Review Article

N-acetylcysteine for non-acetaminophen induced acute liver failure: A review

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Abstract

The use of N-acetylcysteine (NAC) for non-acetaminophen-induced acute liver failure (NAI-ALF) has been increasing despite controversy in its efficacy. National guidelines are in disagreement for NAC use as standard of care; however, many healthcare centers continue to adopt the use of NAC outside of acetaminophen poisoning. While NAC may have multiple mechanisms of action in treatment of ALF, this has not translated to clinical benefit. Murine models have reported antioxidant and anti-inflammatory properties, as well as improvement in liver-specific microcirculation. Multiple case studies and series have reported positive outcomes of NAC treatment for ALF of various etiologies. While prospective studies suggested the benefit of NAC treatment, these studies have methodological and statistical shortcomings that affect the validity of the results. In this review, we aimed to summarize the existing literature on the efficacy of NAC for NAI-ALF including mechanism of action, case studies and series demonstrating outcomes, and prospective studies that have led to its current widespread use, along with the reported rate of adverse events.

Keywords: Acetylcysteine, acute liver failure, clinical pharmacology, liver

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INTRODUCTION

Acute liver failure (ALF) is a rapidly-progressive illness of hepatic dysfunction accompanied by encephalopathy and coagulopathy, with a high incidence of multi-organ failure and death. N-acetylcysteine (NAC) treatment for acetaminophen-induced ALF is clearly established;[1] however, its use for non-acetaminophen-induced ALF (NAI-ALF) is not definitively supported by existing evidence. Nevertheless, there has been increasing use of N-acetylcysteine (NAC) in NAI-ALF over the past two decades[2] despite controversy in its role outside of acetaminophen overdose.

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The uncertainty of NAC treatment for NAI-ALF is reflected in prominent guidelines. The European Association for the Study of the Liver (EASL) guidelines advise NAC treatment in early-stage ALF of all causes, including NAI-ALF, as standard of care.[3] The American Association of the Study of Liver Diseases (AASLD) guidelines state that NAC may improve survival during early stages of hepatic encephalopathy and may benefit ALF associated with drug-induced liver injury (DILI). NAC treatment is recommended for ALF due to mushroom poisoning;[4] however, there is no specific recommendation for NAC in other causes of NAI-ALF.[5] In contrast, the American Gastroenterology Association (AGA) 2017

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guidelines state that NAC treatment for NAI-ALF should be limited to clinical trials only.[6]

Multiple reviews investigating the efficacy of NAC treatment for NAI-ALF have concluded that there is insufficient evidence to recommend its routine use. Two reviews, which included two prospective cohort studies in adults with NAI-ALF, made no recommendation for NAC due to multiple areas of bias in existing studies.[7,8] In a meta-analysis of two adult and two pediatric studies, there was no significant improvement in overall survival with NAC treatment though there was suggestion of better transplant-free survival and post-transplant survival.[8] Another review specifically studied NAC treatment for NAI-DILI leading to ALF, but was too underpowered to draw conclusions.[9] The most recent systematic reviews appear to provide conflicting conclusions. In 2020, Siu *et al*. conducted a Cochrane systematic review on NAC in NAI-ALF including only one adult trial,[10] and deemed the evidence to be inconclusive due to the risk of bias and imprecision.[11] Contrastingly, Shrestha *et al*.[12] conducted a meta-analysis of NAC in acute liver injury in pediatric and adult populations and found mortality benefit in NAC use; however, on closer examination, this finding did not reach significance when including only randomized trials. While these reviews provide a summary of evidence, their findings require contextualization and critical appraisal before they can be clinically applied.

Proposed mechanism of action in ALF

Animal models have studied possible mechanisms of NAC in ALF, whereby oxidative injury leads to hepatocyte apoptosis and mitochondrial failure[13] [Figure 1]. NAC has been shown to have antioxidant properties beyond acting as a precursor to glutathione.[14] In a mouse model of ALF, NAC treatment attenuated hepatocyte apoptosis resulting from oxidative stress.[15] Further, NAC has been shown to improve mitochondrial dysfunction in mouse models of liver injury.[16,17] NAC also exhibits an anti-inflammatory effect by inhibiting activation of toll-like receptors and lowering systemic cytokine levels.[18] This anti-inflammatory effect was shown to normalize mice cerebral edema and decrease neutrophil infiltration of the liver,[19] which mitigates hepatocyte death.[20]

ALF is also associated with tissue hypoxia,[13] which has been shown to improve with NAC treatment in early physiologic studies. After NAC administration to ALF patients, Harrison *et al*.[21] observed improved oxygen delivery and consumption, though this effect was diminished in patients with NAI-ALF. While cyclic guanosine monophosphate (cGMP) is elevated during

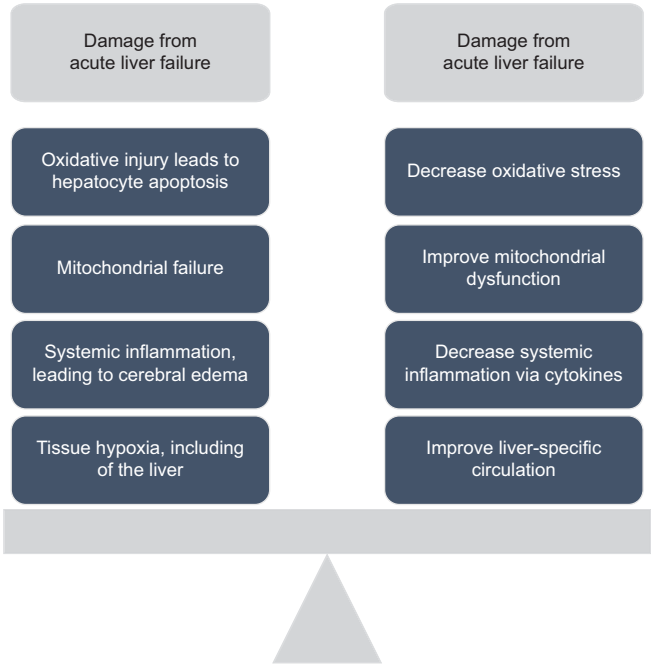

Figure 1: Proposed mechanism of NAC in ALF

ALF,[22] a further increase in cGMP was observed after NAC treatment, leading to the proposal that improved oxygenation was secondary to cGMP-induced vasodilation.[23] This result was criticized as studies by Harrison *et al*. utilized the Fick method to calculate oxygen consumption, which is prone to false elevations.[24,25] Other studies that directly measured systemic oxygen delivery and consumption found no improvement of oxygenation with NAC treatment.[26] Nonetheless, there may be a specific effect in hepatosplanchnic circulation as subsequent studies measured improved blood flow index and associated increased hepatic clearance after NAC treatment.[27] As such, NAC treatment likely improves liver-specific circulation, but none of these effects have translated to clinical outcomes.[28]

Clinical Studies: Case Reports and Case Series

Some case studies and series suggest that NAC treatment in NAI-ALF is effective in the early stages of hepatic encephalopathy (HE). In a case series of eight adults in Sri Lanka with dengue-associated ALF treated with NAC infusions, recovery was seen in patients with grade I-II HE.[29] Similarly, another case series in Israel including seven adults with NAI-ALF treated with intravenous or oral NAC, showed clinical recovery and reversal of coagulopathy in three patients with grade 0–II HE (a fourth patient recovered but died from unrelated causes), though it is unclear whether recovered patients had acute liver injury that was spontaneously reversible or had liver failure that would have been irreversible if NAC had not been provided.[30] Further,

Table 1: Adult case studies on the treatment of NAI-ALF with NAC

Cause of ALF	Reference	Case description	Study outcome
Cocaethylene	Hassen 2018[36]	Middle-aged female presenting with cocaine and alcohol use leading to ALF.	Resolution of clinical and biochemical derangements.
Sickle cell hepatic crisis	Zhang 2019[37]	Young male with sickle cell disease and frequent pain crisis, presenting with ALF.	Resolution of clinical and biochemical derangements.
Dengue hemorrhagic fever (DHF)	Abeysekera 2013[38]	Middle-aged female with DHF, symptom onset 5 days ago, presenting with ALF.	Resolution of clinical and biochemical derangements.
	Manoj 2014[39]	Middle-aged male with DHF, symptom onset 4 days ago, presenting with ALF.	Resolution of clinical and biochemical derangements.
	Dalugama 2017[40]	Middle-aged male with DHF, symptom onset 4 days ago, presenting with ALF.	Resolution of clinical and biochemical derangements.
	Dissanayake 2021[41]	Thirty adults with severe dengue fever leading to ALF.	Resolution of clinical and biochemical derangements.
Shock liver	Parvataneni 2020[42]	Elderly male presenting with sepsis and atrial fibrillation with rapid ventricular response, leading to multi-organ failure, including ALF.	Improvement in clinical status and biochemical derangements, with eventual discharge.
Tyrosine kinase inhibitor - Crizotinib	Brown 2017[43]	Middle-aged female with metastatic non-small cell lung cancer on crizotinib, presenting with acute liver injury, which progressed to ALF.	Worsening bilirubinemia, coagulopathy, and hepatic encephalopathy. The patient ultimately developed subarachnoid hemorrhage and supportive care was withdrawn.
Tyrosine kinase inhibitor - Crizotinib	Adhikari 2018[44]	Middle-aged male with ALK + metastatic non-small cell carcinoma on crizotinib, presenting with ALF and multiorgan dysfunction.	Worsening bilirubinemia, coagulopathy, and hepatic encephalopathy despite improvement in transaminitis. The patient ultimately died from multi-organ dysfunction.
Ifosfamide	Cheung 2011[45]	Middle-aged female with synovial sarcoma of the neck, treated with ifosfamide and doxorubicin leading to ALF.	Resolution of clinical and biochemical derangements. No further liver toxicity in subsequent chemotherapy cycles with doxorubicin alone.
Norfloxacin	Elliot 2016[46]	Older female on treatment with norfloxacin treatment for 3 days presented with ALF.	Resolution of clinical and biochemical derangements.
Rifampin, isoniazid, pyrazinamide, ethambutol (RIPE)	Fox 2020[47]	Young female with tuberculosis presenting with ALF after 4 days of RIPE treatment.	Resolution of clinical and biochemical derangements. Discharged on alternative tuberculosis medications.
Remdesivir (in context of COVID-19 infection)	Carothers 2020[48]	Two patients developed ALF after 3-10 days of remdesivir treatment for COVID-19 pneumonia.	One patient fully recovered while the other died of presumed septic shock.

the reversal of coagulopathy is of unclear significance as NAC treatment has been shown to increase clotting factors in healthy participants with no liver injury.[31]

Multiple case studies have demonstrated outcomes of NAC treatment in NAI-ALF, ranging from DILI, shock liver, and infectious causes [Table 1]. Outcomes are generally positive with complete clinical and biochemical resolution; however, there are also reports of death due to ALF or mortality from other causes. There are also several studies of NAC treatment for ALF in the pediatric population of various etiologies, which have led to conflicting results that may not be directly comparable to the adult population [Table 2].[32–35]

Although these case reports and series are clinically interesting, hypothesis-generating, and suggest the potential for benefit, without a comparator control group of patients on non-NAC standard care alone, it is impossible to determine whether NAC treatment was definitely beneficial.

Clinical studies: Prospective studies

Prospective cohort studies suggesting the benefit of NAC in NAI-ALF are limited in size and heterogeneity [Table 2]. Mumtaz *et al*.[49] preformed a prospective cohort study in Pakistan of oral NAC treatment for NAI-ALF, where ALF was mainly secondary to viral hepatitis (HEV, HBV) and DILI. Compared to a historical control group, NAC treatment was associated with a higher survival rate (47% vs. 27%, $P = 0.05$). The authors acknowledge that there were advances in critical care during the study period, rendering the historical control incomparable, especially as the control group had more deaths attributed to "sepsis/multiorgan failure."

A similar prospective cohort study was conducted in Kuwait by Darweesh *et al*.[51] However, the majority of their participants did not have encephalopathy at enrolment, which represents a major departure from other studies adhering to the strict definition of ALF. Compared with historical controls, Darweesh *et al*. reported significantly improved transplant-free survival with NAC

Table 2: Pediatric case studies on the treatment of NAI-ALF with NAC

Cause of ALF	Reference	Case description	Study outcome
Indeterminant (*n*=55) Autoimmune (*n*=8) Infection (*n*=9) Metabolic (*n*=13) Other (*n*=7)	Squires 2013[32]	Randomized controlled trial of pediatric patients with ALF due to various etiologies.	Similar 1-year survival (*P*=0.19) but lower transplant-free survival in patients treated with NAC with HE grade 0-1 <2 years old (35% vs. 53%, *P*=0.04).
Indeterminant (*n*=42) Metabolic (*n*=16) Infectious (*n*=14) Autoimmune (*n*=7) Hemochromatosis (*n*=7) Drug (*n*=7) Other (*n*=18)	Kortsalioudaki 2008[50]	Randomized controlled trial of pediatric patients with ALF of various etiologies.	Superior survival in patients treated with NAC (75% vs 50% untreated, *P*<0.01) and transplant-free survival (48% vs 22% untreated, *P*<0.01).
Not stated	Rashid 2011[34]	Sixty patients aged 1 to 14 years with ALF of unstated cause were treated with NAC.	Eighty percent of patients treated with NAC survived, compared to 63.3% of patients surviving without NAC treatment.
Dengue viral infection	Senanayake 2013[35]	Seven patients aged 6 months to 12 years with severe dengue infection leading to ALF.	Resolution of clinical and biochemical derangements.

treatment (96.4% vs. 23.3%, $P < 0.01$), and no further analysis was conducted given their substantial result. The transplant-free survival with NAC dramatically exceeds the results of other studies and the authors attributed this to using significantly higher doses of NAC treatment.

Randomized controlled trials

The most rigorous and commonly referenced study reporting benefit of NAC in NAI-ALF is by Lee *et al.* in 2009.[10] This prospective, double-blind, randomized study, included 24 centers across the US from 1998 to 2006, and enrolled 173 patients with NAI-ALF. Eighty-one patients were treated with NAC. The etiologies of ALF were predominantly DILI, unknown, HBV, and autoimmune hepatitis. The primary endpoint of overall survival at 3 weeks was not significantly improved with NAC treatment (70%, 95% CI: 60–81) compared to the control group (66%, 95% CI: 56–77, one-sided $P = 0.2$). The secondary endpoint of transplant-free survival was significantly higher in NAC group (40%, 95% CI: 28–51) compared to the control group (27%, 95% CI: 18–37, one-sided $P = 0.043$). This effect was emphasized in grade I-II HE with an odds ratio of 2.46 (95% CI: 1.14–5.30) compared to HE grade III-IV (OR: 0.33, 95% CI: 0.06–1.74). Further analysis performed on the same dataset found that transplantation or death is associated with higher ALT and advanced HE.[52] Higher IL-17 concentration was inversely associated with transplant-free survival in both NAC and placebo patients.[53]

The trial by Lee *et al.*[10] has been criticized in subsequent literature. The foremost issue is use of one-sided *P* values for overall survival and transplant-free survival instead of the standard two-sided test, that has become accepted as the conventional level of significance (i.e., $P = 0.05$ for a one-sided test becomes 0.10 when one uses the conventional two-sided test). When Siu *et al.*[11] re-analyzed data using two-sided *P* values, they could not replicate the original findings, including the subgroup analysis of transplant-free survival by coma grade. Further, there was no adjustment for multiple comparisons, leading to increased risk of false positive results. Another consideration is that nine participants were excluded despite the intention-to-treat analysis. However, Siu *et al.*[11] performed a "best-worst/worst-best case scenario" analysis and found no change in the effect, suggesting low risk of attrition bias. Lastly, Siu *et al.*[11] found reporting bias due to omission of one-year outcomes.

International RCTs studying the effect of NAC on NAI-ALF have also suggested a survival benefit but require a critical appraisal. Nabi *et al.*[54] conducted a randomized controlled trial in India on the efficacy of NAC infusion in NAI-ALF. The etiology was primarily unknown, DILI, and HEV. On univariate analysis, the NAC group had an improved survival (72.5% vs. 47.5% in the placebo group, $P = 0.025$), though when stratified by etiology, only the DILI group retained slightly superior outcomes with NAC ($P = 0.049$). It is unreported if adjustments were made for multiple comparisons for this marginal *P* value. On logistic regression analysis, predictors of mortality included NAC treatment (adjusted OR: 4.6, $P = 0.01$), grade I-II HE (adjusted OR: 5.254, $P = 0.007$), and presence of ascites (adjusted OR: 7.077, $P = 0.034$). Unfortunately, the lack of reporting in methodology limits validity of the results. There was unclear allocation concealment and blinding, which can lead to selection bias especially as there were significant differences in baseline clinicodemographic factors between treatment arms. There was also no reporting of loss-to-follow-up,

Table 3: NAC doses and adverse events in included studies

Reference	Etiology of ALF	NAC protocol	Adverse Event (rate %)	Patients treated with NAC
Mumtaz 2009[49]	HEV *n*=40 HBV *n*=25 HDV *n*=11 DILI *n*=11 HAV *n*=2 Fatty liver of pregnancy *n*=2 Unknown *n*=5	Oral NAC 140 mg/kg, followed by 70 mg/kg, total 17 doses, 4 h apart within 6 h of admission.	4% maculopapular rash 2% transient bronchospasm 8% vomiting	*n*=47
Lee 2009[10]	DILI *n*=45 AIH *n*=26 HBV *n*=36 Unknown *n*=41	IV NAC 150 mg/kg/h over 1 h, followed by 12.5 mg/kg/h for 4 h, then continuous infusion of 6.25 mg/kg for remaining 67 h.	14% nausea and vomiting 20% infection 2% rash 1% bronchospasm 9% arrhythmia 11% other	*n*=81
Darweesh 2017[51]	DILI *n*=59 HBV *n*=25 HAV *n*=22 CMV *n*=14 HEV *n*=11 Pregnancy *n*=10 HAV and HEV *n*=6 SLE *n*=5 EBV *n*=3	IV NAC 150 mg/kg over 30 min, then 70 mg/kg over 4 h, then 70 mg/kg over 16 h; then continuous infusion of 150 mg/kg over 24 h until two consecutive INR <1.3 with improving LFT, at which point oral NAC 600 mg/day was given until discharge.	96% prolonged cholestasis, with slow decrease in bilirubin for 2-3 months. 13% dyspepsia 10% allergic reaction	*n*=82
Nabi 2017[54]	DILI *n*=15 HEV *n*=14 HAV *n*=8 HBV *n*=8 Other *n*=5 Unknown *n*=30	IV NAC 150 mg/kg over 1 h, then 12.5 mg/kg/h for 4 h, continuous infusion of 6.25 mg/kg/h for 67 h.	No adverse events noted.	*n*=40
Nabi 2019[55]	HEV *n*=18 HAB *n*=9 HBV *n*=8 CMV *n*=1 EBV *n*=1	IV NAC 150 mg/kg over 1 h, then 12.5 mg/kg/h for 4 h, continuous infusion of 6.25 mg/kg/h for 67 h.	Not reported.	*n*=18
Dissanayake 2021[41]	Dengue fever *n*=30	IV NAC 100 mg/h for 3-5 days.	None.	N=30

intention-to-treat design, or stated predefined outcomes to assess for reporting bias.

Nabi *et al*.[55] further studied NAC treatment in viral-specific ALF, predominantly HEV, HBV, and HAV, in a similar population to their 2017 study. The primary analysis showed no significant survival benefit with NAC (61.1% vs. 31.6% in the control group, $P = 0.079$). On subgroup analysis of HEV patients, the NAC group had improved survival (90% vs. 37.5% in the control group, $P = 0.022$). This study faced similar limitations in reporting and methodology.

Adverse events associated with NAC

The above-mentioned clinical studies of NAC treatment report different adverse events, which may be due to differences in dose and formulation[56] [Table 3]. Lee *et al*.[10] reported higher incidence of nausea and vomiting in the NAC treated group (14% vs. 4% in the control group, $P = 0.03$), with other adverse events being similar between both treatment. Using the same intravenous NAC protocol, Nabi *et al*.[54] reported no adverse events. Mumtaz *et al*.[36] used oral NAC and found the most common adverse event was vomiting (8%), followed by rash (4%) and transient bronchospasm (2%). Darweesh *et al*.[51] used considerably higher doses of NAC compared to other studies and found 96.4% of patients with NAC treatment had prolonged cholestasis with elevated bilirubin for 2–3 months. The authors noted that prolonged cholestasis was not seen in the placebo group, concluding that this was not due to natural sequelae of ALF. Other adverse events included allergic reaction (10%) and dyspepsia (13%).

Compared to existing literature, the adverse events noted in the above-mentioned prospective studies are similar except for prolonged cholestasis, which has not been previously reported. The most commonly reported adverse events in NAC treatment are mild anaphylactoid reactions such as nausea, vomiting, and rash, though more severe reactions can include angioedema, bronchospasm, and hypotension.[57]

CONCLUSION

While there is a suggested benefit of NAC treatment in NAI-ALF given the demonstrated effects in early

physiology studies, this has not translated to conclusive evidence of benefit in clinical studies. The published clinical studies are limited by the heterogeneity of NAC dose and duration, patient selection factors, etiology of NAI-ALF, and use of historical controls. The best evidence to date is a multi-center, double-blind, randomized trial by Lee *et al*.;[10] however, the transplant-free survival benefit in early HE could not be re-demonstrated using more conventional analysis.[11]

The efficacy of NAC for NAI-ALF remains unclear and requires more rigorous investigation. While there is no clear and unequivocal benefit, there also appear to be few adverse effects at studied doses, as well as the drug being relatively inexpensive, readily available, and simple to administer. It is important to clarify the role of NAC in NAI-ALF, especially in the treatment of patients who do not qualify for liver transplant or in low-resource settings where transplantation is not accessible.

Ultimately, we conclude that there is insufficient evidence to suggest routine clinical use of NAC for NAI-ALF given the lack of demonstrated clinical benefit. Importantly, omission of NAC in NAI-ALF cannot be regarded as a breach of reasonable care, and clinicians should not be criticized for electing not to administer it. On the other hand, with few adverse drug effects and reasonable costs, clinicians may choose to administer NAC on the grounds that often the exact etiology of acute liver failure is not known and occult acetaminophen use may still have been a factor in the patient's clinical situation; that is to say, there is no harm in giving it and it is better to "cover all bases." Clinical use of NAC in NAI-ALF, however, should follow individualized discussion with patients and families for informed consent to use this medication off-label for this indication. Further study is needed, especially randomized clinical trials to provide an unequivocal answer regarding clinical benefit.

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Conflicts of interest

There are no conflicts of interest.

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