


Intravenous N-Acetylcysteine in Management of COVID-19: A Case Series

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Abstract

A novel coronavirus, severe acute respiratory syndrome coronavirus-2, was isolated from patients' lower respiratory tracts in December 2019. As of May 19, 2021, there were over 33 million reported infections and almost 600,000 deaths in the United States. The infection, coronavirus disease-19 (COVID-19), can lead to cytokine storm, with elevations in interleukin-6 (IL-6), IL-10, tumor necrosis factor- α , nuclear factor-kappaB (NF-kappaB), and glutathione reductase. NF-kappaB activation is necessary for further transcription of other pro-inflammatory markers. Glutathione may play a role in modulation of NF-kappaB activation and elevated glutathione reductase may indicate glutathione depletion. Administration of N-acetylcysteine (NAC) may replenish spent glutathione and attenuate over-activation of NF-kappaB. This retrospective case series included 10 patients who were COVID-19 positive and received intravenous NAC in an attempt to attenuate the cytokine storm. Patients' outcomes were graded based on the World Health Organization symptom severity scale from 0, no evidence of infection, to 8, death. Overall, the median WHO Scale prior to NAC was 6.5, and increased by day seven, which indicated clinical worsening. This retrospective case series showed no benefit of NAC; however, further studies are needed to elucidate if differences in drug regimens would lead to positive results.

Keywords

coronavirus, COVID-19, cytokine storm, glutathione, N-acetylcysteine

Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus-2, was isolated from patients' lower respiratory tracts as early as December 2019 and was found to be transmissible through aerosolized droplets from coughing and sneezing in both asymptomatic and symptomatic patients.^{1,2} As of May 19, 2021, there were over 33 million reported infections and almost 600,000 deaths in the United States.³

Patients with more severe disease can progress to severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ dysfunction, cytokine storm, and death.⁴ Disease progression and promulgation of cytokine storm is marked by a rise in inflammatory cytokines, interleukin-6 (IL-6), IL-10, tumor necrosis factor- α , nuclear factor-kappaB (NF-kappaB), the acute phase reactants C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, and D-dimer.⁵⁻⁸ Liver transaminases, lactate, creatinine, and glutathione reductase may also be elevated.⁹ It has been shown that NF-kappaB activation is necessary for transcription of downstream pro-inflammatory mediators leading to ARDS.⁵ Meanwhile, glutathione has been linked to regulation of NF-kappaB

signaling (Figure 1).⁶ Greater levels of glutathione reductase in patients may indicate increased oxidative stress, glutathione depletion, and reduced NF-kappaB modulation.^{5,6,9}

N-acetylcysteine (NAC) is a mucolytic often used in respiratory diseases that act by disrupting mucoprotein disulfide bonds. NAC is also used in management of acetaminophen toxicity through glutathione regeneration. Similarly, NAC may replenish spent glutathione, reduce further oxidative and inflammatory damage, and prevent initiation or progression of cytokine storm in COVID-19 infection. We performed a retrospective evaluation of patients who received intravenous NAC supplementation in management of COVID-19-associated cytokine storm. The objective of this study is to assess clinical outcomes at day 7 after NAC treatment.

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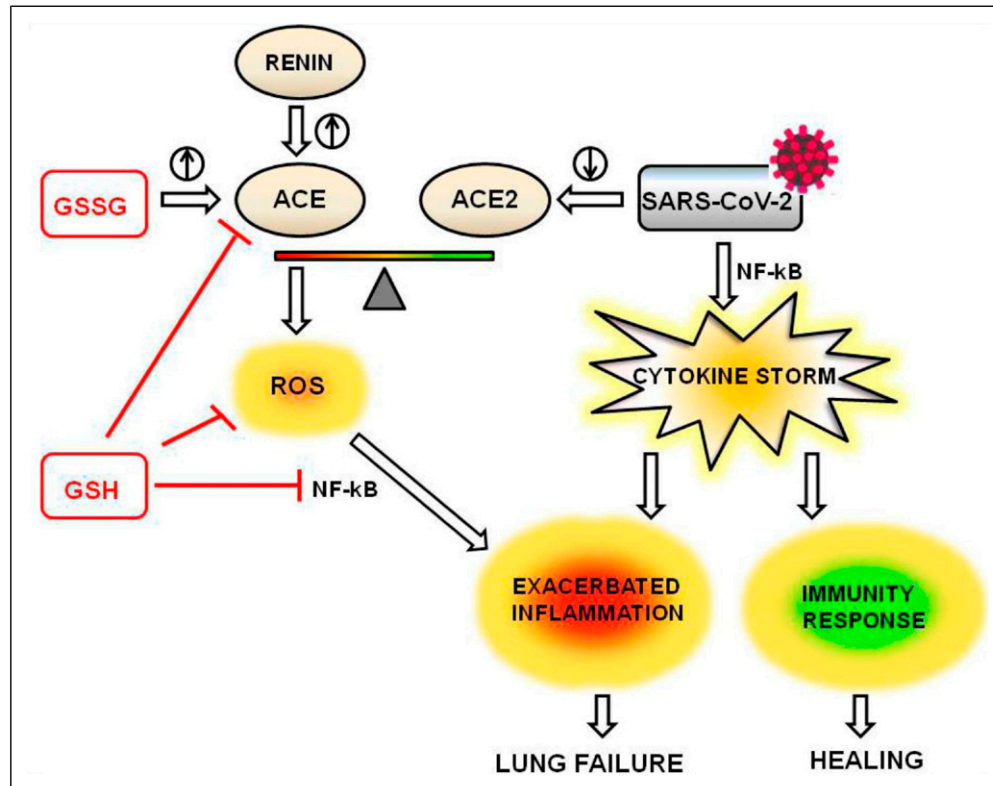


Figure 1. Proposed pathway of reduced glutathione ameliorating SARS-CoV-2 cytokine storm. ACE, angiotensin converting enzyme; ACE2, angiotensin 2 converting enzyme; GSH, reduced glutathione; GSSG, oxidized glutathione; NF-kB, nuclear factor kappaB; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. N-acetylcysteine supplementation may increase supply of GSH. The anti-inflammatory effects of GSH are mediated through decreased production of ROS and reduced activation of NF-kB, signified by the red lines. Figure reprinted with permission by Silvagno et al.

Methods

The Institutional Review Board approved this retrospective case series and a waiver of informed consent was received. Patients admitted in April 2020 were included if they were 18 years and older, had a positive COVID-19 PCR test, and had received at least one dose of intravenous (IV) NAC. IV NAC was prescribed at the discretion of the treating physician. Dosage was based on initial treatment for acetaminophen toxicity, 150 mg/kg, with a maximum recommended dose of 10 g based on institution COVID-19 taskforce recommendations. The total number of doses and duration of treatment were determined through provider discretion. Outcomes were assessed up to 7 days after the last dose of IV NAC or until death or discharge, whichever was earlier. Outcomes were censored at 7 days on the assumption that attributable beneficial effects would present acutely. Information collected from the electronic medical record included patient demographics, treatment regimen, inflammatory marker levels, arterial blood gases, and ventilation modality.

Laboratory values were recorded as close to the administration time of IV NAC as possible for pre-administration values and at least 8 hours after infusion and as close to the seventh day after completing IV NAC therapy for

post-administration values. The primary outcome was any improvement from baseline on an 8-point ordinal illness severity scale as recommended by the World Health Organization (WHO): 0, no clinical or virological evidence of infection; 1, no limitation of activities; 2, limitation of activities; 3, hospitalized, no oxygen therapy; 4, oxygen by mask or nasal prongs; 5, non-invasive ventilation or high-flow oxygen; 6, intubation and mechanical ventilation; 7, and ventilation plus additional organ support (vasopressors, renal replacement therapy, and extracorporeal membrane oxygenation); 8, death. We also assessed lengths of intensive care and hospital stays, transfer to intensive care, ventilation status on day 7, vasopressor and hemodialysis requirements, and mortality.¹⁰ Missing lab values and measurements were not included and we reported the number of patients whose information was available. Descriptive statistics were used to evaluate all outcomes.

Results

Baseline Characteristics

Ten patients received IV NAC during the study period. All patients were included in the evaluation. Patients had a median age of 62 years, weight of 70.8 kg, and 80% had a history of

hypertension (Table 1). Median time from symptom onset to hospital admission was 6 days. Acute phase reactants ferritin, LDH, and CRP were all elevated (Table 2). Half of the patients were on vasopressors and 60% required invasive mechanical ventilation at baseline. Of the patients on mechanical ventilation, the median PaO₂/FiO₂ (PF) ratio was 177.5. Half of the patients were in an intensive care setting prior to being given NAC. At baseline, patients had a median [IQR] WHO scale

score of 6.5 [5–7] indicating a range from non-invasive ventilation modalities to mechanical ventilation plus vasopressor support.

Treatment Course

NAC was administered at a median dose of 10,000 mg (median 141.67 mg/kg) every 12 hours for 1 to 6 doses. NAC

Table 1. Baseline Characteristics Before Last N-Acetylcysteine Dose.

Characteristic	Median (IQR) or Proportion	N
Age	62 (57–73)	10
Sex, male	40%	10
Weight, kg	70.75 (60.95–88.75)	10
Diabetes	30%	10
Hypertension	80%	10
Time from symptoms to ED presentation, days	6 (1.25–7)	10
Vasopressors	50%	10
Hemodialysis	10%	10
Other drugs administered		
Ascorbic acid	100%	10
Melatonin	10%	10
Thiamine	70%	10
Zinc	90%	10

Data presented as median (IQR) or proportion.

Abbreviations: N, number of patients with available results; IQR, interquartile range; ED, emergency department.

Table 2. Treatment Characteristics Before N-Acetylcysteine Dose and at 7 Days After Final N-Acetylcysteine Dose.

Characteristic	Value Prior to NAC	N	Value Post NAC	N
Ferritin, ng/mL	1779 (1554–2430.3)	8	1566 (1349–2254)	5
LDH, unit/L	484 (477–721)	9	423 (422–554)	5
CRP, mg/dL	14 (12–17.4)	9	11.7 (8.92–17.3)	7
D-dimer, ng/mL	>1050	1	>1050 (>1050–>1050)	5
PCT, ng/mL	.29 (.18–.36)	6	No results	0
Mode of ventilation				
Room air	0%	10	10%	10
Nasal cannula	10%	10	0%	10
Non-rebreather	10%	10	0%	10
High-flow nasal cannula	20%	10	0%	10
Mechanical ventilation	60%	10	90%	10
Arterial blood gas				
pH	7.4 (7.36–7.45)	9	7.35 (7.23–7.43)	8
pCO ₂ , mmHg	46 (38–50)	9	50.5 (46.75–51.25)	8
pO ₂ , mmHg	108 (80–133)	9	110 (79–170)	8
CO ₃ , mmol/L	26 (24–28)	9	23.5 (20–29.25)	8
Respiratory rate, min ⁻¹	19 (15–23.5)	10	20 (20–22)	10
Tidal volume, mL	450 (450–500)	7	450 (395–500)	8
FiO ₂ (mechanical ventilation), %	70 (60–100)	7	76.5 (50–85)	8
PF ratio	177.5 (127–185.17)	6	202.11 (146.5–252)	8
WHO scale	6.5 (5–7)	10	7 (6.25–7.75)	10

Data presented as median (IQR) or proportion.

Abbreviations: N, number of patients with available results; IQR, interquartile range; NAC, N-acetylcysteine; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin.

was administered a median of 3.88 days after hospital admission and half of all patients received NAC outside the intensive care unit. The other five patients received NAC a median of 2.69 days after transfer to intensive care (Table 3).

Outcomes

There was a median increase of 0.5 point in the WHO scale on day 7 post NAC administration, indicating clinical worsening. Five patients (50%) worsened, 4 (40%) had no change, and 1 (10%) showed improvement (Table 4). Of the 5 patients outside of intensive care when given NAC, 4 were subsequently escalated to intensive care. The median intensive care and hospital lengths of stay were 6.44 (2.98–10.14) and 10.72 (8.18–12.41) days, respectively.

Four patients were not on invasive mechanical ventilation at baseline; however, three progressed to invasive mechanical ventilation. On day 7 post NAC, 90% were on

mechanical ventilation. Five patients were on vasopressors at baseline. Four remained on vasopressors at the end of the assessment period. Of those that were not on vasopressors at baseline, three progressed to requiring at least one vasopressor.

Inflammatory markers declined slightly and were not clinically significant. Ferritin decreased from a median of 1,779 ng/mL (IQR 1,554–2,430.25 ng/mL) to 1566 ng/mL (1,349–2,254 ng/mL), LDH from 484 units/L (477–721 units/L) to 423 units/L (422–554 units/L), and CRP from 14 mg/dL (12–17.4 mg/dL) to 11.7 mg/dL (8.9–17.25 mg/dL). D-dimer remained elevated at >1,050 ng/mL. Patient-specific laboratory values pre- and post-NAC were reported where available (Table 5).

At the end of the study period, three patients expired and one patient was transferred to another facility to continue care. No patients were discharged by day 7 of follow-up. Ultimately, a total of six patients expired while receiving ICU care

Table 3. N-Acetylcysteine Treatment Information.

Characteristic	Median (IQR) or Proportion	N
NAC dose, mg	10000 (9317.5–10000)	10
NAC dose/body weight, mg/kg	141.67 (102.28–149.11)	10
Number of NAC doses	1.5 (1–3.5)	10
Time from symptoms to NAC, days	8.44 (4.9–15.52)	10
Time from admit to NAC, days	3.88 (1.18–5.64)	10
Critical care prior to NAC	50%	10
Time to ICU from admit, days	3.12 (.82–6.91)	9
Time from NAC to ICU, days	3.05 (2.17–3.55)	4

Data presented as median (IQR) or proportion.

Abbreviations: N, number of patients with available results; IQR, interquartile range; NAC, N-acetylcysteine; ICU, intensive care unit.

Table 4. Primary and Secondary Outcomes at 7 Days After Final N-Acetylcysteine Dose.

Primary outcome	Median (IQR) or Proportion	N
Change in WHO scale	.5 (0–1)	10
Percent worsening	50%	10
Percent no change	40%	10
Percent with improving scale	10%	10
Secondary outcomes		
Upgraded to ICU	80%	5
Progression to mechanical ventilation	75%	4
Vasopressors	70%	10
New vasopressors started	3 (60%)	5
Continued on vasopressors	4 (80%)	5
Vasopressors stopped	1 (20%)	5
New hemodialysis	0%	9
Mortality	30%	10
ICU Length of stay, days	6.44 (2.98–10.14)	9
Hospital length of stay, days	10.72 (8.18–12.41)	10

Data presented as median (IQR) or proportion.

Abbreviations: N, number of patients with available results; IQR, interquartile range; WHO, World Health Organization; ICU, intensive care unit.

Table 5. Patient-Specific Laboratory Values and Disposition.

Patient	Prior to NAC Therapy						Post NAC Therapy Completion Day 7						Final Disposition, Hospital Day
	Ferritin, ng/mL	LDH, unit/L	CRP, mg/dL	D-Dimer, ng/mL	Mode of Ventilation	PF Ratio	Ferritin, ng/mL	LDH, unit/L	CRP, mg/dL	D-Dimer, ng/mL	Mode of Ventilation	PF Ratio	
Patient 1	270	394	17.4	—	NRB	—	—	—	—	—	Ventilator	240	Expired day 11
Patient 2	1152	884	12.9	—	HFNC	—	—	—	33.5	—	Ventilator	70	Expired day 12
Patient 3	1805	484	18.4	—	HFNC	133	—	—	5.6	>1050	Ventilator	288	Expired day 38
Patient 4	—	477	11.2	—	Ventilator	192	—	—	—	—	Ventilator	—	To VA day 3
Patient 5	—	—	—	—	Ventilator	121	—	—	—	—	Ventilator	177	Expired day 8
Patient 6	4174	510	17.2	—	Ventilator	178	2956	421	19.8	>1050	Ventilator	228	To LTC day 91
Patient 7	16500	2665	9.2	—	NC	—	1317	422	14.7	>1050	Room air	—	To SAR day 20
Patient 8	1688	721	12	—	Ventilator	240	1566	554	11.7	>1050	Ventilator	324	To SAR day 29
Patient 9	1753	480	43.6	>1050	Ventilator	104	2254	613	9.8	>1050	Ventilator	56	Expired day 45
Patient 10	1849	449	14	—	Ventilator	178	1349	423	8	—	Ventilator	172	Expired day 37

Data are single lab values taken prior to or after completing NAC therapy. Missing data represented by hyphens. LDH, lactate dehydrogenase; CRP, C-reactive protein; NRB, non-rebreather mask; HFNC, high-flow nasal cannula; NC, nasal cannula; VA, transferred to Veteran's Affairs hospital; LTC, transferred to long-term care facility; SAR, transferred to subacute rehabilitation facility.

and the remaining four were transferred to outside facilities (Table 5).

Discussion

Based on this evaluation, IV NAC had no significant impact on clinical outcomes at day 7. Although acute phase reactants generally decreased and PF ratios increased overall (Table 2 and Table 5), 90% of patients were in critical care at the end of follow up with attributed 30% mortality (Table 4). The changes in inflammatory markers were likely associated with disease progression rather than IV NAC. These patients were heterogeneous in characteristics and not chosen with specific inclusion criteria, which limit both external and internal validity. Patients were prescribed IV NAC on the basis of prescriber discretion and impression of disease severity. There is little literature regarding use of NAC for respiratory viral illnesses and thus guidance for our usage of IV NAC was based on risk-benefit and safety of IV NAC in acetaminophen overdose. Some in vitro and animal studies support the use of NAC in reducing influenza viral replication, but evidence of translation to humans is scarce and uncertain.^{11,12} Quantitative viral load testing was not performed during the study period, which precluded this observation in our patients.

A case series by Ibrahim et al. of one glucose 6-phosphate dehydrogenase (G6PD) deficient COVID-19 patient and 9

other non-G6PD deficient COVID-19 patients showed clinical improvement after administration of IV NAC. Nine of the 10 patients required extracorporeal membrane oxygenation (ECMO). NAC dosing was 30,000 mg and 20,000 mg IV over two days for the first two patients and 600 mg every 12 hours for 4–9 days for the remaining 8 patients. Inflammatory markers such as CRP and ferritin markedly decreased after NAC treatment. CRP decreased from a mean of 160 mg/dL to 31 mg/dL and ferritin decreased from a mean of 3,630 ng/mL to 1,543 ng/mL with sustained reductions during the treatment course. A total of 8 patients were discharged home and 2 remained hospitalized by the end of the study period.¹³ With respect to the present study, it is uncertain if outcomes would have changed had ECMO been an available treatment option. Another notable difference was that inflammatory markers in our patients did not respond nearly as greatly, possibly owing to differences in disease severity or dosing regimen.

A retrospective cohort study by Assimakopoulos et al. evaluated patients with moderate or severe COVID-19 randomized to either standard of care plus oral NAC 600 mg twice a day for 14 days (n = 42) or standard of care (n = 40). Treatment with NAC led to a significantly lower rate of progression to severe respiratory failure requiring mechanical ventilation ($P < .01$). NAC treatment also significantly decreased 14-day and 28-day mortality, 0% compared to 25% ($P < .001$), and 4.8% compared to 30% ($P < .01$), respectively.¹⁴

Interestingly, patients in this study were given NAC orally at a substantially lower dose but over a longer duration than in our current study with improved mortality. However, its retrospective cohort design limits its generalizability.

The most robust study of IV NAC in COVID-19 patients to date was conducted by de Alencar et al. The double-blind, placebo-controlled trial randomized 135 patients to either IV NAC (n = 68), 14 g over 4 hours after enrollment followed by another 7 g over the next 16 hours, or placebo (n = 67). At baseline, 30% of the IV NAC group and 32% of the placebo group did not require supplemental oxygen, 68% of both groups required supplemental oxygen, and 1% and 0% required non-invasive ventilation or high-flow oxygen. The primary endpoint of progression to mechanical ventilation occurred in 24% of IV NAC patients and 21% of placebo patients ($P > .05$). The difference in the secondary endpoint of ICU admission was also not statistically significant, occurring in 43% and 47% of patients, respectively.¹⁵ Patients in this study were less severe by WHO criteria than those in the present study but demonstrated that IV NAC administration prior to requiring high-flow oxygen or mechanical ventilation prevented neither those outcomes nor ICU admission.

Last, a study of seroconversion to symptomatic influenza virus randomized 262 patients to either 600 mg NAC by mouth twice daily or placebo for 6 months. Both groups demonstrated similar seroconversion, but only 25% of the treatment group developed symptoms compared to 79% of the placebo group.¹⁶ Although NAC may improve cell-mediated immunity, therapy may require prolonged treatment to produce an effect as opposed to large boluses over a short period as in our study and in the study by de Alencar et al.

Limitations of this study include a low number of evaluated patients and selection bias due to the retrospective, observational design. These results are hypothesis generating and thus preclude definitive conclusions. All patients also concomitantly received other medications with purported anti-inflammatory and free radical scavenging properties: ascorbic acid, melatonin, thiamine, and zinc (Table 1).¹⁷⁻¹⁹ Notably, patients in this case series did not receive dexamethasone since the results of the RECOVERY trial were not available at the time.²⁰ Larger, randomized control studies are needed to assess intervention efficacy. This study, however, found no acute signal that NAC improves the clinical status of COVID-19 patients.

Conclusion

Routine NAC should not be recommended for COVID-19-associated cytokine storm at this time. Further studies are needed to evaluate whether different dosing regimens and timing of drug administration can affect clinical outcomes.

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Declaration of Conflicting Interests

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