Electronic Supplementary Material

Contents:

MEDLINE search strategy:

Search was adapted appropriately for other databases.

Condition:

1. Acute hypoxic respiratory failure
2. Acute hypoxemic respiratory failure
3. Acute hypoxaemic respiratory failure
4. Acute hypercapnic respiratory failure
5. AHRF
6. Respiratory Distress Syndrome, Adult/
7. Acute respiratory failure
8. ARF
9. Severe hypoxic respiratory failure
10. Severe hypoxemic respiratory failure
11. Severe hypoxaemic respiratory failure
12. Severe hypercapnic respiratory failure
13. Severe respiratory failure
14. Type 1 respiratory failure
15. Type I respiratory failure
16. Type 2 respiratory failure
17. Type II respiratory failure
18. Acute pulmonary failure
19. Pulmonary shock
20. Respiratory shock
21. Acute respiratory distress syndrome
22. ARDS

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23. Acute lung failure
24. Acute lung injury
25. ALI
26. Atelectasis
27. Respiratory secretions
28. Mucus plugging
29. #1 -#28 or #1-#28

and

Intervention (Ventilation & Oxygen):

30. Invasive ventilation
31. Invasively ventilated
32. exp Respiration, Artificial/
33. Mechanical ventilation
34. Mechanically ventilated
35. Invasive mechanical ventilation
36. IMV
37. exp Intubation, Intratracheal/
38. Intubated ventilation
39. Ventilator dependent
40. Non-invasive ventilation
41. Non invasive ventilation
42. NIV
43. exp Positive-Pressure Respiration/
44. exp noninvasive ventilation/
45. NIPPV
46. High flow nasal oxygen
47. HFNO
48. High flow nasal therapy
49. High flow nasal cannula
50. High flow oxygen therapy
51. Nasal high flow oxygen therapy
52. Intensive care unit/
53. Intensive care
54. ICU
55. Critical care/
56. Critically ill
57. #30-#56 or #30-56

and

Intervention (Mucoactive):

58. expectorants/ or acetylcysteine/ or ambroxol/ or bromhexine/ or carbocysteine/ or guaifenesin/ or potassium citrate/

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59. mucolytic*
60. Mucoactive
61. Mucokinetic
62. Mucociliary clearance
63. S-carboxymethylcysteine
64. sobrerol
65. iodinated glycerol
66. human DNase
67. RhDNase
68. exp Deoxyribonucleases/
69. Dornase alfa
70. Pulmozyme
71. Sodium Chloride/
72. NaCl
73. Saline Solution, Hypertonic/
74. HTS
75. Saline
76. Sodium bicarbonate/
77. Carbocisteine/
78. methocarbamol/
79. Ammonium chloride
80. Sodium citrate
81. Guaiphenesin
82. Guaifenesin
83. glyceryl guaiacolate*
84. Erdosteine
85. Mecysteine
86. mannitol/ or mannitol phosphates/ or mitobronitol/
87. Mesna/
88. 2-Mercapto ethane sodium sulfonate
89. Potassium dichromate
90. Guaiacolsulfonate
91. Guaiacolsulphonate
92. Sulfoguaiacolum
93. Tyloxapol
94. Stepronin
95. Heparin
96. #58-#95 ***or*** *#58-#95*

Type of Study:
97. randomized controlled trial
98. randomised controlled trial
99. RCT
100. controlled clinical trial

101. random allocation
102. double blind*
103. single blind*
104. triple blind*
105. open label*
106. examiner blind*
107. outcome blind*
108. masked
109. masking
110. clinical trial*
111. exp clinical trial/
112. clinical study*
113. placebo*
114. comparative study*
115. exp evaluation studies/
116. follow up study*
117. prospective study*
118. #97-#117 ***or*** *#97-#117*

Search: 29 and 57 and 96 and 118
Limit to: Humans and English Language

Number of search results according to data source:

ClinicalTrials.gov Register: 27

Cochrane Central Register of Controlled Trials: 97

EMBASE: 278

EU Clinical Trials Register: 36

Medline: 116

Opengrey: 0

WHO Register: 3

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Inclusion/Exclusion criteria of eligible trials:

Author and year	Age (mean ± SD)	Inclusion criteria	Exclusion criteria	Group differences
Bandeshe 2016	Placebo: 59 Usual care: 62 Intervention: 57 (reported as medians)	Patients aged ≥18 years who had received less than 24 hours of invasive MVat the time of enrolment and commencement of study drug but were likely to require invasive MV formore than 48 hours were eligible	Exclusions included pregnancy, patients with treatment limitations or who were moribund, contraindications to subcutaneously administered heparin, systemic anticoagulation at enrolment and previous enrolment in the study.	There were no significant differences in the characteristics of the study groups.

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Bernard 1997	Control: 47 ± 4 Intervention: 43 ± 6	1) requirement for mechanical ventilation. 2) arterial blood gases revealing a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FlO2) of ≤200mm Hg or ≤ 250 is positive end-expiratory pressure (PEE) was ≥ 10 cm H2O. 3) a chest radiograph (CXR) revealing bilateral diffuse infiltrates consistent with pulmonary edema.	1) refused to provide informed consent. 2) if an etiology mimicking ARDS was suspected (e.g. congestive heart failure). 3) younger than 15 or 18 years (depending on site approval). 4) AIDS/HIV positive. 5) received immunosuppresive drug or chemotherapy within 3 months. 6) history of leukaemia. 7) bone marrow or organ transplant. 8) brain death. 9) moribund at entry. 10) physician not committed to aggressive support. 11) severe or acute hepatic dysfunction. 12) pregnant. 13) known hypersensitivity to NAC or OTZ. 14) participation in another study within past 30 days.	Similar at entry in all three groups.
Dixon 2010	Control: 55.5 ± 17.0 Intervention: 56.0 ± 16.5	Patients were included if, owing to primary respiratory failure or other indications, they were expected to require invasive mechanical ventilation for more than 48 hours.	They were excluded if they received mechanical ventilation for more than 24 hours prior to enrollment, required mechanical ventilation for more than 48 hours in a previous admission to the ICU during the current hospital admission, or received any of the following at the time of screening: high-frequency ventilation, extracorporeal membrane oxygenation, nitric oxide (NO), renal replacement therapy, therapeutic doses of heparin or low molecular-weight heparin, warfarin, drotrecogin alpha activated, or protamine. Also, they were excluded if the physician was not committed to full supports or they	The baseline characteristics of the two groups, including the APACHE II (Acute Physiology and Chronic Health Evaluation II) score and the proportion of patients with respiratory failure or ALI and APTT levels, were similar.

			had a body mass index of 40 kg/m2 or greater, allergy to heparin (including any history of heparin-induced thrombocytopenia), a pulmonary hemorrhage in the previous 3 months, uncontrolled bleeding or a significant bleeding disorder, an intracranial hemorrhage in the past 12 months (a clipped subarachnoid aneurysm was acceptable), or an epidural catheter in place or likely to be placed in the next 48 hours or were younger than 18 years old.	
Domenighetti 1997	Control: 52.4 ± 17 Intervention: 52.1 ± 17.8	All patients met the criteria defined in 1994 by the American-European Consensus Conference on ARDS:' acute onset, Paoz/Ftoz less than 200 mm Hg regardless of PEEP level, bilateral infiltrates on chest radiograph and pulmonary wedge pressure (PWP) less than 18 mm Hg when measured, or with no clinical evidence of left atria1 hypertension if not measured.	Patients younger than 16 years old, pregnant women, and immunocompromised patients were excluded from the trial.	Differences between patient groups are statistically not significant.

Jepsen 1992	Control: 51.5 Intervention: 50.5	The identification of ARDS was essentially based on the criteria of Ashbaugh et al. in their original description of the syndrome: a) Each patient had an underlying disease process known to be associated with diffuse alveolar-capillary lung injury. b) PaO2 was <55 torr (<7.3kPa) on room air or the ration of PaO2 to FIO2 (PaO2/FIO2) was <250 c) Tracheal intubation lasted for 3 to 24 hours.	Patients who previously had been treated for chronic pulmonary, cardiovascular, renal or hepatic disease were not included.	The groups were similar with regard to age and sex distribution and underlying disorder.

Masoompour 2015	Control: 50.6 ± 21 Intervention: 59.7 ± 22	Sedated patients between 15-90 years old, intubated on arrival and mechanically ventilated for more than 72 hours.	Exclusion criteria were hemodynamically unstable patients, those with tracheostomy tubes, organophosphate poisonings, and pulmonary edema.	Apart from the mean arterial blood pressure, no statistical difference was detected between the baseline demographics in either group (table 1). The receiving FIO2 through the study in both groups did not differ statistically (P=0.758). Different underlying diseases, including chronic obstructive pulmonary disease, diabetes mellitus, ischemic heart diseases, and congestive heart failure have been distributed in both groups without any significant difference.

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Moradi 2009	Control: 49.2 ± 4.5 Intervention: 48.4 ± 5.5	Mechanically ventilated patients meeting criteria for ALI/ARDS, ALI/ARDS was defined according to the criteria established by the American–European Consensus Conference on ARDS29 (acute onset, PaO2/FiO2 < 300 mmHg, bilateral infiltrates seen on frontal chest radiograph, and pulmonary artery occlusion pressure below 18 mmHg). Must also have SIRS concomitantly (Systemic Inflammatory Response Syndrome: 2 or more of the following conditions, temperature > 38 °C or <36 °C, heart rate > 90 beats/min, respiratory rate > 20/minor PaCO2 < 32 mmHg, WBC > 12,000 or <4000 cells/mm3 or 10% bands).	Patients with PaO2/FiO2 > 300, age < 18 years, hepatic or renal failure not due to septic shock and pregnancy were excluded.	No baseline difference between groups
Ortolani 2000	Control: 55 ± 13 Intervention: 57 ± 14	1. required artificial ventilation 2. the ration of partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FiO2) was 200 mmHg, or lower, the value could be as high as 250 mmHg if the PEEP was 10cmH2O or higher 3. pulmonary bilateral infiltrates were consistent with pulmonary oedema.	1. unable to maintain hemodynamic conditions allowing optimal conventional resuscitation, and with mean arterial pressure persistently under 70 mmHg, despite inotropic support 2. with severe heart or hepatic disease 3. using calcium channel antagonists or angiotensin converting enzyme inhibitors 4. using NAC or other drugs with antioxidant	The groups were similar with respect to patient demographics, diagnostic categories and comorbidities, age, sex, weight, APACHE II, and organ failure score.

			activity 5. underwent septic complications during the trial 6. developed ARDS more than 24 hours before evaluation for enrolment in the study.	
Saleh 2017	Control: 34.8 ± 14.8 Intervention: 34.3 ± 14.6	A polytrauma patient is defined as a patient who has two or more severe injuries in at least two areas of the body. ARDS was defined according to Berlin criteria by timing (within 1 week of clinical insult or onset of respiratory symptoms), radiographic changes (bilateral opacities not fully explained by effusions, consolidation, or atelectasis), origin of edema (not fully explained by cardiac failure or fluid overload), and severity based on the PaO2/FiO2 ratio on 5 cm of continuous positive airway pressure.	Any patients with any of the following were excluded: died within 24 h of admission, age less than 18 years, pregnant females, thrombocytopenia defined as less than 50 000 platelets/mm3, and coagulopathy defined as international normalized ratio greater than 1.5.	No significant differences between groups.
Suter 1994	Control: 48.1 ± 21.9 Intervention: 46.6 ± 19.7	In order to collect patients with comparable lung dysfunction for a pharmacologic treatment regimen, we used the expanded defini- tion suggested by Murray et al, and only considered patients presenting with an initial lung injury score (US) between 0.1 and 2.5. Patients with cardiogemc pulmonary edema and/or chronic heart failure were excluded on the basis of medical history, results of clinical examination, and the use of a pulmonary artery catheter in all unclear situations. The	1. Younger than 16 years 2. Pregnant women 3. Immunocompromised 4. Severe lung injury (LIS > 2.5) 5. Cardiogenic pulmonary oedema and/or chronic heart failure.	Differences between the two patient groups are statistically not significant.

		following predisposing factors for the development of ARDS were considered. Sepsis, defined as proposed by Bone, was clinical evidence of infection, i.e., respiratory rate above 20 cycles/mm or minute ventilation over 10 L/min if mechanically ventilated, heart rate more than 90 beats/mm, core or rectal temperature outside the range of 35.5 degrees to 38.0 degrees Celsius, a white blood cell count above 12,000 or below 4,000/pi or 20 percent or more immature cells plus evidence of altered organ perfusion (le, acute change in mental status, PaO,/FIo,less than 280, plasma lactate concentration greater than upper limit of normal, and urine output below 0.5 mI/kg of body weight for at least 1 h). Multiple trauma included patients with multiple major fractures (two or more major long bones or unstable pelvic fracture) associated with trauma to another region of the body such as craniocerebral or abdominal, requiring surgical intervention. Aspiration was defined as recent (during the previous 6 h) inhalation of gastric contents, documented by suctioning of gastric material from the bronchial tree or by fiberoptic bronchoscopy showing typical mucosal lesions. Necrotizing pancreatitis was seen as severe abdominal pain, vomiting,		

		increased serum amylase levels, circulatory shock, and a Ranson score of 3 or above. Hemorrhagic shock was defined as requiring administration of more than 20 U of blood within 24 h. Near drowning was defined as an immersion accident requiring endotracheal intubation.		
Van Meenen 2018	Control: 66 Intervention: 65 (Median values reported)	The trial enrolled patients receiving invasive ventilation that started shortly before admission to or in the ICU of a participating hospital and who were expected to not be extubated within 24 hours after randomization.	Exclusion criteria were age younger than 18 years; pregnancy; ventilation lasting more than 24 hours before randomization; previous invasive ventilation in another ICU; a known allergy to acetylcysteine or salbutamol; a medical history mandating use of mucolytics or bronchodilators; expected need for long-term ventilation because of a known neuromuscular disease or suspected complete spinal cord lesions; patients receiving palliative care only; or previously included in this trial.	Baseline characteristics were well balanced between the randomization groups.
YongJun 2014	Control: 57 ± 8 Intervention: 58 ± 12	According to the 2011 ARDS Berlin Diagnostic Criteria: 1 time: after a known cause, or within a week after the emergence of new or existing respiratory symptoms; 2 imaging changes: reduced lung transmittance, and can not be complete Interpretation with pleural effusion, atelectasis or nodules; 3 Causes of pulmonary edema: respiratory failure that cannot be explained by heart failure or	1 patients with advanced tumor; 2 immunosuppressed patients, patients with blood diseases; 3 original respiratory diseases or severe pulmonary infection; 4 ambroxol allergic.	Baseline characteristics are similar for both groups.

		excessive fluid load; 4 oxygenation status: mild: positive end-expiratory Pressure,PEEP)/ Continuous positive airway pressure (CPAP)≥5cmH2O (1 cmH2O = 0.098 kPa) 200 mmHg (1 mmHg = 0.133 kPa) < Oxygenation index ≤ 300 mmHg, moderate: PEEP /CPAP ≥ 5 cmH2O 100 mmHg < oxygenation index ≤ 200 mmHg, severity: PEEP / CPAP ≥ 5 cmH2O oxygenation index ≤ 100 mmHg.		
Zaytoun 2017	Control: 41.87 ± 16.44 Intervention: 41.30 ± 14.13	Both genders meeting the criteria of ARDS according to Berlin's definition.	Not reported.	There was no statistically significant difference between the two studied groups regarding age, sex and APACHE II score on admission.

List of excluded studies after full text review:

Wrong patient population:

1. Asfar, Pierre, Frédérique Schortgen, Julie Boisramé-Helms, Julien Charpentier, Emmanuel Guérot, Bruno Megarbane, David Grimaldi et al. "Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial." *The Lancet Respiratory Medicine* 5, no. 3 (2017): 180-190.

2. Baranwal, Arun K., Aparna S. Murthy, and Sunit C. Singhi. "High-dose oral ambroxol for early treatment of pulmonary acute respiratory distress syndrome: an exploratory, randomized, controlled pilot trial." *Journal of tropical pediatrics* 61, no. 5 (2015): 339-350.

3. Bastin, Anthony J., Anna L. Lagan, Sharon Mumby, Gregory J. Quinlan, and Mark JD Griffiths. "Effect Of N-acetylcysteine In Preventing Inflammation After Lung Resection And One-Lung Ventilation. A Randomised Controlled Trial." In *D42. INTERVENTIONAL PULMONOLOGY AND THORACIC SURGERY*, pp. A5860-A5860. American Thoracic Society, 2010.

4. Jepsen, S., Klaerke, A., Nielsen, P. H., Nielsen, S. T., & Simonsen, O. (1989). Systemic administration of N–acetylcysteine has no effect on postoperative lung function following elective upper laparotomy in lung healthy patients. *Acta anaesthesiologica scandinavica*, *33*(3), 219-222.

5. KIM, J. C., HONG, S. W., SHIM, J. K., YOO, K. J., CHUN, D. H., & KWAK, Y. L. (2011). Effect of N-acetylcystein on pulmonary function in patients undergoing off-pump coronary artery bypass surgery. *Acta anaesthesiologica scandinavica*, *55*(4), 452-459.

6. Li, Q., Yao, G., & Zhu, X. (2012). High-dose ambroxol reduces pulmonary complications in patients with acute cervical spinal cord injury after surgery. *Neurocritical care*, *16*(2), 267-272.

7. Miller, A. C., Rivero, A., Ziad, S., Smith, D. J., & Elamin, E. M. (2009). Influence of nebulized unfractionated heparin and N-acetylcysteine in acute lung injury after smoke inhalation injury. *Journal of burn care & research*, *30*(2), 249-256.

8. Refai, M., Brunelli, A., Xiumé, F., Salati, M., Sciarra, V., Socci, L., ... & Sabbatini, A. (2009). Short-term perioperative treatment with ambroxol reduces pulmonary complications and hospital costs after pulmonary lobectomy: a randomized trial. *European journal of cardio-thoracic surgery*, *35*(3), 469-473.

9. Sayiner, A., Aytemur, Z. A., Baysak, A., & Ozdemir, O. (2011). N-acetylcysteine in exacerbations of chronic obstrutive pulmonary disease associated with increased sputum. In *B47. COPD EXACERBATIONS: MISCELLANEOUS* (pp. A3123-A3123). American Thoracic Society.

10. Spapen, H., Zhang, H., Demanet, C., Vleminckx, W., Vincent, J. L., & Huyghens, L. (1998). Does N-acetyl-L-cysteine influence cytokine response during early human septic shock?. *Chest*, *113*(6), 1616-1624.

11. Youness, H. A., Mathews, K., Elya, M. K., Kinasewitz, G. T., & Keddissi, J. I. (2012). Dornase alpha compared to hypertonic saline for lung atelectasis in critically ill patients. *Journal of aerosol medicine and pulmonary drug delivery*, *25*(6), 342-348.

12. Zandstra, D. F., Stoutenbeek, C. P., & Miranda, D. R. (1985). Effect of mucolytic and bronchodilator aerosol therapy on airway resistance in mechanically ventilated patients. *Intensive care medicine*, *11*(6), 316-318.

13. Zitter, J. N., Maldjian, P., Brimacombe, M., & Fennelly, K. P. (2013). Inhaled Dornase alfa (Pulmozyme) as a noninvasive treatment of atelectasis in mechanically ventilated patients. *Journal of critical care*, *28*(2), 218-e1.

No relevant outcomes:

1. Chan, Hak-Kim, Dorrilyn Rajbhandari, Patricia Tang, John D. Brannan, and Paul Phipps. "Safety of administering dry powder mannitol to stimulate sputum clearance in intubated intensive care patients with sputum retention: a pilot study." In *B105. Devices and Monitoring in the Intensive Care Unit*, pp. A6809-A6809. American Thoracic Society, 2012.

2. Konrad, F., Schreiber, T., Haehnel, J., Kilian, J., & Georgieff, M. (1994). The effect of theophylline on the mucociliary clearance function in ventilated intensive care patients. *Der Anaesthesist*, *43*(2), 101-106.

3. Konrad, F., Schoenberg, M. H., WIEDMANN, W., Kilian, J., & Georgieff, M. (1995). THE USE OF N-ACETYLCYSTEINE AS AN ANTIOXIDANT AND MUCOLYTIC AGENT IN VENTILATED PATIENTS-A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY. *ANAESTHESIST, 44*(9), 651-658.

4. Sadegh Soltan-Sharifi, M., Mojtahedzadeh, M., Najafi, A., Reza Khajavi, M., Reza Rouini, M., Moradi, M., ... & Abdollahi, M. (2007). Improvement by N-acetylcysteine of acute respiratory distress syndrome through increasing intracellular glutathione, and extracellular thiol molecules and anti-oxidant power: evidence for underlying toxicological mechanisms. *Human & experimental toxicology*, *26*(9), 697-703.

5. Zhang, C., Luo, H., Zhang, S., & Zhang, W. X. (2010). Effect of high dose ambroxol on the time of weaning from mechanical ventilation of patients with ARDS in ICU. *Proc Clin Med*, *19*(5B), 578-581.

Wrong intervention:

1. Frass, Michael, Christoph Dielacher, Manfred Linkesch, Christian Endler, Ilse Muchitsch, Ernst Schuster, and Alan Kaye. "Influence of potassium dichromate on tracheal secretions in critically ill patients." *Chest* 127, no. 3 (2005): 936-941.

Wrong comparator:

1. Comparison of Different Mucoactive Agents for the Care of the Intubated Patient in a Surgical Trauma Intensive Care Unit. *ClinicalTrials.gov Identifier: NCT00131521*

2. N-Acetyl-cysteine in Early Acute Respiratory Distress Syndrome (NARDS). *ClinicalTrials.gov Identifier: NCT03346681.*

Duplicate:

1. Konrad, F., Schreiber, T., Haehnel, J., Kilian, J., & Georgieff, M. (1994). The effect of theophylline on the mucociliary clearance function in ventilated intensive care patients. *Der Anaesthesist*, *43*(2), 101-106.

2. Konrad, F., Schoenberg, M. H., WIEDMANN, W., Kilian, J., & Georgieff, M. (1995). THE USE OF N-ACETYLCYSTEINE AS AN ANTIOXIDANT AND MUCOLYTIC AGENT IN VENTILATED PATIENTS-A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY. *ANAESTHESIST, 44*(9), 651-658.

3. Zitter, J. N., Maldjian, P., Brimacombe, M., & Fennelly, K. P. (2013). Inhaled Dornase alfa (Pulmozyme) as a noninvasive treatment of atelectasis in mechanically ventilated patients. *Journal of critical care*, *28*(2), 218-e1.

4. Impact of Nebulized Dornase Alpha on Mechanically Ventilated Patients. *ClinicalTrials.gov Identifier: NCT01095276.*

Wrong indication:

1. Krenn, K., Croize, A., Klein, K. U., Böhme, S., Markstaller, K., Ullrich, R., ... & Fischer, B. (2014). Oral inhalation of AP301 peptide activates pulmonary oedema clearance: initial results from a phase IIa clinical trial in mechanically ventilated ICU patients. *European Respiratory Journal*, *44*(Suppl 58), 1386.

2. Krenn, K., Lucas, R., Croizé, A., Boehme, S., Klein, K. U., Hermann, R., ... & Ullrich, R. (2017). Inhaled AP301 for treatment of pulmonary edema in mechanically ventilated patients with acute respiratory distress syndrome: a phase IIa randomized placebo-controlled trial. *Critical Care*, *21*(1), 194.

Reporting of adverse events and development of other pathologies:

Study	**Number of adverse events**	
	Mucoactive	**Placebo/Standard Care**
Bandeshe* [38]	5	4 in placebo 1 in standard care
Bernard [33]	0	0
Domenighetti [31]	0	No value reported
Jepsen [35]	1	No value reported
Masoompour [30]	0 (Authors however could not evaluate all adverse effects)	No value reported
Suter [32]	0	No value reported
Van Meenen* [26]	137	0
	Development of other pathologies/pulmonary complications	
Bandeshe* [38] (VAP)	20	17 in placebo 19 in standard care
Van Meenen* [26]	228	204
Zaytoun [29] (VAP)	Values not reported however VAP was reported as more common in the control group (P = 0.014).	

*these trials reported adverse events in detail such as reporting on severity and relatedness to the intervention.

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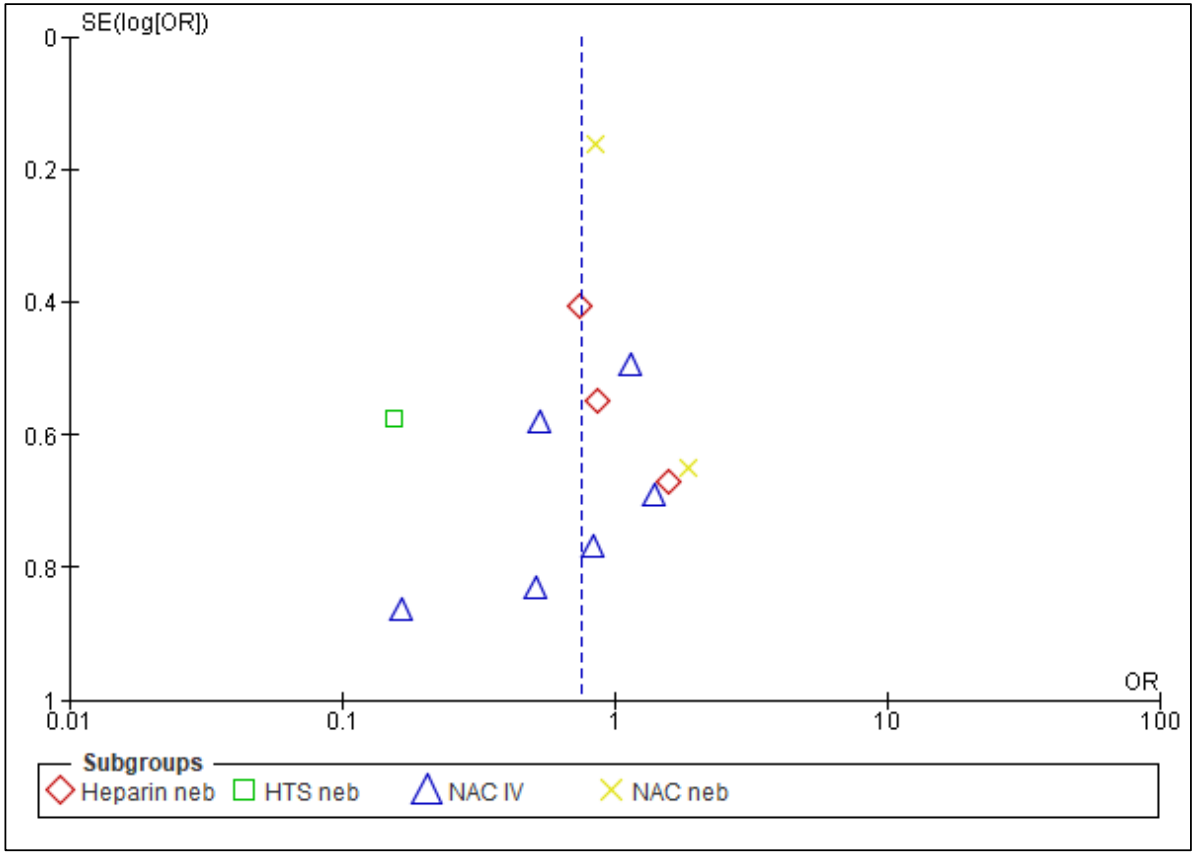
Deviations between this review and protocol:

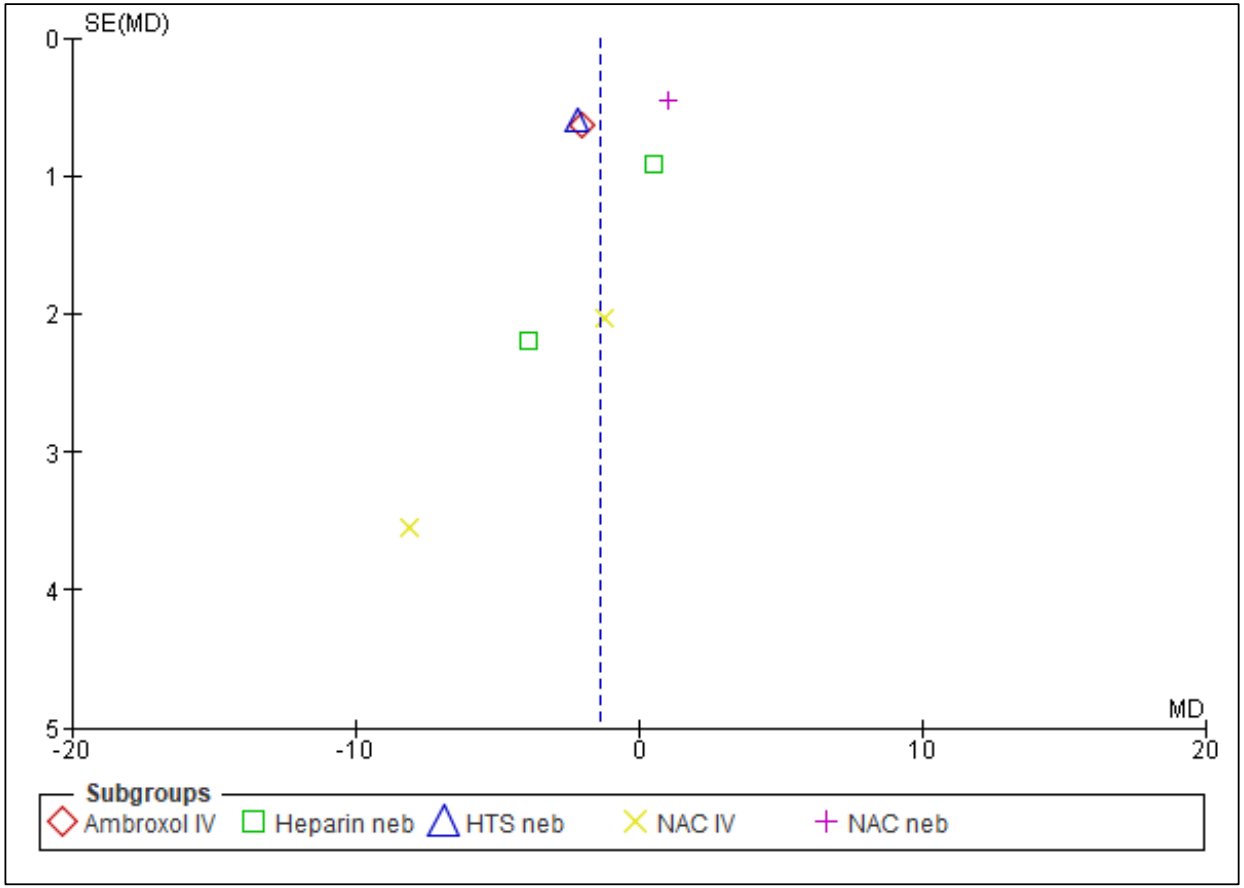
We acknowledge the following differences between the PROSPERO review protocol and this report:

1. This analysis included two studies where not all patients were fully ventilated at the beginning of the trial[31, 32]. After discussion, these trials were considered eligible for this review as current clinical practice such patients would be highly likely to be receiving HFNO before ventilation.
2. As a limited number of trials were found we expanded to include trials of any language eligible during the full text screening stage of the review. To facilitate this, we had access to translation of texts.
3. The authors of the NEBULAE trial[26] regarded their standard care for the trial as routine nebulisation of mucoactive and their intervention as on demand nebulisation. For this review we decided that their intervention (on demand nebulisation) would be more suitable when assigned as standard care. We therefor switched these groups as described in our review. However, we appreciate that our approach to assign routine nebulisation as intervention group is in fact standard care in many centres in the Netherlands.
4. One trial[30] stated an age range of 15-90 years in their eligibility criteria We decided to include this trial as the mean ages of participants were 59.7±22 and 50.6±21 in the two groups.
5. Covidence was used for all screening and extraction of records rather than the use of standardised screening/data extraction forms.
6. Risk of bias was assessed separately for the blinding of participants and the blinding of personnel, rather than together.

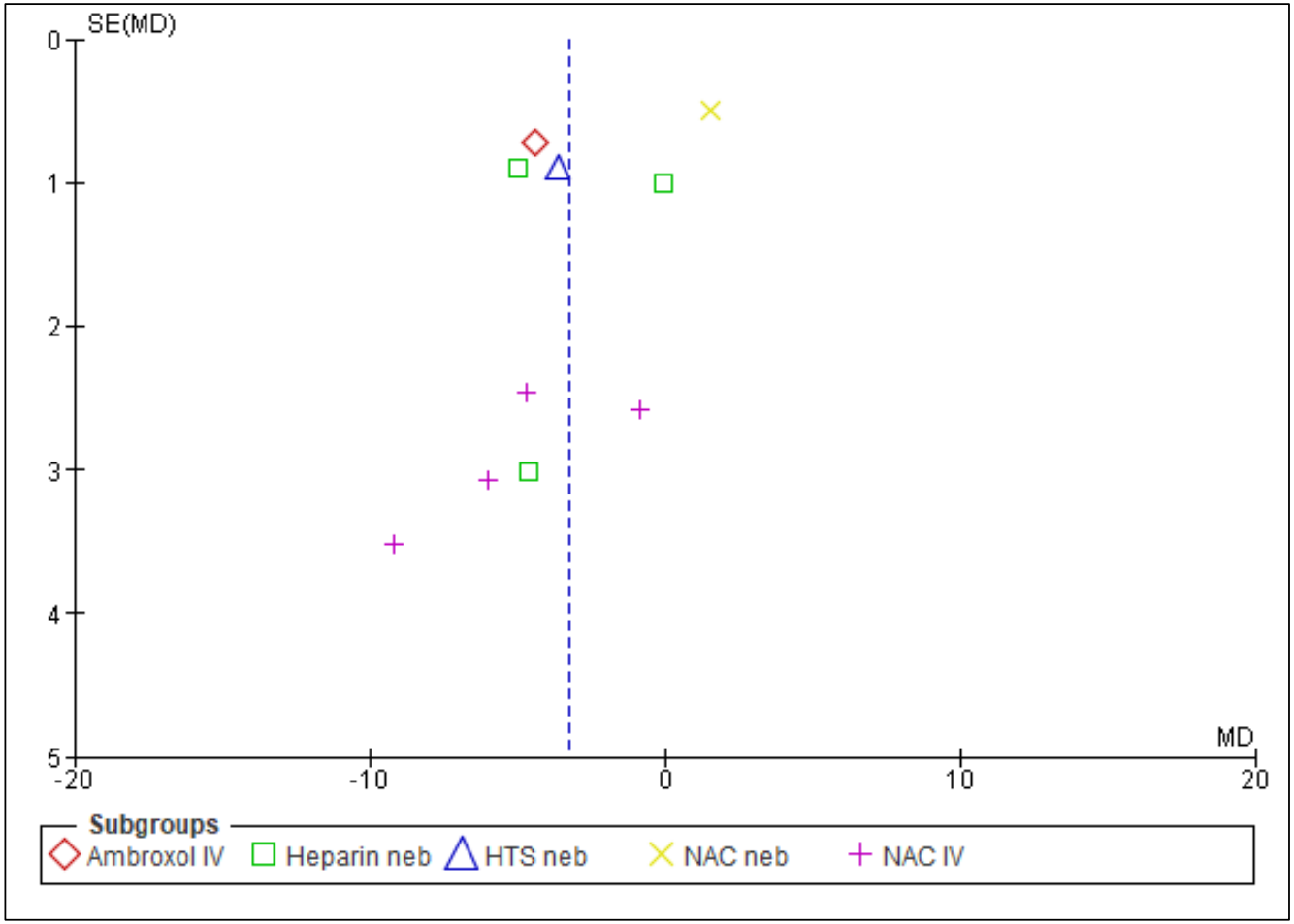
Funnel Plots:



Funnel plot of comparison: Mucoactives versus non-mucoactives, for outcome of mortality



Funnel plot of comparison: Mucoactives versus non-mucoactives for outcome of Duration of Ventilation



Funnel plot of comparison: Mucoactives versus non-mucoactives for outcome of Duration of ICU stay.

Explanation for observed Risk of Bias differences for included trials between this review and Tarrant 2019 review:

- For Bandeshe, we assessed incomplete outcome data (attrition bias) as low, as all patients were accounted for in Tables 1, 3, 4 and 5 of their paper. Tarrant assessed this as high.
- For Dixon, our risk of bias assessment is the same as per the Tarrant review.
- For Masoompour, we assessed risk of bias for random sequence generation and allocation concealment as high as their methodology was: “For this purpose, 40 cards were placed in a closed box, each having “case” or “control” written on it. Prior to the study, a card was pulled out of the box and a patient was labelled as the case or control.” This is high as it is not securely concealed nor is the sequence randomly generated. Tarrant assessed this as low. We also assessed selective reporting (reporting bias) as low as they reported their said outcomes of respiratory secretion, plateau and peak airway pressures, and O2 saturation at baseline, 12 and 24 hours later in Table 2 and Figure 2. Tarrant assessed this as unclear.
- For Saleh, we assessed random sequence generation (selection bias) as unclear as the paper only states, “Following enrolment, patients were randomly divided into two groups” and makes no further elaboration. Tarrant assessed this as low.

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