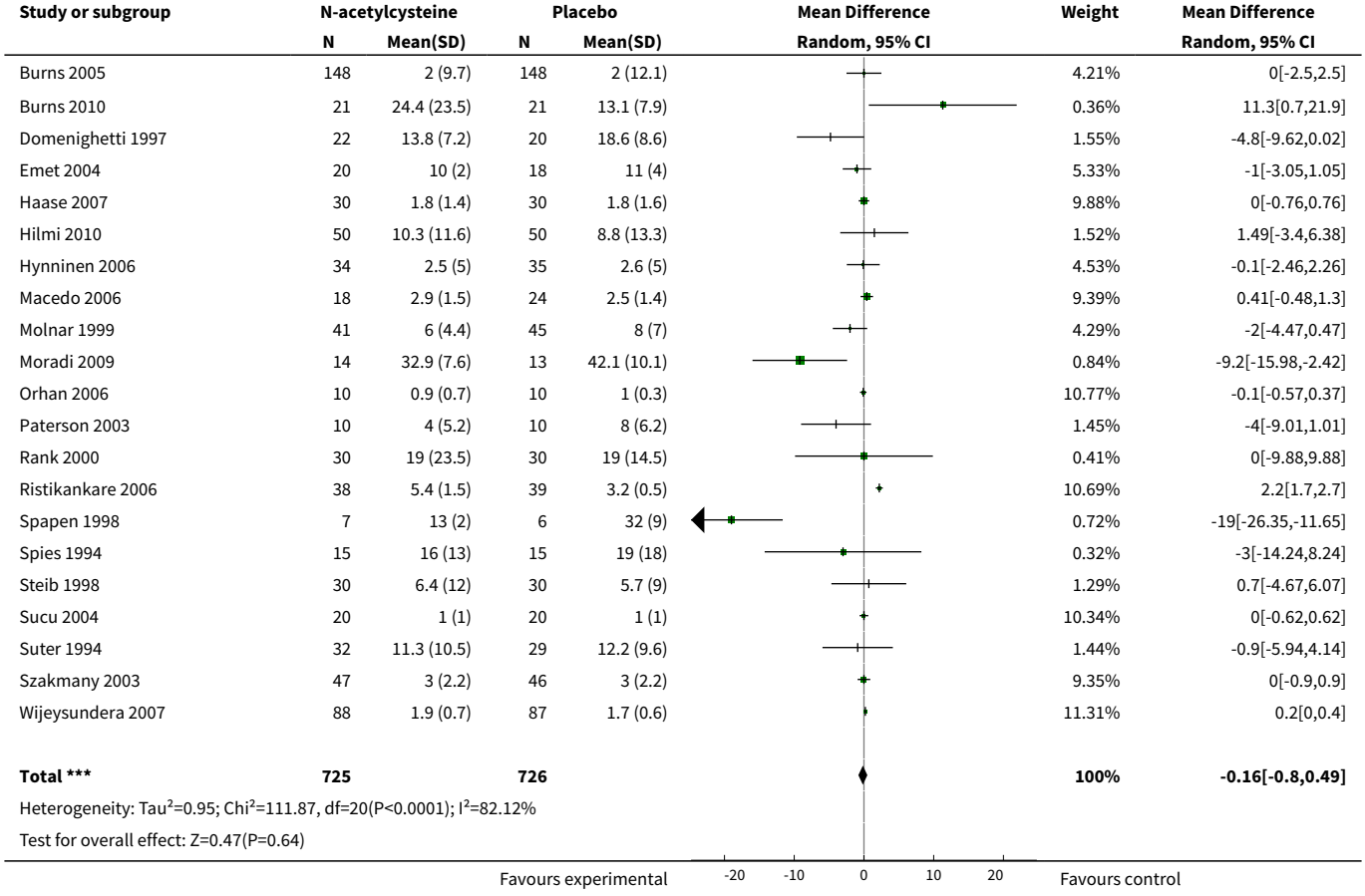


Study or subgroup	N-acetylcysteine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Szakmany 2003	47	1 (1)	46	1 (1)		16.7%	0[-0.41,0.41]
Total ***	**259**		**257**			**100%**	**-0.04[-0.26,0.17]**
Heterogeneity: Tau²=0.03; Chi²=25.95, df=9(P=0); I²=65.31%							
Test for overall effect: Z=0.41(P=0.68)							

Comparison 4. N-acetylcysteine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of stay on the intensive care unit	21	1451	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.80, 0.49]

Analysis 4.1. Comparison 4 N-acetylcysteine versus placebo, Outcome 1 Length of stay on the intensive care unit.



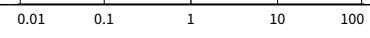
Study or subgroup	N-acetylcysteine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Burns 2005	148	2 (9.7)	148	2 (12.1)		4.21%	0[-2.5,2.5]
Burns 2010	21	24.4 (23.5)	21	13.1 (7.9)		0.36%	11.3[0.7,21.9]
Domenighetti 1997	22	13.8 (7.2)	20	18.6 (8.6)		1.55%	-4.8[-9.62,0.02]
Emet 2004	20	10 (2)	18	11 (4)		5.33%	-1[-3.05,1.05]
Haase 2007	30	1.8 (1.4)	30	1.8 (1.6)		9.88%	0[-0.76,0.76]
Hilmi 2010	50	10.3 (11.6)	50	8.8 (13.3)		1.52%	1.49[-3.4,6.38]
Hynninen 2006	34	2.5 (5)	35	2.6 (5)		4.53%	-0.1[-2.46,2.26]
Macedo 2006	18	2.9 (1.5)	24	2.5 (1.4)		9.39%	0.41[-0.48,1.3]
Molnar 1999	41	6 (4.4)	45	8 (7)		4.29%	-2[-4.47,0.47]
Moradi 2009	14	32.9 (7.6)	13	42.1 (10.1)		0.84%	-9.2[-15.98,-2.42]
Orhan 2006	10	0.9 (0.7)	10	1 (0.3)		10.77%	-0.1[-0.57,0.37]
Paterson 2003	10	4 (5.2)	10	8 (6.2)		1.45%	-4[-9.01,1.01]
Rank 2000	30	19 (23.5)	30	19 (14.5)		0.41%	0[-9.88,9.88]
Ristikankare 2006	38	5.4 (1.5)	39	3.2 (0.5)		10.69%	2.2[1.7,2.7]
Spapen 1998	7	13 (2)	6	32 (9)		0.72%	-19[-26.35,-11.65]
Spies 1994	15	16 (13)	15	19 (18)		0.32%	-3[-14.24,8.24]
Steib 1998	30	6.4 (12)	30	5.7 (9)		1.29%	0.7[-4.67,6.07]
Sucu 2004	20	1 (1)	20	1 (1)		10.34%	0[-0.62,0.62]
Suter 1994	32	11.3 (10.5)	29	12.2 (9.6)		1.44%	-0.9[-5.94,4.14]
Szakmany 2003	47	3 (2.2)	46	3 (2.2)		9.35%	0[-0.9,0.9]
Wijeysundera 2007	88	1.9 (0.7)	87	1.7 (0.6)		11.31%	0.2[0,0.4]
Total ***	**725**		**726**			**100%**	**-0.16[-0.8,0.49]**
Heterogeneity: Tau²=0.95; Chi²=111.87, df=20(P<0.0001); I²=82.12%							
Test for overall effect: Z=0.47(P=0.64)							

Comparison 5. N-acetylcysteine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of new organ failure	13	1324	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.83, 1.27]

Analysis 5.1. Comparison 5 N-acetylcysteine versus placebo, Outcome 1 Incidence of new organ failure.

Study or subgroup	N-acetylcysteine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bernard 1997	6/14	11/15		9.51%	0.58[0.3,1.15]
Burns 2005	44/148	42/145		38%	1.03[0.72,1.46]
El-Hamamsy 2007	2/50	0/50		0.45%	5[0.25,101.58]
Hilmi 2010	18/50	16/50		14.33%	1.13[0.65,1.95]
Keays 1991	10/25	17/25		15.22%	0.59[0.34,1.02]
Macedo 2006	7/14	6/22		4.18%	1.83[0.78,4.33]
Ozaydin 2008	1/58	0/57		0.45%	2.95[0.12,70.92]
Peake 1996	4/4	4/8		2.88%	1.8[0.88,3.68]
Ristikankare 2006	1/30	0/30		0.45%	3[0.13,70.83]
Sisillo 2008	10/129	6/125		5.46%	1.61[0.61,4.31]
Suter 1994	3/31	3/29		2.78%	0.94[0.2,4.27]
Tossios 2003	0/20	0/20			Not estimable
Wijeysundera 2007	4/88	7/87		6.3%	0.56[0.17,1.86]
Total (95% CI)	**661**	**663**		**100%**	**1.02[0.83,1.27]**
Total events: 110 (N-acetylcysteine), 112 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=14.52, df=11(P=0.21); I^2=24.25%					
Test for overall effect: Z=0.21(P=0.83)					



Favours experimental — Favours control

APPENDICES

Appendix 1. Search strategy to identify eligible trials in MEDLINE

Search terms
#52 #25 and #51
#51 #34 or #50
#50 #49 not #34
#49 #47 not #48
#48 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))

(Continued)

#47 #35 or #36 or #37 or #38 or #40 or #41 or #42 or #43 or #44 or #45 or #46
#46 RESEARCH-DESIGN
#45 random* in AB
#44 random* in TI
#43 placebo* in AB
#42 placebo* in TI
#41 PLACEBOS
#40 (#39 in TI) or (#39 in AB)
#39 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
#38 (clin* near trial*) in AB
#37 (clin* near trial*) in TI
#36 explode CLINICAL-TRIALS / all subheadings
#35 CLINICAL-TRIAL in PT
#34 #32 not #33
#33 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
#32 #26 or #27 or #28 or #29 or #30 or #31
#31 SINGLE-BLIND-METHOD
#30 DOUBLE-BLIND-METHOD
#29 RANDOM-ALLOCATION
#28 RANDOMIZED-CONTROLLED-TRIALS
#27 CONTROLLED-CLINICAL-TRIAL in PT
#26 RANDOMIZED-CONTROLLED-TRIAL in PT
#25 #15 and #24
#24 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#23 Free?Radical* Scavenger*
#22 explode "Free-Radical-Scavengers" / all SUBHEADINGS in MIME,MJME
#21 Antioxidant*
#20 explode "Antioxidants-" / all SUBHEADINGS in MIME,MJME

(Continued)

#19 NAC
#18 N?acetylcystein*
#17 acetylcystein*
#16 explode Acetylcysteine/ all subheadings
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#14 peri?operat*
#13 "Perioperative-Care" / all SUBHEADINGS in MIME,MJME
#12 ("Intensive-Care" / all SUBHEADINGS in MIME,MJME) or ("Intensive-Care-Units" / all SUBHEADINGS in MIME,MJME)
#11 explode Septicemia/ all subheadings
#10 septi* or sepsis
#9 septic shock or ARDS or Multiple?Organ* Failure or Sepsis complication* or Sepsis Syndrome or organ dysfunction* or pancreatitis or surgery
#8 ("Surgical-Procedures-Operative" / all SUBHEADINGS in MIME,MJME) or ("Specialties-Surgical" / all SUBHEADINGS in MIME,MJME) or ("Surgery-" / all SUBHEADINGS in MIME,MJME)
#7 explode "Respiratory-Distress-Syndrome-Adult" / all SUBHEADINGS in MIME,MJME
#6 (explode "Pancreatitis-" / all SUBHEADINGS in MIME,MJME) or (explode "Pancreatitis-Acute-Necrotizing" / all SUBHEADINGS in MIME,MJME)
#5 explode "Multiple-Organ-Failure" / all SUBHEADINGS in MIME,MJME
#4 explode Shock-Septic/ all subheadings
#3 system* infla?mator* response syndrome
#2 explode "Sepsis-Syndrome" / all SUBHEADINGS in MIME,MJME
#1 explode "Sepsis-" / all SUBHEADINGS in MIME,MJME

Appendix 2. Search strategy to identify eligible trials from the CENTRAL database

Search terms
#1 MeSH descriptor Sepsis explode all trees
#2 MeSH descriptor Sepsis Syndrome explode all trees
#3 system* infla?mator* response syndrome
#4 MeSH descriptor Shock, Septic explode all trees

(Continued)

#5 MeSH descriptor Multiple Organ Failure explode all trees
#6 MeSH descriptor Pancreatitis, this term only
#7 MeSH descriptor Respiratory Distress Syndrome, Adult, this term only
#8 MeSH descriptor Surgery explode all trees
#9 MeSH descriptor Surgical Procedures, Operative, this term only
#10 MeSH descriptor Specialties, Surgical explode all trees
#11 MeSH descriptor Intensive Care explode all trees
#12 MeSH descriptor Intensive Care Units explode all trees
#13 MeSH descriptor Perioperative Care explode all trees
#14 MeSH descriptor Perioperative Care explode all trees
#15 septic shock or ARDS or Multiple?Organ* Failure or Sepsis complication* or Sepsis Syndrome or organ dysfunction* or pancreatitis or surgery
#16 peri?operat* or septi* or sepsis
#17 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 oR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 MeSH descriptor Acetylcysteine explode all trees
#19 MeSH descriptor Antioxidants explode all trees
#20 MeSH descriptor Free Radical Scavengers explode all trees
#21 (FreeRadical* Scavenger*) or (Free-Radical* Scavenger*) or (Free Radica
#22 (18 OR 19 OR 20 OR 21)
#23 (17 AND 22)

Appendix 3. Search strategy to identify eligible trials from the CINAHL database

Search terms
#1 explode Sepsis- / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#2 explode Systemic-Inflammatory-Response-Syndrome / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#3 explode Shock-Septic / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#4 explode Multiple-Organ-Dysfunction-Syndrome / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#5 Pancreatitis- / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE

(Continued)

#6 (explode Respiratory-Distress-Syndrome / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) or (explode Respiratory-Distress-Syndrome-Acute / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE)
#7 explode Surgery-Operative / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#8 (Critical-Care / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) or (Intensive-Care-Units / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE)
#9 Perioperative-Care / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#10 system* infla?mator* response syndrome
#11 septic shock or ARDS or Multiple?Organ* Failure or Sepsis complication* or Sepsis Syndrome or organ dysfunction* or pancreatitis or surgery or septi* or sepsis or peri?operat*
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 explode "Acetylcysteine-" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#14 explode "Antioxidants-" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#15 explode "Free-Radical-Scavengers" / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#16 (Free?Radical* Scavenger*) or Antioxidant* or NAC or N?acetylcystein* or acetylcystein*
#17 #13 or #14 or #15 or #16
#18 #12 and #17

Appendix 4. Search strategy to identify eligible trials in the EMBASE database

Search terms
#40 #22 and #39
#39 #34 not #38
#38 #36 not #37
#37 #35 and #36
#36 (ANIMAL or NONHUMAN) in DER
#35 HUMAN in DER
#34 #31 or #32 or #33
#33 (SINGL* or DOUBL* or TREBL* or TRIPL*) near ((BLIND* or MASK*) in TI,AB)
#33 (SINGL* or DOUBL* or TREBL* or TRIPL*) near ((BLIND* or MASK*) in TI,AB)
#32 (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI,AB

(Continued)

#31 #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#30 "SINGLE-BLIND-PROCEDURE"/ all subheadings
#29 "DOUBLE-BLIND-PROCEDURE"/ all subheadings
#28 "PHASE-4-CLINICAL-TRIAL"/ all subheadings
#27 "PHASE-3-CLINICAL-TRIAL"/ all subheadings
#26 "MULTICENTER-STUDY"/ all subheadings
#25 "CONTROLLED-STUDY"/ all subheadings
#24 "RANDOMIZATION"/ all subheadings
#23 "RANDOMIZED-CONTROLLED-TRIAL"/ all subheadings
#22 #15 and #21
#21 #16 or #17 or #18 or #19 or #20
#20 acetylcystein* or N?acetylcystein* or NAC or Antioxidant* or (Free?Radical* Scavenger*)
#19 explode "scavenger-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#18 explode "antioxidant-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#17 explode "antioxidant-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#16 explode "acetylcysteine-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#14 peri?operat*
#13 "perioperative-period" / all SUBHEADINGS in DEM,DER,DRM,DRR
#12 "intensive-care" / all SUBHEADINGS in DEM,DER,DRM,DRR
#11 explode "septicemia-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#10 septi* or sepsis
#9 septic shock or ARDS or (Multiple?Organ* Failure) or (Sepsis complication*) or (Sepsis Syndrome) or (organ dysfunction*) or pancreatit* or surg*
#8 explode "surgical-technique" / all SUBHEADINGS in DEM,DER,DRM,DRR
#7 explode "surgery-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#6 "adult-respiratory-distress-syndrome" / all SUBHEADINGS in DEM,DER,DRM,DRR
#5 ("acute-pancreatitis" / all SUBHEADINGS in DEM,DER,DRM,DRR) or ("pancreatitis-" / all SUBHEADINGS in DEM,DER,DRM,DRR)
#4 explode "multiple-organ-failure" / all SUBHEADINGS in DEM,DER,DRM,DRR

(Continued)

#3 system* infla?mator* response syndrome
#2 explode "septic-shock" / all SUBHEADINGS in DEM,DER,DRM,DRR
#1 explode "sepsis-" / all SUBHEADINGS in DEM,DER,DRM,DRR

WHAT'S NEW

Date	Event	Description
14 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Tamas Szakmany (TSZ)
Co-ordinating the review: TSZ
Undertaking manual searches: Balázs Hauser (BH), TSZ
Screening search results: BH, TSZ
Organizing retrieval of papers: BH
Screening retrieved papers against inclusion criteria: BH
Appraising quality of papers: TSZ, BH
Abstracting data from papers: TSZ, BH
Writing to authors of papers for additional information: TSZ
Providing additional data about papers: TSZ
Obtaining and screening data on unpublished studies: BH
Data management for the review: TSz
Entering data into Review Manager (RevMan 5.1): TSz, BH
RevMan statistical data: TSZ
Other statistical analysis not using RevMan: TSZ
Double entry of data: (data entered by person one: TSZ; data entered by person two: BH)
Interpretation of data: TSZ, BH, Peter Radermacher (PR)
Statistical inferences: TSZ
Writing the review: TSZ, BH, PR
Securing funding for the review: TSZ, BH, PR
Performing previous work that was the foundation of the present study: TSZ, BH, PR
Guarantor for the review (one author): TSZ
Person responsible for reading and checking review before submission: TSZ

DECLARATIONS OF INTEREST

Dr Tamas Szakmany: received a Clinical Research Fellowship from the Welsh Assembly Government and numerous travel grants and speaker fees from Edwards Lifesciences, Philips, GSK and B Braun. None of these funds were in relation to the work published here. He conducted clinical trials using N-acetylcysteine postoperatively (Szakmany 2003).

Dr Balázs Hauser: Grants pending; Young Investigator Award of the European Society of Intensive Care Medicine 2001: Experimental study with N-acetylcysteine in porcine endotoxaemia; Roman Herzog Research fellowship of the Alexander von Humboldt Stiftung and the Gemeinnützige Hertie Stiftung 2003 to 2005: Experimental studies in porcine endotoxaemia. He has no competing financial interest regarding this manuscript

Prof Peter Radermacher: Prof Radermacher's institution received a research grant from the Deutsche Forschungsgemeinschaft (DFG project Ra 396/3-2 entitled “ROS, iNOS, and HO-1 in endotoxic shock”) that allowed a research fellow from his institution to perform a study (Vassilev 2004) on N-acetylcysteine in porcine endotoxaemia.

Tamas Szakmany, Balázs Hauser and Peter Radermacher conducted animal studies using N-acetylcysteine.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol Martin Matejovic was one of the authors, however due to personal circumstances he could not contribute to the study any further. The authors are grateful for his contribution and help.

The authors decided to omit the planned subgroup analysis comparing bolus and continuous infusion administration of N-acetylcysteine.

The authors decided to introduce a further primary outcome variable: mortality in the longest reported follow-up period.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetylcysteine [*administration & dosage]; Antioxidants [*administration & dosage]; Injections, Intravenous; Randomized Controlled Trials as Topic; Sepsis [*drug therapy] [mortality]; Systemic Inflammatory Response Syndrome [*drug therapy] [mortality]; Treatment Outcome

MeSH check words

Adult; Humans