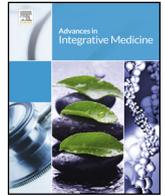




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The effects of N-acetyl cysteine on acute viral respiratory infections in humans: A rapid review

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BRIEF OVERVIEW

Current evidence suggests that N-Acetyl Cysteine (NAC) administration may help improve outcomes in people with acute respiratory distress syndrome and acute lung injury – conditions that closely resemble the signs and symptoms of COVID-19. Few mild and transient adverse events were reported in published randomised-controlled trials, indicating that NAC may be reasonably safe. These findings suggest that NAC may complement the management of COVID-19 infection, particularly when administered intravenously within an intensive care unit (ICU) environment.

Verdict

Current evidence suggests that N-Acetyl Cysteine (NAC) administration may help improve outcomes in people with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) – conditions that closely resemble the signs and symptoms of COVID-19. In this rapid review, NAC was predominately administered intravenously to patients with ARDS or ALI, who were at risk of or requiring mechanical ventilation, and were admitted to a hospital intensive care unit. Findings indicated that NAC administration may assist in improving markers of inflammation or oxidation, systemic oxygenation, the need for / duration of ventilation, rate of patient recovery and clinical improvement score. The effects of NAC on patient length of stay, CT/x-ray images, mortality rate and pulmonary complications were inconclusive.

Few mild and transient adverse events were noted, indicating that NAC may be safe for use in acute respiratory distress syndrome or acute lung injury. Based on the evidence identified, and the similar symptomatic profiles of ARDS/ALI and COVID-19, the findings suggest that NAC may be used to complement the management of COVID-19 infection within an acute care setting. The safety and efficacy of orally administered NAC for the management of milder forms of COVID-19 infection within the community setting, remains uncertain. The current research evidence suggests NAC warrants further research for acute respiratory viral infections, including COVID-19.

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1. Background

NAC is described as a mucolytic nutrient with anti-inflammatory, antioxidant and immunomodulating properties. NAC is reported to be used by naturopathic practitioners in some countries to assist in the management of some respiratory complaints. NAC has been found to be a glutathione (GSH) agonist with previous studies demonstrating that NAC

administration increases GSH levels in red blood cells, granulocytes, and plasma of patients with acute respiratory distress syndrome or acute lung injury. Increasing GSH levels in the early phases of acute lung injury with NAC could reduce or limit the extent of epithelial and endothelial damage and improve the clinical course.

2. Search strategy

2.1. Research question

What are the effects of N-acetyl cysteine on acute respiratory viral infections (ARVI) and associated complications?

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2.2. Inclusion/exclusion criteria

2.2.1. Inclusion criteria

Studies were included if they reported human prospective intervention studies sampling adults (aged 18 years and over) with reported acute respiratory viral infection (ARVI).

2.2.2. Exclusion criteria

Studies were excluded if the study sample was not reported as diagnosed with ARVI.

2.3. Databases

Medline (Ovid), AMED (Ovid), CINAHL (EBSCO), EMBASE (Ovid)

2.4. Search terms (example)

2.4.1. Medline (Ovid)

((randomised Controlled Trials as Topic/ OR randomised controlled trial/ OR Random Allocation/ OR Double-Blind Method/ OR Single Blind Method/ OR clinical trial/ OR clinical trial, phase i. pt. OR clinical trial, phase ii.pt. OR clinical trial, phase iii.pt. OR clinical trial, phase iv.pt. OR controlled clinical trial.pt. OR randomised controlled trial.pt. OR multicenter study.pt. OR clinical trial.pt. OR exp Clinical Trials as topic/ OR (clinical adj trial\$.tw. OR ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. OR PLACEBOS/ OR placebo\$.tw. OR randomly allocated.tw. OR allocated adj2 random\$.tw.) NOT (letter/ OR historical article/)) AND ((Acetylcysteine or N-Acetyl-L-cysteine or N-Acetylcysteine or NAC or N-AC or N-acetyl).af.) AND (Influenza, Human/ OR Influenza A Virus, H1N1 Subtype/ OR Influenza A virus/ OR Influenza A Virus, H3N2 Subtype/ OR H1N1.mp. OR breathing OR lung OR pulmonary OR respir\$)

2.5. Critical appraisal

The risk of bias (RoB) of study findings was assessed using the revised Cochrane RoB tool for randomised trials (RoB 2) <https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2?authuser=0>.

3. Results

The search identified 640 citations. Seven duplicates were removed leaving 633 citations to be screened. After title and abstract reviews, 91 citations were left with 76 citations further excluded as they didn't meet the inclusion and exclusion criteria [wrong patient population = 48, wrong study design = 13, wrong intervention = 7, paediatric population = 6, wrong comparator = 1 and wrong outcome = 1]. The remaining 13 articles were included in this rapid review. Table 1 show a summary of included studies.

All but two studies were identified as randomised controlled trials (RCTs). The two non-RCTs comprised of a case report [1] and a controlled clinical trial [2]. Eight of the 13 (61.5 %) included trials were placebo-controlled [3–10], and 6/13 (46.1 %) were double-blinded [3,5–7,9,10].

Studies were conducted across five of six World Health Organisation (WHO) regions, with most undertaken in the European region (6/13 [46.2 %] [4,6,7,10–12]), followed by the Eastern Mediterranean (3/13 [23.0 %] [2,8,9]), Americas (2/13 [15.4 %] [3,5]), South East Asia (1/13 [7.7 %] [1]) and Western Pacific (1/13 [7.7 %] [13]) regions. All studies were conducted in a hospital setting, and all but two [1,13] were reportedly undertaken in an intensive care unit.

The 13 included studies comprised a total pool of 1337 subjects, with study sample sizes ranging from 1 to 842 (median 42). All

subjects had an acute respiratory condition, with diagnoses including ALI/ARDS (7/13 [53.9 %]; [2–4,6–8,10]) or pneumonia (2/13 [15.4 %] [1,13]). Four studies (30.8 %) did not define the respiratory disorder [5,9,11,12].

N-Acetyl Cysteine (NAC) was predominantly administered intravenously (10/13 [76.9 %]; 40–480 mg/kg/day or 400 mg TDS via intravenous infusion; [1–8,10,11]), and to a lesser extent, as an oral tablet (2/13 [15.4 %]; 600 mg BD [9,13]); or via nebuliser (1/13 [7.7 %]; 300 mg QID or on demand [12]). Control interventions included 5% dextrose in water (3/13 [23.1 %] [3,8,11]), saline (2/13 [15.4 %] [4,7]), water-soluble vitamin tablets (1/13 [7.7 %] [9]), conventional treatment only (1/13 [7.7 %] [13]), and non-specified placebo (3/13 [23.1 %] [5,6,10]). The duration of treatment ranged from 3 to 28 days, with a median period of 3 days.

4. Critical appraisal

In the first Domain (randomisation process), two studies were rated as high risk of bias [1,4] with all other studies rated as low. For Domain 2 (treatment assignment), one trial was identified as high risk of bias [6], with seven trials rated as low [2–5,9,12]. Under Domain 3 (missing outcome data), two trials were considered to have high risk of bias [6,7], with eight trials rated as low [3,3,4,5,8,10,12,13]. For Domain 4 (measure of outcomes), all trials were rated as low risk of bias, except Lai et al. [1], which was assessed as having some concerns. In Domain 5 (selective reporting), one trial [11] was identified as high risk of bias, with the remaining trials rated as having some concerns or low risk of bias. Overall, five studies were judged as having high risk of bias [1,4,6,7,11], six rated as having some concerns [2,5,8–10,13] and two judged as low risk of bias [3,12]. These judgements should be taken into consideration when interpreting the findings of this review.

5. Summary of findings

The 13 included studies reported on nine broad outcomes: markers of inflammation and oxidation, changes in CT or x-ray images, patient length of stay, mortality rate, pulmonary complications, ventilation-related issues, recovery rate, clinical improvement and adverse events.

Four RCTs [3,7,11,13] reported changes in markers of inflammation or oxidation. These studies reported significant improvements in GSH, tumour necrosis factor - α (TNF- α), malondialdehyde, total thioles, lipoperoxidation, total antioxidant power and polymorphonuclear cell activity following NAC administration when compared to controls. These findings were consistent with those reported in the two non-RCTs [1,2]). No differences between groups were reported for superoxide dismutase and elastase.

Changes in CT or x-ray images were measured in two RCTs [6,13]. Both studies found no differences in this outcome between NAC and control.

Three RCTs [5,9,12] assessed patient length of stay. Although one RCT [9] reported a significant reduction in ICU and hospital length of stay in the NAC group versus control, two studies [5,12] found no differences between groups in patient length of stay.

Mortality rate was measured in six RCTs [3–5,8,10,12]. Four studies [3,5,10,12] reported no differences in mortality rates between NAC and control. The remaining studies reported conflicting results, with one RCT [8] revealing a reduction in the rate of mortality following NAC administration (relative to control), and the other RCT [4] reporting an increase in mortality rate with NAC administration.

Three RCTs [9,10,12] examined the efficacy of NAC in preventing pulmonary complications. When compared to control, NAC administration was associated with a significant reduction in

Table 1
Summary of studies examining the effect of NAC in acute viral respiratory infections humans.

Author	Country	WHO Region (see WHO tab)	Design (eg Cohort, cross-sectional)	Study duration	Study Population / Disease or Condition	Administration of NAC	Dose	Duration of Treatment	Control or Placebo	Total Number of Subjects	N in intervention and placebo	Measure of Outcome	Outcome
Bernard, et al. [3]	USA, Canada	The Region of the Americas	DBPC RCT	March 17, 1992 to Feb 26, 1993	ICU, diagnosed with ARDS and needing ventilation	IV solution of 10% NAC diluted with 5% dextrose in water	70 mg (0.4 mol)/kg body weight; OTZ, 63 mg (0.4 mol)/kg of body weight	30 min., every 8 h for a total of 30 doses during a 10-day treatment period	Placebo (5% dextrose in water)	n = 48	NAC: n = 14 OTZ: n = 17 Placebo: n = 15	RBC glutathione levels	NAC: increased from baseline 47% (p < .05) OTZ: not significant Placebo: not significant
Domenighetti, et al. [4]	Switzerland	European	PC RCT	16-month period	ICU patients diagnosed with ARDS	IV solution	190 mg/kg/day of NAC or placebo	Continuous infusion over the first 3 days	Placebo (saline)	n = 42	NAC: n = 22; Placebo: n = 20	Mortality Organ-failure free days Incidence of ventilatory support PaO ₂ /FIO ₂ Lung Injury Score	No difference No difference NAC: 1.53 (SD 0.21) Placebo: 2.15 (SD 0.19) (p < .04)
Howe, et al. [5]	America USA	The Region of the Americas	DBPC RCT		ICU patients requiring mechanical ventilation	Enterally administered antioxidant supplementation via a bolus	Group 1: 5 mL dose of placebo; Group 2: 5 mL dose of vitamin E (100IU) and 5 mL dose of placebo; Group 3: rml dose of vitamin C (1000 mg), 5 mL dose of vitamin E (1000IU) and 5 mL dose of NAC (400 mg)	Bolus given every 8 h for 28 days or until they were weaned from mechanical ventilation (whichever was shorter)	Placebo	n = 72	C + E+NAC: n = 23; Placebo: n = 22; C + E n = 27	Chest radiograph All-cause mortality Days in ICU Days in hospital Number of days on mechanical ventilation	No difference No difference No difference C + E group: Mean, 10 days C + E+NAC: Mean, 12 days Placebo: Mean, 19 days (p = .02)
Jepsen, et al. [6]	Denmark and Sweden	European	DBPC RCT		ICU patients diagnosed with ARDS	IV solution	NAC 150 mg/kg as a loading dose and then 20 mg/kg/hr	Initial dose was given for 30 min. on day one. Then continuous for the next 6 days	Placebo	n = 66	NAC: n = 32; Placebo: n = 34	Adverse events Oxygenation Administration of corticosteroids, prostaglandin E ₁ or NSAIDs Time taken to recover from ARDS Chest radiographs	NAC: a rash was observed in one patient after the loading dose. No difference No difference No difference No difference

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Table 1 (Continued)

Author	Country	WHO Region (see WHO tab)	Design (eg Cohort, cross-sectional)	Study duration	Study Population / Disease or Condition	Administration of NAC	Dose	Duration of Treatment	Control or Placebo	Total Number of Subjects	N in intervention and placebo	Measure of Outcome	Outcome
Lai, et al. [1]	Hong Kong	South East Asia	Case report	Not applicable	One patient diagnosed with novel H1N1 influenza pneumonia, septic shock, type 1 respiratory failure	IV solution	NAC 100 mg/kg continuous IV infusion for 3 days.	Initial treatment with norepinephrine infusion, hydrocortisone for septic shock. Oral oseltamivir 75 mg twice daily, IV antibiotics next day. Next day, oseltamivir 150 mg BD, IV NAC daily for 3 days.	None	n = 1	n = 1		Patient improved rapidly after high dose NAC therapy plus antiviral medications. CRP concentrations were also seen to decrease with the introduction of NAC high dose.
Laurent, et al. [7]	Switzerland	European	DB PC RCT		ICU patients diagnosed with severe ARDS	IV solution	190 mg/kg/day of NAC	Continuous infusion over the first 3 days	Placebo (isotonic saline solution)	n = 16	NAC n = 8; Placebo n = 8	Unstimulated oxygen radical production Granulocyte GSH	No difference Significantly higher in the NAC group compared to placebo (p < 0.01). Difference was abolished by day 5 (all treatment stopped on day 3).
Moradi, et al. [8]	Iran	Eastern Mediterranean	SB PC RCT	July 2005 and April 2006	Ventilated ICU patients with ALI/ARDS	IV solution	150 mg/kg at first day, followed by 50 mg/kg for 3 days	Initial dose was given for day one, then followed by continuous infusions for 3 days	Placebo (5% dextrose in water)	n = 30	NAC: n = 14; Placebo: n = 13	Elastase release Mortality rate Duration of mechanical ventilation Length of ICU stay PaO ₂ /FiO ₂ (Day 2) PaO ₂ /FiO ₂ (Day 3) PaO ₂ /FiO ₂ (Day 4)	No difference NAC: 35.7 %; Placebo: 76.9 % (p = .03) No difference No difference NAC: 227.3 (SD 23.9); Placebo: 155.0 (SD 15.5) (p = .02) NAC: 344.0 (SD 38.3); Placebo: 166.5 (SD 119.0) (p < .001) NAC: 440.9 (SD 47.5); Placebo: 151.2 (SD 24.6) (p < .001)

Ortolani, et al. [11]	Italy	European	RCT	May 1995 to October 1997	ICU patients, diagnosed early ARDS requiring ventilation	IV solution of 5% NAC diluted with 5% dextrose in water alone or combined with Rutin 0.5 %	NAC 50 mg/kg OR NAC 50 mg/kg + Rutin 5 mg/kg every 8 h	9 days (trial length) then as long as artificial ventilation was needed	Control 250 mL 5% dextrose in water	n = 36	NAC: n = 12; NAC + Rutin: n = 12; Control: n = 12;	Oxidised and total glutathione in epithelial lining fluid (ELF) Oxygenation Lipid peroxidation (ethane expiration)	No difference NAC: Improved [Day 9] NAC: reduced 43 % NAC + Rutin: reduced 46 % Placebo: reduced 15 % (p < .01) Polymorphonuclear (PMN) cell count in ELF NAC: Reduced 50 % NAC + Rutin: Reduced 30 % Placebo: No change (p < .05) Mortality [day 9 and day 30] Incidence of ventilator-associated pneumonia Time to recovery
Sharafkhah, et al. [9]	Iran	Eastern Mediterranean	DBPC RDT	March 2014 to June 2016	Adult ICU admitted patients undergoing endotracheal intubation and mechanical ventilation	NAC (600 mg; water-soluble tablets) through nasogastric tube	Twice daily	Administered within the first 12 h of mechanical ventilation after hospital admission, and continued until performing extubation, tracheostomy, discharge, or death.	Placebo (water-soluble vitamin tablets)	n = 60	NAC: n = 30; Placebo: n = 30	Incidence of ventilator associated pneumonia (VAP) Time to VAP (days) Duration of mechanical ventilation (days) ICU stay (days)	NAC: 26.6 % Placebo: 46.6 % (p = .032) Patients who survived in the treatment group showed a more rapid recovery compared with the control group. Patients treated with NAC were significantly less likely to develop clinically confirmed VAP compared with patients treated with placebo. NAC: 6.42 (SD 1.9) Placebo: 3.46 (SD 2.53) (p = .002) No difference NAC: 14.36 (SD 4.69) Placebo: 17.81 (SD 6.37) (p = .028)

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Table 1 (Continued)

Author	Country	WHO Region (see WHO tab)	Design (eg Cohort, cross- sectional)	Study duration	Study Population / Disease or Condition	Administration of NAC	Dose	Duration of Treatment	Control or Placebo	Total Number of Subjects	N in intervention and placebo	Measure of Outcome	Outcome
Soltan-Sharifi, et al. [2]	Iran	Eastern Mediterranean	Controlled clinical trial	24 July 2005 and 30 April 2006	ICU patients with illness known to be associated with ALI/ ARDS who required mechanical ventilation	"Infused" NAC (150 mg/kg) diluted in 5% dextrose and 50 mg/kg/day diluted in 5% dextrose	NAC (150 mg/ kg) infused for 20 min the first day and then 50 mg/kg/day for three days.	3 days	None	n = 24	NAC: n = 14; Control: n = 10	Hospital stay (days)	NAC: 19.23 (SD 5.54 Placebo: 24.61 (SD 6.81) (p = .030)
												Recovery rate of VAP	Complete - NAC: 56.6%; Placebo: 30% (p = .006) Modest - no difference Lack - NAC: 10.0%; Placebo: 26.6% (p = .040) Death: no difference
												Adverse events	No adverse events related to NAC were identified.
												Acute Physiology and Chronic Health Evaluation (APACHE II) score	NAC: Increased Placebo: Decreased (p < .01)
												Intracellular glutathione (GSH) (48 h)	NAC: Increased 59 % Placebo: Decreased 23 % (p < .001)
												GSH/GSSG ratio	NAC: Increased (22 vs 64.2) Placebo: No change (p < .01)
Suter, et al. [10]	Switzerland	European	DBPC RDT	12- month period	Patients with risk factors for ARDS, and presenting with mild-to- moderate acute lung injury	Continuous IV infusion	NAC 40 mg/kg/ day	3 days	Placebo	n = 61	NAC: n = 32; Placebo: n = 29	Incidence of ventilatory support	NAC: Reduced (69 % vs 17 %) Placebo: Reduced (76 % vs 48 %) (p = .01)
												FiO ₂ administered	NAC: Reduced (0.29 vs 0.48) Placebo: No difference (0.35 vs 0.48) (p < .05)

van Meenen, et al. [12]	Netherlands	European	RCT	June 22, 2014, to November 24, 2016	ICU patients receiving invasive ventilation	Nebulized 5 mL solution (300 mg acetylcysteine) administered alone or in combination with 5 mL solutions containing salbutamol (2.5 mg)	On demand nebulization group: 5 ml solutions containing acetylcysteine (300 mg) OR 5 ml solutions containing salbutamol (2.5 mg) dependent on patient presentation. Routine nebulization group: acetylcysteine (300 mg) with salbutamol (2.5 mg) four times daily	Maximum 28 days. On demand group were reassessed daily. Routine group - from start to end of invasive ventilation and, in the case of ventilation through a tracheostomy tube, until ventilator support was discontinued for longer than 24 h.	None	n = 842	On-demand group: n = 389; Routine group: n = 453	Number of ventilator-free days Mortality ICU and hospital length of stay Adverse events	No difference NAC: Decreased (1.39 vs 0.67) Placebo: No difference (p < .01) NAC: No change at day 3; Decreased at discharge (1.8 vs 1.1) Placebo: Increased at day 3 (p < .05) No difference No difference <i>Total</i> On demand: 13.8 % Routine: 29.3 % (p < .001) <i>Tachyarrhythmia</i> On demand: 12.5 % Routine: 25.9 % (p < .001) <i>Agitation</i> On demand: 0.2 % Routine: 4.3 % (p < .001)
Zhang, et al. [13]	China	Western Pacific Region	RCT	August 2016 and March 2017	All patients admitted to the hospital with community acquired pneumonia	Oral 600 mg tablet	NAC 1200 mg (600 mg tablet twice daily)	10 days	Standard care	n = 39	NAC: n = 21; Standard care: n = 18	Malondialdehyde (7 days) Tumour-necrosis factor- α Total antioxidant capacity Superoxide dismutase CT Image comparison	NAC: +1.34 (SD 1.35) Non-NAC: +0.43 (SD 1.28) (p = .004) NAC: +9.5 (SD 3.62) Non-NAC: 6.25 (SD 3.98) (p < .001) NAC: +4.16 (SD 2.95) Non-NAC: +1.78 (SD 3.21) (p = .005) No difference No difference

ventilator-associated pneumonia and time to ventilator-associated pneumonia in 1 RCT [9]. However, in two RCTs [10,12], no difference was found between groups in the prevalence of pulmonary complications.

Ventilation-related issues were reported as an outcome in four RCTs [4,5,8,10]. NAC administration was associated with improvements in systemic oxygenation in two [8,10] of 3 RCTs, and a reduction in the need for / duration of ventilation in two [5,10] of three RCTs.

Four RCTs [3,6,9,11] and one case report [1] examined recovery rate following NAC administration. All but one study [6] reported a significant improvement in the rate of recovery from an acute respiratory condition with NAC administration when compared with control.

Clinical improvement was assessed in one controlled clinical trial [2]. The authors indicated that NAC administration was associated with an improvement in Acute Physiology and Chronic Health Evaluation (APACHE II) score – a measure of clinical improvement and a predictor of mortality risk.

Adverse event monitoring was reported in three RCTs [6,9,13]. Two studies [9,13] reported no adverse events with NAC administration, and 1 [6] reported a rash during the administration of a loading dose of NAC.

6. Clinical significance

From the evidence identified in this review, it is recommended that NAC could be used for people who have contracted Covid-19. At early stages of the disease, health practitioners could recommend oral NAC [600 mg BD] to assist in reducing respiratory mucus and inflammation, increasing systemic GSH levels and possibly averting hospital admission. As only three trials assessed the oral administration of NAC, and there were some concerns with the risk of bias of these studies, these suggestions need to be considered with caution until conclusive evidence becomes available. If health professionals have access and ability to administer NAC via nebuliser or IV, the review findings suggest that doses of NAC ranging from 40–480 mg/kg/day for at least 3 days may be suitable for patients who are deteriorating. Again, as two of the ten studies on IV administration of NAC were rated as high risk of bias, patients who are administered NAC intravenously need to be monitored closely.

Health practitioners are advised that these recommendations should complement, and not replace, standard medical care, and if required, the patient is recommended to obtain emergency care where needed.

Disclaimer

This article should not replace individual clinical judgement. The views expressed in this rapid review are the views of the authors and not necessarily from the host institutions. The views are not a substitute for professional medical advice.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.aimed.2020.07.006>.

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