Should N-acetylcysteine be used as adjunct treatment for COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of N-acetylcysteine as adjunct in treating patients with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

There is very low-quality direct evidence that suggests the effectiveness of N-acetylcysteine as adjunct treatment for COVID-19. Further studies are needed to demonstrate its efficacy.

- NAC is a widely-used drug for respiratory problems, as an effective mucolytic, and in paracetamol poisoning.
- NAC possesses an acceptable safety profile and is well-tolerated.
- In vitro studies have shown NAC to reduce cell death, lower infectious H5N1 viral yields, and decrease the production of pro-inflammatory molecules.
- In COVID-19, patients with worse clinical outcomes are thought to experience an inflammatory cytokine storm that produces immunopathological changes in the lungs and other organs. In this scenario, NAC may exert anti-inflammatory action that lines it up as a potential therapeutic agent or adjunct in the management of COVID-19.
- Very low-quality direct evidence from observational studies suggest the effectiveness of NAC as adjunct treatment for COVID-19.
- Current guidelines do not include NAC among therapeutic agents being considered. There are also no completed randomized controlled trials as of this time. However, there are four registered clinical trials that will investigate the role of NAC in the treatment of COVID-19.

RESULTS

We found one retrospective cohort and two case reports, but no completed trials or randomized controlled studies that directly investigated the efficacy and safety of NAC as adjunct treatment for COVID-19.

A retrospective single-arm cohort of 73 patients with COVID-19 in Hubei, China were given nebulized acetylcysteine solution twice daily, in addition to lopinavir/ritonavir and levofloxacin. Zheng and coworkers reported that there were no deaths in the group.

Two case reports from China in early 2020 looked into the use of NAC in patients diagnosed with COVID-19. Song and coworkers noted the use of NAC in a 22-year-old man who presented with diarrhea, and was given a regimen that included oral lopinavir and ritonavir tablets, aerosol inhalation of interferon alpha-2b, and oral administration of acetylcysteine tablets as a mucolytic. The patient fully recovered and was discharged after 18 days in the hospital. Another case report by Lyu et al. documented a 38-year-old man with COVID-19 who presented with three-day fever and cough. He was initially given ganciclovir and oseltamivir plus hormones, then later abidol, meropenem, azithromycin, xuebijing, acetylcysteine effervescent and Jinkang Suoli as anti-phlegm and antifibrosis. Despite developing pneumothorax, the patient eventually recovered and was discharged after one month in the hospital.

In summary, a total of 75 patients with COVID who received NAC as an adjunct therapy with antiviral therapy and other supportive care survived. Adverse effects were not reported.

A rapid review by Van Hecke and Lee that searched up to 3 April 2020 also found no direct evidence for NAC in treating COVID. The review cited indirect evidence with one small RCT (n=262) in the 1990s that used NAC (600 mg twice daily for 6 months) versus placebo in subjects who were elderly or had chronic, nonrespiratory tract disease, who did not receive the influenza vaccine in the same or previous season. In this particular RCT of de Flora et al., NAC significantly decreased the frequency (RR 0.67, 95% CI 0.47 to 0.95) and severity of influenza (A/H1N1 virus) and influenza-like episodes (chi squared statistic=7.59; p-value =0.02), particularly in elderly high-risk persons, compared to placebo. No deaths and hospitalized cases were reported in either group.

NAC was well tolerated in the large majority of this pre-COVID study (elderly or with chronic non-respiratory degenerative diseases) after chronic use (six months). Only 12/125 (9%) reported adverse events, mainly gastrointestinal (epigastric pain, diarrhea, dysuria, flushing, nausea/vomiting, and constipation).

There are four registered and recruiting trials on the use of NAC in the treatment of COVID-19 summarized in Table 1 (Characteristics of Ongoing Clinical Trials).

CONCLUSION

It is unclear based on very low-quality direct evidence from single-arm observational studies whether NAC is effective and safe as an adjunct treatment for COVID-19.

Very low-quality direct evidence from observational studies suggest the effectiveness of NAC as adjunct treatment for COVID-19. These consisted of one retrospective single-arm cohort and two case reports that observed recovery of patients who were given NAC as part of their treatment regimen. Ongoing clinical trials may provide high-quality evidence of efficacy and safety of NAC for COVID-19 upon their completion.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of Ongoing Clinical Trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04370288 The Clinical Trial of Application of Methylene Blue Vial for Treatment of Covid-19 Patients	Recruiting	April 19, 2020 – September 20, 2020	Randomized Clinical Trial with parallel assignment	Iran	Patients with COVID-19 (by RT-PCR, HRCT) aged 19 to 90 years	Mixture of MCN (Methylene blue, vitamin C, N-acetyl cysteine).	Standard medical therapy/supportive therapy	Primary Outcome Measures: : - Proportion of patients remaining free of need for mechanical ventilation in both groups at Day 7 Secondary Outcome Measures : - Mortality rate in both groups at Day 28 - Improvement in Pa02/Fi02 ratio in both groups at Day 2 - Duration of hospital stay in both groups, assessed at Day 28 - Duration of Intensive Care Unit stay in both groups, assessed at Day 28 - Days free of dialysis in both groups, assessed at Day 28 - C-reactive proteins at 3-5 Days - WBC Count at 3-5 Days
2	NCT04374461 Phase II Study of N-acetylcysteine in Severe or Critically Ill Patients With Refractory COVID-19 Infection	Recruiting	May 1, 2020 – May 2021	Non-randomized, parallel assignment clinical trial	USA	Documented COVID-19 infection (either performed on site or documented external report, Age ≥ 18 Arm A: Admission to an intensive care unit at MSK (M-11 or M-18) and/or receiving mechanical ventilation	Experimental: Patients in both arms will receive N-acetylcysteine IV 6 g/day in addition to supportive and/or COVID-19 directed treatments at the discretion of the treating physician.	None listed	Primary Outcome Measures : - Arm A: number of patients who are successfully extubated and/or transferred out of critical care due to clinical improvement, assessed at 1 year

						Absolute lymphocyte count ≤ 1.0/mm3 As the ALC of patients with lymphoid malignancies is unreliable, they may be enrolled at the discretion of the treating physician after review of their blood work. Arm B: Arm B: requiring mechanical ventilation or admission to an intensive care unit at MSK (M11 or M18)	Patients will receive treatment for a maximum of 3 weeks or until one of the following: Arm A (mechanically ventilated &/or managed in a critical-care) : Transfer out of the critical-care unit Extubation Toxicity Death Arm B (non-mechanically ventilated, non critical care) Discharge from hospital Admission to a critical-care unit Intubation Toxicity Death		- Arm B: number of patients who are discharged from the hospital due to clinical improvement, assessed at 1 year
3	IRCT20200324046850N1 Comparison of vitamin D3 and N-acetylcysteine prescription in COVID19 patients and their effect on recovery process	Ongoing	March 29, 2020 – May 21, 2020	A randomised factorial trial with single blinded outcome assessment	Iran	Persons diagnosed with COVID-19 confirmed by CT scan	National Medicines Standard Protocol + (Perl Vitamin D3 50,000 units) once a week National standard drug + N acetylcysteine (NAC) tablets receiving 600mg every 12 hours for 14 days National standard protocol drug + (Perl vitamin D3 50,000 units) once a week + N acetylcysteine	Standard national protocol drugs	Shortness of breath Cough Chills Night sweats

							(NAC) tablet 600mg every 12 hours for 14 days		
4	RBR-8969zg Clinical Trial using N-acetylcysteine for treatment of 2019-nCoV Pneumonia	Not yet recruiting	April 4, 2020 – October 14, 2020	Clinical trial, single-center, randomized, placebo-controlled, double-blind.	Brazil	Volunteers; Both genders; Admitted to the Emergency Department with diagnosis of Acute Respiratory Syndrome, presumed or confirmed; Age equal to or greater than 18 years; Informed consent form (ICF) signed by the patient or legal guardian	Intravenous infusion in peripheral venous access of N acetylcysteine in a total dose of 300 mg / kg, with the first dose being 200 mg / kg in 4 hours and the second dose 100 mg/kg in 16 hours	Intravenous infusion in peripheral venous access of Placebo (Glucose 5% 100mL) in 20h (single dose)	Reduction in in-hospital mortality in 5%, verified by medical record analysis, in patients receiving N-acetylcysteine compared to the group receiving Placebo Reduction in 5% in the need for endotracheal intubation, verified by medical record analysis, in patients receiving N-acetylcysteine compared to the group receiving Placebo