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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.

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.

Search Strategy

Research question

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

Inclusion/exclusion criteria

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).

Exclusion criteria

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

Databases

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

Search terms (example)

Medline (Ovid)

((Randomized Controlled Trials as Topic/ OR randomized 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 randomized 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$).tw.) NOT (letter/ OR historical article/)) AND ((Acetylcysteine or N-Acetyl-L-cysteine or N-Acetylcysteine or NAC or N-AC or N-acetyl).af.) AND (Influenza, Human/ OR Influenza A Virus, H1N1 Subtype/ OR Influenza A virus/ OR Influenza A Virus, H3N2 Subtype/ OR H1N1.mp. OR breathing OR lung OR pulmonary OR respir$)

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.

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.

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 1,337 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.

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 [3-5, 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.

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 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.

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 has not been peer-reviewed; it 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.

Included studies

1. Lai KY, Ng WY, Osburga Chan PK, Wong KF, Cheng F: **High-dose N-acetylcysteine therapy for novel H1N1 influenza pneumonia**. *Annals of Internal Medicine* 2010, **152**(10):687-688.
2. Soltan-Sharifi MS, Mojtahedzadeh M, Najafi A, Reza Khajavi M, Reza Rouini M, Moradi M, Mohammadirad A, Abdollahi M: **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**.
3. Bernard GR, Wheeler AP, Arons MM, Morris PE, Paz HL, Russell JA, Wright PE: **A trial of antioxidants N-acetylcysteine and procysteine in ARDS. The Antioxidant in ARDS Study Group**.
4. Domenighetti G, Suter PM, Schaller MD, Ritz R, Perret C: **Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study**.
5. Howe KP, Clochesy JM, Goldstein LS, Owen H: **Mechanical Ventilation Antioxidant Trial**.
6. Jepsen S, Herlevsen P, Knudsen P, Bud MI, Klausen NO: **Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study**.
7. Laurent T, Markert M, Feihl F, Schaller MD, Perret C: **Oxidant-antioxidant balance in granulocytes during ARDS. Effect of N-acetylcysteine**.
8. Moradi M, Mojtahedzadeh M, Mandegari A, Soltan-Sharifi MS, Najafi A, Khajavi MR, Hajibabayee M, Ghahremani MH: **The role of glutathione-S-transferase polymorphisms on clinical outcome of ALI/ARDS patient treated with N-acetylcysteine**.
9. Sharafkhah M, Abdolrazaghnejad A, Zarinfar N, Mohammadbeigi A, Massoudifar A, Abaszadeh S: **Safety and efficacy of N-acetyl-cysteine for prophylaxis of ventilator-associated pneumonia: a randomized, double blind, placebo-controlled clinical trial**.
10. Suter PM, Domenighetti G, Schaller MD, Laverriere MC, Ritz R, Perret C: **N-acetylcysteine enhances recovery from acute lung injury in man. A randomized, double-blind, placebo-controlled clinical study**.
11. Ortolani O, Conti A, De Gaudio AR, Masoni M, Novelli G: **Protective effects of N-acetylcysteine and rutin on the lipid peroxidation of the lung epithelium during the adult respiratory distress syndrome**.
12. van Meenen DMP, van der Hoeven SM, Binnekade JM, de Borgie C, Merkus MP, Bosch FH, Endeman H, Haringman JJ, van der Meer NJM, Moeniralam HS *et al*: **Effect of On-Demand vs Routine Nebulization of Acetylcysteine With Salbutamol on Ventilator-Free Days in Intensive Care Unit Patients Receiving Invasive Ventilation: A Randomized Clinical Trial**.
13. Zhang Q, Ju Y, Ma Y, Wang T: **N-acetylcysteine improves oxidative stress and inflammatory response in patients with community acquired pneumonia: A randomized controlled trial**.

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
Bernard, et al. (1997)	USA, Canada	The Region of the Americans	Not specified	DBPC RCT	March 17, 1992 to Feb 26, 1993	Nonparametric Kruskal-Wallis one-way ANOVA, Fisher's protected least significant difference approach, unpaired t tests	ICU, diagnosed with ARDS and needing ventilation	IV solution of 10% NAC diluted with 5% dextrose in water	70 mg (0.4 moles)/kg body weight; OTZ, 63mg (0.4moles) /kg of body weight	30 mins, every 8 hours for a total of 30 doses during a 10-day treatment period	1. Requirement for mechanical ventilation 2. Pa[O.sub.2]/ Flo.sub.2 is ≤ 200 mg Hg or is ≤ 250 if PEEP was ≥ 10cm [H.sub.2]0 3. Chest radiograph revealing bilateral diffuse infliatrates consistent with	1. Refusal of informed consent 2. Suspected etiology mimicking ARDS e.g. congestive heart failure 3. <15 or <18 years old depending IRB 4. Diagnosed with AIDS, AIDS-related complex or known to be HIV postive 5. Using immunosuppressive drugs in last 3 months. 6. History of leukemia, bone	Placebo (5%dextrose in water)	n=48	NAC: n=14 OTZ: n=17 Placebo: n=15	RBC glutathione levels Mortality Organ-failure free days	NAC: increased from baseline 47% (p<.05) OTZ: not significant Placebo: not significant No difference No difference

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											pulmonary edema	marrow or solid organ transplant. 7. Known or suspected brain death. 8. Moribund on admission 9. Attending physician was not committed to aggressive support 10. Severe acute or chronic hepatic dysfunction, 11. Pregnant 12. Known hypersenstivity to NAC or OTZ 13. NAC administered in last 12h 14. Enrolled in another investigational drug study within past 30 days					
Domenighetti, et al. (1997)	Switzerland	European		PC RCT	16 month period	Paired T test, Wilcoxon-Pratt test or Nemar test , X^2 test, Student t test, Mantel-haenszel	ICU patients diagnosed with ARDS	IV solution	190mg/kg/day of NAC or placebo	Continuous infusion over the first 3 days	1. ARDS:' acute onset 2. Paoz/Ftoz less than 200 mm Hg regardless of PEEP level	1. Younger than 16 yo; 2. Pregnant 3. Immunocompromised	Placebo (saline)	n=42	NAC: n=22; Placebo: n=20	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)

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						test according to distribution of data					3. 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.					Chest radiograph	No difference
Howe, et al. (2015)	America USA	The Region of the Americans	University of South Florida College of Nursing	DBPC RCT		F tests, X^2 test and t tests used for inbetween groups.	ICU patients requiring mechanical	Enterally administered antioxidant supplement	Group 1: 5ml dose of placebo; Group 2: 5ml dose of vitamin	Bolus given every 8 hours for 28 days or until they were	1. Age 21 years or older 2. Required 72 hrs	1. Patients with brainstem infarcts/hemorrhage, global hypoxic encephalopathy	Placebo	n=72	C+E+NAC: n=23; Placebo: n=22; C+E n=27	All-cause mortality Days in ICU Days in hospital	No difference No difference No difference

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
						Survival anlytic techniques used for time to event data.	ventilation	ation via a bolus	E (100IU) and 5ml dose of placebo; Group 3: rml dose of vitamin C (1000mg), 5ml dose of vitamin E (1000IU) and 5ml dose of NAC (400mg)	weaned from mechanical ventilation (whichever was shorter)	mechanical ventilation 3. Mechanical ventilation initiated at the study site during the current hospital stay	, spinal cord injury/ lesions, phrenic nerve injury/paralysis, myasthenia gravis, and Guillain-Barré syndrome who had impaired neuromuscular integrity. 2. History of allergy to agents, if they are warfarin or heparin, aspirin				Number of days on mechanical ventilation	C+E group: Mean, 10 days C+E+NAC: Mean, 12 days Placebo: Mean, 19 days (p=.02)
Jepsen, et al. (1992)	Denmark and Sweden	European	ASTRA, Department of Anesthesiology and intestive care	DBPC RCT		Non parametric descriptive statistics, Wilcoxon test for unpaired data, students t test, chi-square test.	ICU patients diagnosed with ARDS	IV solution	NAC 150mg/kg as a loading dose and then 20mg/kg/hr	Initial dose was given for 30 mins on day one. Then continuous for the next 6 days	1. Adults 2. Diagnosed with ARDS 3. PaO_2 <55 torr (<7.3 kPa) on room air or the ratio of PaO_2 to $F1O_2$ was <250. 4. Tracheal intubation lasted for 3 to 24 hours.	1. Patients who have previously had been treated for chronic pulmonary, cardiovascular, renal, or hepatic disease	Placebo	n=66	NAC: n=32; Placebo: n=34	Adverse events Oxygenation Administration of corticosteriods, 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

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
Lai, et al. (2010)	Hong Kong	South East Asia	Queen Elizabeth Hospital	Case report	Not applicable	None	One patient diagnosed with novel H1N1 influenza pneumonia, septic shock, type 1 respiratory failure	IV solution	NAC 100mg/kg continuous IV infusion for 3 days.	Intial treatment with norepinephrine infusion, hdyrozortisone for septic shock. Oral oseltamivir 75mg twice daily, IV antibiotics next day. Next day, oseltamivir 150mg BD, IV NAC daily for 3 days.	Not applicable	Not applicable	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. (1995)	Switzerland	European	Institue de Physiopathologie Clinique	DB PC RCT		A two-factors repeated measures ANOVA; If F value was significant, relevant comparison were made with Fisher's least	ICU patients diagnosed with severe ARDS	IV solution	190mg/kg/day of NAC	Continuous infusion over the first 3 days	1. Severe ARDS 2. Rapid appearance of bilateral alveolar infiltrates on chest radiograph 3. Severe hypoxemia with a		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).

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
						significant difference. A z test used for plasma elastase levels					PaO_2/FIO_2 ratio < 120 4. Pulmonary capillary wedge pressure <15 mm Hg					Elastase release	No difference
Moradi, et al. (2009)	Iran	Eastern mediterranian	University of Medical Sciences, Tehran, Iran	SB PC RCT	July 2005 and April 2006	Chi-square tests, one-way and two way ANOVA with Tukey post-test and independent sample t-test.	Ventilated ICU patients with ALI/ARDS	IV solution	150mg/kg at first day, followed by 50mg/kg for 3 days	Initial dose was given for day one, then followed by continuous infusions for 3 days	1. ALI/ARDS diagnosis 2.Acute onset 3. PaO_2/FiO_2 <300mmHg 4. Bilateral infiltrates on chest radiograph 5. Pulmonary artery occlusion pressure below 18 mmHg. 6. Concomintant SIRS	1. PaO_2/FiO_2 >300mmHg 2. Age <18 years old, 3. Hepatic or renal failure not due to septic shock 4. Pregnant	Placebo (5%dextrose in water)	n=30	NAC: n=14; Placebo: n=13	Mortality rate Duration of mechanical ventilation Length of ICU stay PaO_2/FiO_2 2nd day PaO_2/FiO_2 3rd day PaO_2/FiO_2 4th day	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. (1999)	Italy	European	Intensive care units of the Universities of Naples and Florence	RCT	May 1995 to October 1997	ANOVA with Tukey post hoc test, Student's t-test.	ICU patients, diagnosed early ARDS requiring	IV solution of 5% NAC diluted with 5% dextrose in water alone or combined	NAC 50mg/kg OR NAC 50mg/kg+ Rutin 5mg/kg	9 days (trial length) then as long as artificial ventilation	1. Early ARDS 2. No evidence of infection	1. Unable to maintain hemodynamic conditions allowing optimal conventional	Control 250ml 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	No difference NAC: Improved

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							ventilation	with Rutin 0.5%	every 8 hours	was needed	3. Require artificial ventilation 4. PaO2/FIO2 ratio < 200mmHg (up to 250mmHg if PEEP was 10cm H2O or higher). 5. Pulmonary bilateral infiltrates consistent with pulmonary oedema	resuscitation, and with mean arterial pressure persistently < 70 mmHg, despite inotropic support; 2. Severe heart or hepatic disease 3. Use of calcium channel antagonists or ACE inhibitors; 4. Using NAC or other drugs with antioxidant activity 5. Septic complications during trial 6. Developed ARDS more than 24hr before evaluation for enrolment in study.				Lipid peroxidation (ethane expiration) Polymorphonuclear (PMN) cell count in ELF Mortality [day 9 and day 30]	[Day 9] NAC: reduced 43% NAC+Rutin: reduced 46% Placebo: reduced 15% (p<.01) NAC: Reduced 50% NAC+Rutin: Reduced 30% Placebo: No change (p<.05) No differene
Sharafkhah, et al. (2018)	Iran	Eastern mediterranian	Academic infectious department of Vali-asr Hospital and funded by Arak University of Medical Sciences Arak, Iran	DBPC RDT	March 2014 to June 2016	T-test, Mann-Whitney U-test, chi-square test.	Adult ICU admitted patients undergoing endotracheal intubation and mechanical	NAC (600 mg; water-soluble tablets) through nasogastric tube	Twice daily	Administered within the first 12 hours of mechanical ventilation after hospital admission, and continued	1. Adult ICU admitted patients undergoing endotracheal intubation and mechanica	1. <72-hour intubation 2. Death within 72 hours after intubation 3. Transference to other hospitals, and termination of NAC administration:	Placebo (water-soluble vitamin tablets)	n=60	NAC: n=30; Placebo: n=30	Incidence of ventilator-associated pneumonia Time to recovery	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.

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
							ventilation			until performing extubation, tracheostomy, discharge, or death.	l ventilation	4. Pregnancy 5. Recent gastrointestinal tract injury 6. Oropharyngeal mucosal injury 7. Tracheostomy 8. Presence of pneumonia at hospital admission 9. History of antibiotic consumption within the last 4 weeks prior to ICU admission. 10. Unable to obtain informed written consent and administer the first dose of the study drug within 12 hours of intubation.				Incidence of ventilator associated pneumonia (VAP) Time to VAP (days) Duration of mechanical ventilation (days) ICU stay (days) Hospital stay (days) Recovery rate of VAP Adverse events	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) NAC: 19.23 (SD 5.54 Placebo: 24.61 (SD 6.81) (p=.030) *Complete* - NAC: 56.6%; Placebo: 30% (p=.006) *Modest* – no difference *Lack* – NAC: 10.0%; Placebo: 26.6% (p=.040) *Death*: no difference No adverse events related to NAC were identified.

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
Soltan-Sharifi, et al. (2007)	Iran	Eastern mediterranian	SINA University Hospital, Tehran University of Medical Sciences Grant - TUMS	Controlled clinical trial	24 July2005 and 30 April 2006	ANOVA and post hoc Tukey's test, Fisher's Exact test	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 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.	24 July 2005 and 30 April 2006	1. ICU patients with Illness associated with ALI/ARDS who required mechanical ventilation 2. PaO2/FiO2 of ≤200 mmHg	1. PaO2/FiO2 >200 mmHg 2. Cardiovascular disease 3. Age <18 years 4. Pregnancy	None	n=24	NAC: n=14; Control: n=10	Acute Physiology and Chronic Health Evaluation(APACHE II) score Intracellular glutathione (GSH) (48h) GSH/GSSG ratio Total antioxidant power (TAP) (mmol/L) (72h)	NAC: Increased Placebo: Decreased (p<.01) NAC: Increased 59% Placebo: Decreased 23% (p<.001) NAC: Increased (22 vs 64.2) Placebo: No change (p<.01) NAC: 3.6 (SD 0.38) Placebo: 1.8 (SD 0.25) (p=.013)
Suter, et al. (1993)	Switzerland	European	Intensive care units of the departments of anaesthesia and medicine, Universtiy Hospitals of Geneva, Lausanne and Basel; and the Regional Hospital "La Carita" Locarno	DBPC RDT	12-month period	T-test, chi-squared, paired t-test, Wilcoxon-Pratt test, student t-test, Wilcoxon Mann-Whitney U test	Patients with risk factors for ARDS, and presenting with mild-to-moderate acute lung injury	Continuous IV infusion	NAC 40mg/kg/day	Three days	1. Patients with risk factors for ARDS and initial lung injury score (LIS) between 0.1 and 2.5	1. <16 years old 2. Pregnant women 3. Immunocompromised 4. Severe lung injury {LIS > 2. 5) or cardiogenic pulmonary edema and/or chronic heart failure	Placebo	n=61	NAC: n=32; Placebo: n=29	Incidence of ventilatory support FiO_2 administered PaO_2/FiO_2 Lung injury score	NAC: Reduced (69% vs 17%) Placebo: Reduced (76% vs 48%) (p=.01) NAC: Reduced (0.29 vs 0.48) Placebo: No difference (0.35 vs 0.48) (p<.05) No difference NAC: Decreased (1.39 vs 0.67) Placebo: No difference (p<.01)

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervention and placebo	Measure of Outcome	Outcome
																Chest radiograph score	NAC: No change at day 3; Decreased at discharge (1.8 vs 1.1) Placebo: Increased at day 3 (p<.05)
van Meenen, et al. (2018)	Netherlands	European	ICUs of 7 hospitals in the Netherlands	RCT	June 22, 2014, to November 24, 2016	2-tailed superiority hypothesis tests, Mann-Whitney U test, Hodges-Lehman statistic, Kaplan-Meier survival curves, 2-tailed Fisher exact test, generalized linear mixed-effects model.	ICU patients receiving invasive ventilation	Nebulized 5ml solution (300mg acetylcysteine) administered alone or in combination with 5mL solutions containing salbutamol (2.5 mg)	On demand nebulization group: 5mL solutions containing acetylcysteine (300 mg) OR 5mL solutions containing salbutamol (2.5 mg) dependent on patient presentation. Routine nebulization group: acetylcysteine (300mg) with salbutamol (2.5mg) 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 hours.	1. Patients receiving invasive ventilation initiated shortly before admission to or in ICU and who were expected to not be extubated within 24 hours after randomization.	1. Age <18 years 2. pregnancy 3. ventilation >24hrs before randomization 4. Previous invasive ventilation in another ICU 5. Known allergy to acetylcysteine or salbutamol 6. Medical history mandating use of mucolytics or bronchodilators 7. Expected need for long-term ventilation because of a known neuromuscular disease or suspected complete spinal cord lesions 8. Patients receiving palliative care only 9. Previously included in this trial	None	n = 842	On-demand group: n=389; Routine group: n=453	Number of ventilator-free days	No difference
																Mortality	No difference
																ICU and hospital length of stay	No difference
																Adverse events	*Total* On demand: 13.8% Routine: 29.3% (p<.001) *Tachyarrhythmia* On demand: 12.5% Routine: 25.9% (p<.001) *Agitation* On demand: 0.2% Routine: 4.3% (p<.001)

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
Zhang, et al. (2018)	China	Western Pacific Region	Department of Respiratory, Weihai Municipal Hospital.	RCT	August 2016 and March 2017	Kolmogorov–Smirnov test, t-test, Mann-Whitney U test, Fisher exact test, ANCOVA, Wilcoxon rank sum test	All patients admitted to the hospital with community acquired pneumonia	Oral 600mg tablet	NAC 1200mg (600mg tablet twice daily)	10 days	1. Bacterial CAP; 2. Age 18 yrs and over.	1. ≥70 years old 2.Severe obesity 3. Heavy smoking 4. Severe or multiple systemic diseases 5. Pneumonia severity index [PSI] score IV–V) 6. Tuberculosis 7. Fungus infection 8. Primary viral pneumonia 9. Other diseases including: lung	Standard care	n=39	NAC: n=21; Standard care: n=18	Malondialdehyde (7 days) Tumour-necrosis factor-α Total antioxidant capacity Superoxide dismutase	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

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
												tumors, diffuse connective tissue diseases, sarcoidosis, pulmonary tuberculosis, parasitic infestations, bronchiectasis, pulmonary edema, 10. immunosuppression or were receiving immunosuppressive therapy (daily dose of≥20mgprednisolone equivalent for>2 weeks) 11. HIV 12. Granulocytopenia 13. Antimicrobial treatment prior to hospital admission 14. Using other antioxidant drugs. 15. Diabetic patients with blood glucose levels >150mg/dL.				CT Image comparison	No difference

Author	Country	WHO Region (see WHO tab)	Sponsorship source/association	Design (eg Cohort, cross-sectional)	Study duration	Statistical method (s)	Study Population / Disease or Condition	Administration of NAC	*Dose*	*Duration of Treatment*	Inclusion criteria	Exclusion criteria	Control or Placebo	Total Number of Subjects	N in intervetion and placebo	Measure of Outcome	Outcome
																Changes in oxidative stress parameters (malondialdehyde (MDA), superoxide dismutase (SOD), total antioxidant capacity(TAOC)) and TNF-alpha, and difference in chest CT scores after treatment in the NAC group compared with the non-NAC group	Addition of NAC therapy for CAP patients reduced plasma levels of MDA and TNF-alpha and increased TAOC. There was no significant difference in increased plasma superoxide dismutase (SOD) activity between the groups, and the NAC group did not show a greater improvement from CT scores. No NAC-related adverse effects were observed. Treatment with NAC may help to reduce oxidative and inflammatory damage in pneumonia patients.

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 intervetion and placebo	Measure of Outcome	Outcome
Bernard, et al. (1997)	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 moles)/kg body weight; OTZ, 63mg (0.4moles)/kg of body weight	30 mins, every 8 hours 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 Mortality Organ-failure free days	NAC: increased from baseline 47% (p<.05) OTZ: not significant Placebo: not significant No difference No difference
Domenighetti, et al. (1997)	Switzerland	European	PC RCT	16-month period	ICU patients diagnosed with ARDS	IV solution	190mg/kg/day of NAC or placebo	Continuous infusion over the first 3 days	Placebo (saline)	n=42	NAC: n=22; Placebo: n=20	Incidence of ventilatory support PaO_2/FIO_2 Lung Injury Score Chest radiograph	No difference No difference NAC: 1.53 (SD 0.21) Placebo: 2.15 (SD 0.19) (p<.04) No difference
Howe, et al. (2015)	America USA	The Region of the Americas	DBPC RCT		ICU patients requiring mechanical ventilation	Enterally administered antioxidant supplementation via a bolus	Group 1: 5ml dose of placebo; Group 2: 5ml dose of vitamin E (100IU) and 5ml dose of placebo; Group 3: rml dose of vitamin C (1000mg), 5ml dose of vitamin E (1000IU) and 5ml dose of NAC (400mg)	Bolus given every 8 hours 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	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. (1992)	Denmark and Sweden	European	DBPC RCT		ICU patients diagnosed with ARDS	IV solution	NAC 150mg/kg as a loading dose and then 20mg/kg/hr	Initial dose was given for 30 mins on day one. Then	Placebo	n=66	NAC: n=32; Placebo: n=34	Adverse events Oxygenation	NAC: a rash was observed in one patient after the loading dose. No difference

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 intervetion and placebo	Measure of Outcome	Outcome
								continuous for the next 6 days				Administration of corticosteriods, prostaglandin E_1 or NSAIDs Time taken to recover from ARDS Chest radiographs	No difference No difference No difference
Lai, et al. (2010)	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 100mg/kg continuous IV infusion for 3 days.	Intial treatment with norepinephrine infusion, hdyrozortisone for septic shock. Oral oseltamivir 75mg twice daily, IV antibiotics next day. Next day, oseltamivir 150mg 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. (1995)	Switzerland	European	DB PC RCT		ICU patients diagnosed with severe ARDS	IV solution	190mg/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 Elastase release	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). No difference
Moradi, et al. (2009)	Iran	Eastern Mediterranean	SB PC RCT	July 2005 and April 2006	Ventilated ICU patients with ALI/ARDS	IV solution	150mg/kg at first day, followed by 50mg/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	Mortality rate Duration of mechanical ventilation Length of ICU stay	NAC: 35.7%; Placebo: 76.9% ($p=.03$) No difference No difference

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 intervetion and placebo	Measure of Outcome	Outcome
												PaO_2/FiO_2 (Day 2) PaO_2/FiO_2 (Day 3) PaO_2/FiO_2 (Day 4)	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. (1999)	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 50mg/kg OR NAC 50mg/kg+Rutin 5mg/kg every 8 hours	9 days (trial length) then as long as artificial ventilation was needed	Control 250ml 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) Polymorphonuclear (PMN) cell count in ELF Mortality [day 9 and day 30]	No difference NAC: Improved [Day 9] NAC: reduced 43% NAC+Rutin: reduced 46% Placebo: reduced 15% (p<.01) NAC: Reduced 50% NAC+Rutin: Reduced 30% Placebo: No change (p<.05) No difference
Sharafkhah, et al. (2018)	Iran	Eastern Mediterranean	DBPC RDT	March 2014 to June 2016	Adult ICU admitted patients undergoing	NAC (600 mg; water-soluble tablets) through nasogastric tube	Twice daily	Administered within the first 12 hours of mechanical	Placebo (water-soluble	n=60	NAC: n=30; Placebo: n=30	Incidence of ventilator-associated pneumonia	NAC: 26.6% Placebo: 46.6% (p=.032)

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 intervetion and placebo	Measure of Outcome	Outcome
					endotracheal intu-bation and mechanical ventilation			ventilation after hospital admission, and continued until performing extubation, tracheostomy, discharge, or death.	vitamin tablets)			Time to recovery	Patients who survived in the treatment group showed a more rapid recovery compared with the control group.
												Incidence of ventilator associated pneumonia (VAP)	Patients treated with NAC were significantly less likely to develop clinically confirmed VAP compared with patients treated with placebo.
												Time to VAP (days)	NAC: 6.42 (SD 1.9) Placebo: 3.46 (SD 2.53) (p=.002)
												Duration of mechanical ventilation (days)	No difference
												ICU stay (days)	NAC: 14.36 (SD 4.69) Placebo: 17.81 (SD 6.37) (p=.028)
												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

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 intervetion and placebo	Measure of Outcome	Outcome
												Adverse events	No adverse events related to NAC were identified.
Soltan-Sharifi, et al. (2007)	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 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	Acute Physiology and Chronic Health Evaluation(APACHE II) score Intracellular glutathione (GSH) (48h) GSH/GSSG ratio Total antioxidant power (TAP) (mmol/L) (72h)	NAC: Increased Placebo: Decreased (p<.01) NAC: Increased 59% Placebo: Decreased 23% (p<.001) NAC: Increased (22 vs 64.2) Placebo: No change (p<.01) NAC: 3.6 (SD 0.38) Placebo: 1.8 (SD 0.25) (p=.013)
Suter, et al. (1993)	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 40mg/kg/day	3 days	Placebo	n=61	NAC: n=32; Placebo: n=29	Incidence of ventilatory support FiO_2 administered PaO_2/FiO_2 Lung injury score	NAC: Reduced (69% vs 17%) Placebo: Reduced (76% vs 48%) (p=.01) NAC: Reduced (0.29 vs 0.48) Placebo: No difference (0.35 vs 0.48) (p<.05) No difference NAC: Decreased (1.39 vs 0.67) Placebo: No difference (p<.01)

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 intervetion and placebo	Measure of Outcome	Outcome
												Chest radiograph score	NAC: No change at day 3; Decreased at discharge (1.8 vs 1.1) Placebo: Increased at day 3 (p<.05)
van Meenen, et al. (2018)	Netherlands	European	RCT	June 22, 2014, to November 24, 2016	ICU patients receiving invasive ventilation	Nebulized 5ml solution (300mg acetylcysteine) administered alone or in combination with 5mL solutions containing salbutamol (2.5 mg)	On demand nebulization group: 5mL solutions containing acetylcysteine (300 mg) OR 5mL solutions containing salbutamol (2.5 mg) dependent on patient presentation. Routine nebulization group: acetylcysteine (300mg) with salbutamol (2.5mg) 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 hours.	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 No difference No difference *Total* On demand: 13.8% Routine: 29.3% (p<.001) *Tachyarrhythmia* On demand: 12.5% Routine: 25.9% (p<.001) *Agitation* On demand: 0.2% Routine: 4.3% (p<.001)
Zhang, et al. (2018)	China	Western Pacific Region	RCT	August 2016 and March 2017	All patients admitted to the hospital with community acquired pneumonia	Oral 600mg tablet	NAC 1200mg (600mg 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	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)

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 intervetion and placebo	Measure of Outcome	Outcome
												Superoxide dismutase CT Image comparison	No difference No difference