

Acetylcysteine (N-acetylcysteine, NAC) for the management of non-acetaminophen-induced acute liver failure

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Project | Remedi aims to uncover new therapeutic uses for hundreds of medicines on the Essential Medicines List, seek approval to add them to the EML, and amplify availability of new uses to benefit priority populations.

Contents

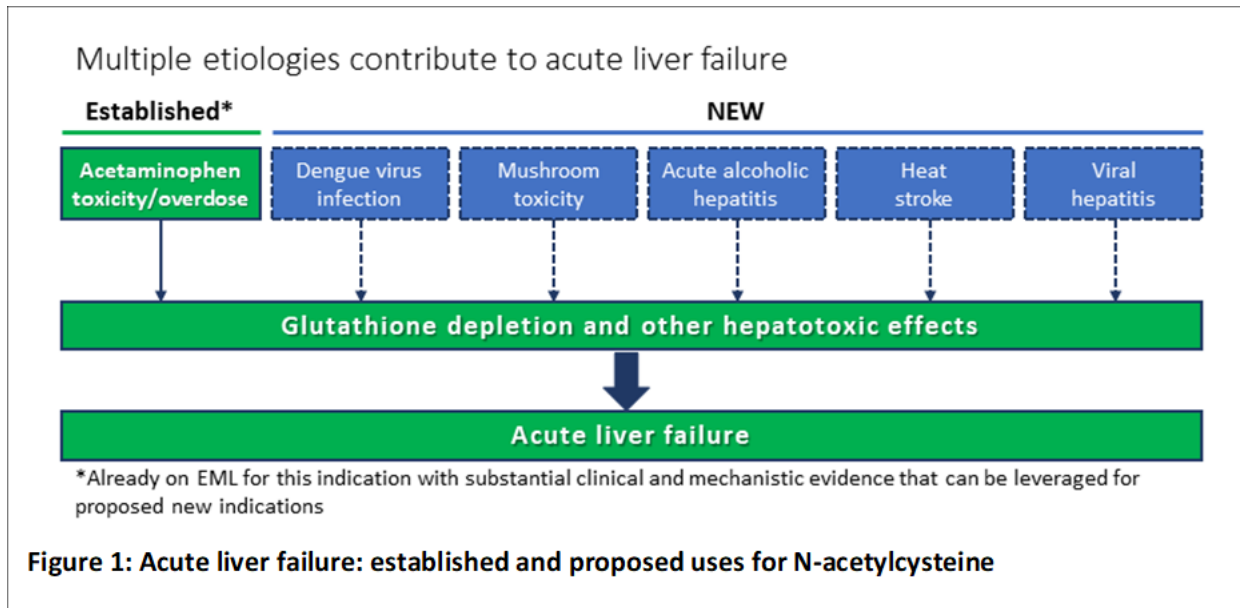
1. Summary statement of the proposal for inclusion, change or deletion	4
2. Relevant WHO technical department and focal point (if applicable).	
3. Name of organization(s) consulted and/or supporting the application.....	6
4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.	6
5. Dose forms(s) and strength(s) proposed for inclusion	6
6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.	6
7. Treatment details (requirements for diagnosis, treatment and monitoring).	7
8. Information supporting the public health relevance.	8
9. Review of benefits: summary of evidence of comparative effectiveness.....	9
Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data).....	9
Summary of available data (appraisal of quality, outcome measures, summary of results).....	9
Summary of available estimates of comparative effectiveness.....	12
10. Review of harms and toxicity: summary of evidence of safety.....	12
Estimate of total patient exposure to date:	12
Description of the adverse effects/reactions when used in non-acetaminophen induced acute liver failure:.....	12
Description of the adverse effects/reactions and estimates of their frequency (drawn from the broader NAC literature on human use).....	12
Summary of available data	13
Identification of variation in safety that may relate to health systems and patient factors	15
11. Summary of available data on comparative cost and cost-effectiveness of the medicine.....	16
12. Summary of regulatory status and market availability of the medicine.	16
13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia). Summary of available data on comparative cost and cost-effectiveness of the medicine.	17
Literature summaries: non-acetaminophen acute liver failure, organized by precipitating exposure/condition	18
LITERATURE SUMMARY: Evidence describing use of NAC in general non-acetaminophen-induced acute liver injury.....	18
LITERATURE SUMMARY: Evidence describing use of NAC in heatstroke-associated acute liver injury.....	24
LITERATURE SUMMARY: Evidence describing use of NAC in alcohol poisoning-associated acute liver injury	25
LITERATURE SUMMARY: Evidence describing use of NAC in mushroom toxin-induced acute liver injury..	25

LITERATURE SUMMARY: Evidence describing use of NAC in virus-associated acute liver injury (hepatitis A, hepatitis B, dengue fever)	26
14. Comprehensive reference list and in-text citations.	31
Appendix 1: Additional contributors	41
Appendix 2: Evidence describing hepatic effects of N- acetylcysteine in other conditions (excluding acetaminophen toxicity).....	42
Appendix 3: Summary of adverse events reported in systematic reviews, by indication.....	51

1. Summary statement of the proposal for inclusion, change or deletion

We propose a new listing to the EML to add an additional use of a medicine already on the EML, **N-acetylcysteine (NAC)**. The new indication is for the **management of non-acetaminophen-induced acute liver failure (ALF) caused by etiologies that deplete glutathione** (see **Figure 1**). This indication leverages a sound foundation of trial and observational evidence supporting the safety and utility of NAC in preventing further progression of liver failure in adults and children. This indication includes a range of etiologies for ALF with known connection to glutathione depletion which leads to hepatic injury; NAC replenishes intracellular glutathione and exerts antioxidant effects which help to ameliorate the adverse consequences of the hepatic insult and its sequelae. This request is being sought for the complementary EML, as patients with ALF are typically cared for in a hospital/specialized setting.

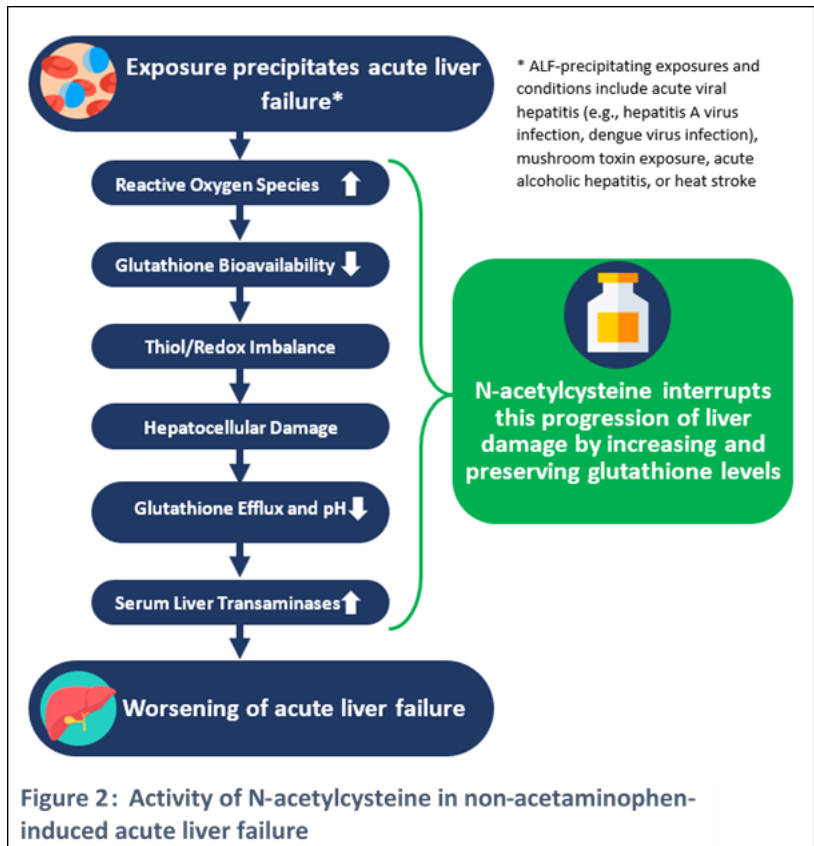
Generally, N-acetylcysteine (NAC) is known via preclinical and clinical studies for its hepatoprotective effects by increasing intracellular glutathione particularly in the liver and by its antioxidant properties which counteract oxidative stress and inflammation.(1) NAC has been in widespread use since the 1960s and has been proven to be safe and well tolerated; its use as an antidote for acetaminophen toxicity (a use in which oral and intravenous NAC have been shown to be equally effective in preventing and minimizing hepatotoxicity), and **is already represented on the EML for this use. Based on similar mechanisms, NAC shows promise in protecting the liver against the effects of and response to insults precipitating non-acetaminophen induced acute liver injury due to glutathione depletion, including virus-induced acute hepatic failure; mushroom toxin-induced liver failure; acute alcoholic hepatitis; and heat stroke-induced ALF (Figure 1).** In addition to the range of studies reporting the benefit and safety of NAC use in these indications (*see section 9 and 10, Literature Summary table*), a body of literature describing NAC use in heterogeneous populations of non-acetaminophen induced ALF(2-4) further supports this new indication for NAC. (*see Literature Summary section* for a synthesis of relevant systematic reviews, trials, and observational studies).



Briefly, various insults (e.g. hepatitis A virus, dengue virus, toxic mushroom consumption, excess alcohol intake, heat stroke) directly deplete **glutathione, which is a necessary enzyme for proper liver function**. Each of these etiologies for ALF has supporting data indicating that glutathione depletion plays an important role in development of ALF; the mechanisms of acute liver dysfunction and failure in these conditions are believed to result directly from hepatocyte apoptosis/necrosis, hypoxic damage due to impaired liver perfusion resulting from fluid leakage, as well as oxidative stress and immune mediated injury. (5-17) NAC, through enhancing glutathione S-transferase activity, affects several of these

mechanisms (Figure 2).(1,18–21) In addition, NAC has antioxidative, anti-inflammatory, and vasodilatory effects,(22) which can help counteract the adverse effects of impaired liver perfusion and reducing hepatocytes apoptosis due to oxidative stress and immune-mediated injury.

While ALF remains relatively rare, it affects children and adults across the world and confers significant morbidity and mortality. (23,24) Care for ALF associated with these etiologies is supportive in nature, with no targeted options for minimizing further injury to the liver. To address an unmet medical need with an existing, safe therapy, we propose a new use for NAC in the treatment of ALF caused by hepatitis A, dengue virus, heat stroke, acute alcohol poisoning, and mushroom toxicity. NAC should be administered to affected patients as soon as possible based on presence of hepatic injury (i.e. laboratory data indicating increase in liver function test results). The goal of this strategy, based on the evidence described below, is to prevent or limit severity of acute liver failure and related morbidity and mortality.



The literature describing clinical use of NAC in general non-acetaminophen-induced ALF patients, as well as those with ALF due to heat stroke, acute alcoholic hepatitis, mushroom poisoning, or acute viral hepatitis, supports the safety and efficacy of this therapeutic approach in complementing usual supportive care for patients affected by these types of ALF. The literature indicates that use of NAC represents at least a significant incremental gain over supportive care alone, with a reasonable expectation of direct effects on morbidity, including averting the need for transplantation in some patients. In addition, with its long-standing history of use in acetaminophen-induced acute liver injury, NAC has a strong foundation of data supporting its safety in children and adults.

There is precedent for this approach with the use of NAC from past EML committee decision related to use as an antidote to acetaminophen toxicity, as real-world data was deemed sufficiently compelling. The relevant excerpt from 2008 review states: "...subsequent human investigations have consisted mostly of observational studies due to ethical concerns of withholding a potential lifesaving treatment. Thus, there are no randomized controlled trials that evaluate NAC therapy for prevention of acetaminophen-induced hepatotoxicity. Likewise, no randomized efficacy trials have been conducted in children. Many of the trials evaluate efficacy based on the outcomes of historical control patients."(25)

2. Relevant WHO technical department and focal point (if applicable).

Department of Neglected Tropical Diseases

Other interested groups may include Alcohol, Drugs and Addictive Behaviors Unit, Global HIV Hepatitis and STIs Programme

3. Name of organization(s) consulted and/or supporting the application.

Dr. Robert Wallis, MD; Chief Scientific Officer, AURUM was consulted and reviewed this submission.

Dr. Gordon Bernard, MD; Executive Vice President for Research, Vanderbilt University Medical Center was consulted and reviewed this submission.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN: Acetylcysteine

A05: Bile and liver therapy

5. Dose forms(s) and strength(s) proposed for inclusion

This request is for the inclusion of NAC in intravenous or oral form for the EML. [Acetylcysteine is the nonproprietary name for the N-acetyl derivative of the naturally occurring amino acid, L-cysteine (N-acetyl-L cysteine)]. NAC is a generic medicine and is widely available internationally. Regarding formulation, the WHO 2008 review of use of NAC in pediatric acetaminophen toxicity notes that oral administration is preferred when there are not contraindications to its use (e.g. aspiration, persistent vomiting)(25); intravenous use is recommended in this guidance when fulminant hepatic failure is present, thus we suggest following this recommendation for the new indication of NAC use in various types of acute liver failure, with use of intravenous NAC. Oral NAC may be considered when the i.v. formulation is not available. In its use in the overdose setting to prevent hepatotoxicity, both oral and i.v. NAC regimens are commonly used and well-tolerated, with no significant differences in safety or efficacy.

Availability is supported given NAC is already on EML (in both injectable and oral forms) with strengths (Injection: 200 mg/mL in 10- mL ampoule; oral liquid: 10%; 20%) appropriate for the detailed treatment approach described below in Section 7. While the existing evidence base on use of NAC in various types of non-acetaminophen-induced liver failure represents some variation in dosage and administration schedules, these plans generally paralleled the NAC strategy used in acetaminophen overdose and are similar for patients with acute liver failure due to other causes.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

Individual medicine

7. Treatment details (requirements for diagnosis, treatment and monitoring).

NAC administration should be initiated intravenously in patients with significant acute liver injury as soon as ALF is detected, typically via presence of one of the precipitating conditions (e.g. acute viral hepatitis, heat stroke, dengue, acute alcoholic hepatitis, mushroom toxicity) combined with alterations in clinical status and liver function tests indicating acute liver failure as per local clinical standards.

The recommended IV protocol described in a previous review by WHO, focused on NAC use in paracetamol toxicity in pediatrics,(25) adapted to incorporate regimen provisions in the literature describing use of NAC in non-acetaminophen ALF, includes:

- Loading dose: administer 150 mg/kg IV over 1 hour
- Maintenance: followed by 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours, then 100 mg/kg/day until up to 7 days after initial start of NAC depending on clinical response.
- Modified IV dosing in those weighing less than 40 kg is recommended to avoid fluid overload.

Administration should continue for a minimum of three days but longer as needed based on assessment of the patient's clinical status, laboratory testing of liver function and related measures such as international normalized ratio (INR), and the time course of the underlying medical condition (e.g. mushroom toxicity follows a shorter time course than dengue fever, which has a longer disease course). To avoid fluid overload, the volume of diluent should be reduced whenever clinically needed. The literature does not indicate that the dose of NAC in infected patients with hepatic impairment should be reduced. Reduced clearance of NAC was observed in seven patients affected by chronic liver disease as compared with six healthy controls, suggesting that it is possible that cirrhotic patients may be at increased risk of hypersensitivity reactions.(26) The existing NAC literature indicates that hypersensitivity reactions may be managed by decreasing the infusion rate or discontinuing the infusion altogether.

If IV NAC is not available/feasible, oral NAC could be substituted using the protocol noted in the WHO NAC review,(25) 140 mg/kg followed in 4 hours by a maintenance dose of 70 mg/kg orally given every 4 hours for up to 5 days, tailored to the condition of the patient under treatment.

Use in Children: NAC has a well-established safety profile, including extensive safety data in children due to its use in acetaminophen toxicity. Use of NAC in ALF associated with the indications described in this application, which each may affect this age group, would be appropriate in children.

Use in Pregnancy: The US Food and Drug Administration lists NAC as a Pregnancy Category B agent, noting: "Limited case reports of pregnant women exposed to acetylcysteine during various trimesters did not report any adverse maternal, fetal or neonatal outcomes."(27) No significant adverse effects involving the mother or fetus were observed in a prospective comparative study (n=80) of oral NAC for treatment of recurrent unexplained pregnancy loss;(28) an RCT of oral NAC in women with severe early onset preeclampsia or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets);(29) an RCT of IV NAC in maternal chorioamnionitis;(30) and an RCT of oral NAC in pregnant women with low antioxidant status.(31) A randomized, double-blind, placebo-controlled trial of oral NAC for prevention of recurrent preterm birth found no major maternal or fetal adverse effects; approximately 11% of participants discontinued NAC due to nausea and vomiting.(32)

8. Information supporting the public health relevance.

While a relatively rare condition, acute liver failure is a serious clinical condition irrespective of country and region, with high morbidity, as well as high mortality in the absence of supportive clinical care and potentially liver transplantation. (23,24) ALF affects all age groups, and the causes of ALF are heterogeneous; as noted above, we focus this application on ALF subsets with known involvement of glutathione, given the targeting of this protein by NAC.

Acute viral hepatitis infections are responsible for most ALF cases globally, with variation in causative viral pathogen in various regions (e.g. hepatitis A, B, E; dengue virus). (33) Considering dengue virus as one key cause of acute liver injury and failure, the data suggests notable impact in some regions. Among an estimated 390 million people infected with dengue each year, the WHO further estimates that 500 000 people with severe dengue require hospitalization and there is a 2.5% case fatality annually.(34) In addition, there are growing reports of links between climate variations and the emergence of “climate-sensitive infectious diseases”, which would include all of the mosquito-borne diseases dengue, chikungunya, and Zika,(35) suggesting the global burden could be worsening. In the last 50 years, incidence has been reported to have increased 30-fold. Although only nine countries had experienced severe dengue epidemics prior to 1970, the disease is now **endemic in over 120 countries** resulting in ~3.9 billion people are at risk of infection.(36) Further, liver injury and failure may complicate the disease course in a significant portion of individuals affected by dengue infection; in an analysis of 347 patients hospitalized for dengue fever during one outbreak in Thailand, 63% (n=219) had hepatic failure.(37) The WHO notes:(34) “Dengue is increasing at a higher rate than any other communicable disease, with 400% increase over 13 years (2000-2013). Annual dengue incidence is estimated to be in the order of 100 million symptomatic cases a year, with another ~300 million asymptomatic infections. The greatest burden is seen in Asia (75%) followed by Latin America and Africa.”

Heat stroke is another important cause of ALF. Incidence is difficult to estimate globally due to lack of an accepted system for capture and reporting. In the US, for example, one study estimated over 4100 emergency department visits per year for heat stroke, an annual national incidence rate of 1.34 visits/100,000 people; this analysis noted a case fatality rate of 3.4%.(38) A 2015 report by the WHO notes that heat waves are an emerging public health problem as climate change worsens, (39) which further suggests that conditions such as heat stroke and its sequelae may become more common in the future. This report also points to existing supportive evidence regarding increased mortality and morbidity during past heat waves in Europe and other regions.(39)

Amatoxin toxicity due to consumption of poisonous mushrooms is a global problem, though difficult to estimate incidence to do high likelihood of underreporting; while more common in some regions such as Europe, the literature includes reports of mushroom poisoning in numerous regions around the world and those with poisoning who develop ALF have a poor prognosis in the absence of significant supportive care and potentially liver transplantation.(40,41)

ALF caused by excess alcohol intake is another serious condition, with estimated 30 day mortality of 30%.(42) Its exact incidence is unknown, but some have estimated that its incidence in alcoholics may be up to 20%.(43) Providing global context, a WHO report in 2018 estimated that the prevalence of heavy episodic drinking was around 18% in 2016 globally, and more common in some areas such as Eastern Europe and sub-Saharan Africa,(44) suggesting that some regions may be at risk of increased prevalence of this type of ALF.

Despite the prevalence of a range of conditions precipitating ALF in countries around the world and the potentially catastrophic nature of ALF for affected child and adults, **the EML does not contain any specific, targeted treatment for this condition, outside of use of NAC specifically for**

acetaminophen-induced toxicity. The literature indicates growing use of across a range of subtypes of non-acetaminophen-induced liver failure, with significant off label use and supportive prospective and retrospective data, described further below and suggesting that this intervention would provide a valuable addition to the supportive care provided to these patients. Adding this information to the EML would also provide critical guidance to health workers regarding standard dosing and administration of NAC as supplemental treatment.

9. Review of benefits: summary of evidence of comparative effectiveness.

Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

The studies from the literature for this analysis were identified by a trained information scientist searching the PubMed and Web of Science databases, as well as a broad Google search to identify unindexed and grey literature. The search terms used were: “acute liver failure”, “acute liver injury”, “acetylcysteine”, “N-acetylcysteine” and “acetylcysteine”. This search was not date limited; studies were assessed without restriction by a publication date threshold to ensure inclusiveness. The reference lists of reviewed articles were also assessed, to identify any studies not found by the initial search and to better clarify preclinical and mechanistic underpinnings of both the disease and the therapy. No studies investigating the use of NAC in treatment of ALF with the specified etiologies (selected due to glutathione involvement, including hepatitis A or B, dengue fever, heat stroke, alcohol poisoning, and mushroom toxicity) were excluded from this exploration; we further included any studies examining general non-acetaminophen-induced ALF to complement the evidence pool identified related to the specified ALF etiologies. Evidence was systemically extracted (see **Literature Summary**); when comprehensive systematic reviews and meta-analyses were identified, additional primary evidence was extracted from other papers to represent 1) data not covered in those reviews/meta-analysis and 2) nuances of data to complement the data summarized in the systematic reviews. This review also identified studies evaluating hepatic effects of NAC beyond the selected indications described in the current application to aid in contextualization; this broader evidence is provided for additional context in **Appendix 2**.

Summary of available data (appraisal of quality, outcome measures, summary of results)

Full details of the literature describing each of the subsets of literature described in this section are included in the evidence tables represented in the **Literature Summary** section later in this application. Here, we focus on key characteristics of the primary and secondary literature supporting each of the ALF subsets proposed in the current application, including the literature describing use of NAC in general non-acetaminophen-induced ALF as these studies typically represent a number of the narrower populations we propose.

General non-acetaminophen-induced acute liver failure: Three systematic reviews, published in 2004,(2) 2013,(3) and 2015(4) provide useful insights into the evolution of evidence regarding the use of NAC in non-acetaminophen-induced ALF. While the two older articles note potential utility of NAC in this subset of ALF based on data pools comprised primarily of retrospective case reports and series,(2,3) the 2015 review included four RCTs and concluded significant benefit with use of NAC as compared with control in terms of transplant-free survival and post-transplantation survival. All three systematic reviews noted that adverse effects in this population were consistent with those observed in its use in acetaminophen-induced ALF and that no hepatotoxic effects were seen with the dose used for acetaminophen toxicity. One additional RCT in non-acetaminophen-induced ALF (n=80) published in 2017, after the 2015 review, also found positive effects of NAC administration; more patients (72.5%) survived in the NAC group than in the control group (47.5%) (p=0.025) and among those who survived,

hospital length of stay was approximately 2.5 days shorter in the NAC-treated group (p=0.002).(45) Further, a large prospective multisite cohort in the US found increasing use of NAC over time suggesting significant acceptance of this agent as a clinically attractive off-label use across centers, with almost 70% of patients with non-acetaminophen-induced ALF receiving this intervention in an 8-year time period through 2013, further paralleling an increase in survival rates during this time.(46)

Heat stroke associated acute liver failure: In addition to representation of this ALF population in the general ALF studies described above, we identified 3 case reports suggesting improvement in liver function and other clinical outcomes associated with use of IV NAC in patients with heat-related ALF.(47–49) No adverse effects discordant with use of NAC in other indications were identified.

Severe acute alcoholic hepatitis: Severe acute alcoholic hepatitis is somewhat unique among the causes of ALF, in that it represents an acute event likely embedded within chronic disease; NAC has been used with success during this acute event, thus we include it here. In addition to representation of this subgroup of patients in the general ALF studies summarized above, a systematic review in 2015 analyzed the literature regarding use of various therapies in treatment of acute alcoholic hepatitis requiring hospitalization.(50) This review identified 22 RCTs comprising a total of 2621 patients and including 5 different interventions. A network meta-analysis of this moderate quality evidence pool found that the use of corticosteroids alone (relative risk [RR], 0.54; 95% credible interval [CrI], 0.39-0.73) or in combination with NAC (RR, 0.15; 95% CI, 0.05-0.39), to reduce short-term mortality. No trials published since the date of this literature review have been identified in the literature.

Mushroom-induced acute liver failure: In addition to representation in the general ALF studies described above, acute liver injury and failure are a common and severe consequence of mushroom poisoning. A 2020 systematic review examine the literature on use of NAC in this population, identifying 13 studies including a total of 506 patients.(51) Mortality in patients treated with NAC was 8-11%, liver transplantation rate was 4.3%. Various laboratory values related to liver function and coagulopathy improved over 4-7 days after ingestion. Anaphylactoid reactions occurred in 5%. The review concludes that NAC appears to be safe and beneficial in this type of poisoning.

Acute viral hepatitis: In addition to representation in the ALF studies described above, two small retrospective case series of NAC use in children with ALF in the context of acute viral hepatitis have been published, including 40(52) and 12(53) patients respectively. Hepatitis A appeared to be the most common etiology. Both reports indicate improvement of liver enzymes and coagulation parameters and satisfactory medication tolerance with use of NAC in the population.

Dengue fever: Given the size of the literature describing use in dengue virus-associated liver injury and failure, we elected to describe these data separately from the studies of acute viral hepatitis, in which hepatitis A was most common as the precipitating viral infection. The data collected from various studies of dengue-infected patients do not include a large, randomized, double-blind, controlled trial. Given the sporadic and epidemic nature of the disease, such a study would be time-consuming and costly. We have assembled the existing evidence base on this use, comprising retrospective cohort studies, case series, and case reports and totaling 43 patients with dengue infection receiving NAC in addition to usual care. Dengue-related illnesses ranged in severity (but none appeared to be affected by mild disease). Outcome measures included liver function testing, mortality, measures of morbidity such as need for transplant, length of stay, and other laboratory measures relevant for dengue fever and its sequelae. Observed adverse effects were consistent with the broader evidence base on NAC use in humans, and all patients recovered except 3 patients, with disease level III–IV who already had dengue-associated ALF prior to treatment, who died. Notably, in one case with dengue associated severe hepatitis in a 53 year old, prior to NAC treatment, liver enzymes reached peak values of AST 16261 U/L and ALT 4545 U/L on 4th day of admission (7th day of illness).(54) Authors note marked improvement in liver enzyme values, and AST and ALT levels dropped by more than half by 48 hours of treatment. In a retrospective case series, 13 people with moderate to severe hepatitis received NAC and had hepatic

recovery faster than less sick patients who did not receive NAC.(55) Data from case series and case reports, gradual normalization of liver function tests was noted in 26 other patients (15 adults; 11 infants and children) receiving NAC in moderate to severe dengue illness. (56–67)

PheWAS data: We also reviewed a set of data in which a phenome-wide association study (PheWAS) analysis was undertaken. PheWAS can identify diseases or conditions (phenotypes) that are associated with a specific gene/genetic variant.(68) PheWAS leverages existing data from the Exomechip genotyping platform (~250,000 coding variants across the protein coding region of the genome) and electronic health records for approximately 35,000 patients. Because the logic of PheWAS can be extended to predict phenotypic manifestations of pharmacological targeting (such as with NAC) of a given gene product in humans, we use these methods for **drug repurposing**.(69) As a glutathione synthetase (gene: GSS) ‘stimulator’, NAC is hepatoprotective. This is established in its use in acetaminophen overdose. The phenotypes associated with a missense single nucleotide polymorphism (SNP) (R418Q) in the GSS gene are risk causing, so in this regard we can say the SNP is behaving like a glutathione synthetase inhibitor (the opposite of the drug). Thus, the variety of liver phenotypes in the below analysis (Table 1) strengthen, with human data, that decreased glutathione synthetase is associated with a broad range of liver injury, as is true in the ALF etiologies represented in the current application for a new NAC indication on the EML.

Table 1: PheWAS results, GSS variation and liver disease

Note: The SNP in this table appears to be functioning as a glutathione synthetase inhibitor (GSS ↓); thus, a glutathione synthetase stimulator such as NAC (GSS ↑) is indicated for management of relevant phenotypes.

rsID (Mutation)	Gene	Phecode	Phenotype	Cases (n)	Controls (n)	Odds ratio (OR)	P	AFF_11	AFF_12
rs150141794 (Missense_R418Q)	GSS	530.2	Esophageal bleeding (varices/hemorrhage)	394	18594	5.9300	0.002337	0	5
rs150141794 (Missense_R418Q)	GSS	261.2	Vitamin B-complex deficiencies	557	21366	4.5910	0.00661	0	5
rs150141794 (Missense_R418Q)	GSS	571.8	Liver abscess and sequelae of chronic liver disease	598	22795	4.2490	0.008865	0	5
rs150141794 (Missense_R418Q)	GSS	573.7	Abnormal results of function study of liver	890	22795	3.4230	0.01187	0	6
rs150141794 (Missense_R418Q)	GSS	571	Chronic liver disease and cirrhosis	1312	22795	2.7070	0.02196	0	7
rs150141794 (Missense_R418Q)	GSS	571.51	Cirrhosis of liver without mention of alcohol	769	22795	3.3010	0.02317	0	5
rs150141794 (Missense_R418Q)	GSS	571.5	Other chronic nonalcoholic liver disease	1092	22795	2.7880	0.0282	0	6
rs150141794 (Missense_R418Q)	GSS	573.2	Liver replaced by transplant	368	22795	4.1420	0.04077	0	3
rs150141794 (Missense_R418Q)	GSS	571.81	Portal hypertension	399	22795	3.8190	0.04958	0	3

Key: GSS glutathione synthetase gene; AFF_11 cases carrying two copies of the variant minor allele; AFF_12 cases carrying one copy of the variant minor allele

Summary of available estimates of comparative effectiveness

With typical comparators in this literature on use of NAC in various types of non-acetaminophen-induced ALF including either supportive care alone or placebo, the evidence indicates that use of NAC represents at least an incremental benefit over usual care alone. The literature does not include head-to-head comparisons with other “active” interventions, precluding a more thorough and quantified estimate of the comparative effectiveness of NAC. The safety profile reported in this use is consistent with published adverse effects of NAC use for other indications, suggesting that the risk benefit for this approach is not weakened by a disparate safety signal.

10. Review of harms and toxicity: summary of evidence of safety.

Estimate of total patient exposure to date:

The WHO EML currently lists N-acetylcysteine as an antidote for the treatment of acetaminophen overdose.(70) Based on exposure reported in the literature, and given that both oral and IV NAC have been approved as a first-line therapy for acetaminophen overdose **for 40+ years**, it is estimated that hundreds of thousands of patients have been exposed to date (likely many more worldwide).

Description of the adverse effects/reactions when used in non-acetaminophen induced acute liver failure:

The safety data collected for studies of NAC in non-acetaminophen induced liver failure is captured from clinical trials, retrospective cohorts, case series, and case reports, comprising data from approximately 2500 patients.(3,4,45–49,51–54,57–59,61,63–65,67,71–81) The adverse effects observed in this literature are consistent with the broader evidence base on NAC use in humans showing that it is safe and well tolerated. Investigators report an adverse effect profile observed with use of NAC in non-acetaminophen induced ALF (general, heat stroke, acute alcoholic hepatitis, mushroom poisoning, acute viral hepatitis, dengue fever) concordant with the established safety profile of this agent in its use for acetaminophen induced ALF. Review of adverse effects observed in studies exploring therapeutic use of NAC in other liver-related conditions and indications (see **Appendix 3**) also indicates risks similar to those observed during NAC use for acetaminophen overdose.

Description of the adverse effects/reactions and estimates of their frequency (drawn from the broader NAC literature on human use)

- **Oral** administration of NAC is documented to be safe and well-tolerated. The most common side effects include nausea and vomiting, which is reported to occur in up to 23% of patients(82) (this may be attributed to its distasteful odor). Oral NAC is rarely associated with more severe side effects like angioedema.(83,84)
- **IV** administration of NAC is also usually well-tolerated but is associated with a higher risk of adverse effects, the most common include:
 - o Nausea, vomiting – occurs at a frequency of up to 9%(82)
 - o Anaphylactoid reactions (rash, pruritis, angioedema, bronchospasm) – occurs at a frequency of 8.2% (out of 6455 treatment courses). 75% of anaphylactoid reactions were cutaneous(85)
 - **Risk factors for anaphylactoid reactions:**
 - Females(86) and patients with asthma(87) appear to be at higher risk of developing the anaphylactoid response and both are associated with a more severe reaction(85)

- Anaphylactoid reactions occur more commonly with lower acetaminophen levels rather than high levels (this may be because acetaminophen decreases the histamine released from mast cells and mononuclear cells, proportionate to the dose ingested). (88)
 - It is noted that hypersensitivity reactions may be managed by decreasing the infusion rate or discontinuing the infusion.(83,89)
- Serious adverse reactions and fatalities are rare but have occurred with IV treatment (these patients also had a history of asthma)(90)
- A tabular summary of the results of systematic reviews of NAC safety when used in non-dengue indications is included in **Appendix 3**.
- While thorough analyses of pharmacovigilance databases (e.g. US FDA FAERS, WHO Vigibase) are not currently available in the published literature for NAC, the package inserts for NAC benefit from the long-standing use of this agent for management of acetaminophen overdose. **Post marketing events** summarized in these materials(27,91) include:
 - Adverse effects identified through post-marketing experience for NAC injection: rash, urticaria, and pruritus. The frequency of adverse reactions have been reported to be between 0.2% and 21%, and they most commonly occur during the initial loading dose of acetylcysteine.
 - Adverse effects identified through post-marketing experience for oral NAC: nausea and vomiting, other gastrointestinal symptoms, and rash with or without fever, and upper GI hemorrhage. (Frequency not reported.)

Summary of available data

- NAC therapies, given via various routes of administration (oral, IV, or inhaled), have been marketed in the US (and other countries) for over 40 years. Systematic reviews of NAC treatment for approved and non-approved indications are abundant and suggest that it is a safe and well-tolerated drug in both pediatric(75,92) and adult populations(83,85,93–96), although particular attention should be paid to dosing per body weight in pediatric populations to avoid toxicity related to dosing errors.(97)
- Side effects associated with NAC treatment are typically mild and while nausea and vomiting is the most common side effect with both IV and oral routes, the rate of nausea and vomiting is higher with oral NAC. Anaphylactoid reactions are more common with IV NAC and typically subside upon ceasing treatment. Symptoms characteristic of anaphylactoid reactions include flushing, pruritus, and rash and can also include angioedema, bronchospasm, and hypotension. Severe adverse reactions and fatalities are rare.(82)
- NAC drugs are available internationally.(89,98) For example regarding availability of various formulations, there are 7 drugs currently on the market in the US given via IV route of administration, 4 given orally (effervescent tablet or oral solution), and 3 given via inhaled solution.(99)
- Safety information from package inserts for example NAC therapies is presented below (Table 2; adverse events for various routes of NAC administration including oral, IV, and inhaled routes).
- Several randomized control trials of NAC for acetaminophen overdose have also been reported. One relatively small randomized control trial (n = 50) randomized patients with hepatic failure after acetaminophen overdose to either IV NAC in addition to standard liver care or standard liver care alone.(100) The NAC regimen in this study included: 150 mg/kg body weight in 200 ml 5% dextrose over 15 minutes, followed by 50 mg/kg in 500 ml 5% dextrose over four hours, then 100 mg/kg in 1 L over 16 hour. The final infusion rate was continued until recovery from

encephalopathy or death. The rate of survival was higher in patients receiving NAC. No adverse side effects were reported in this study.

- Another larger trial(101) that randomized 223 patients to different 150 mg/kg N-acetylcysteine loading infusion rates (15 minutes or 60 minutes) reported adverse event rates of 75% and 61% for the 15 minute and 60-minute arms, respectively. Anaphylactoid reactions were the most reported adverse reactions in both arms, occurring in 18% in the 15-minute arm and 15% in the 60-minute arm. Two patients (one in each arm) experienced a severe anaphylactoid reaction and were withdrawn from the study. Nausea and vomiting, classified within the broader GI disorders category in study analyses, were experienced by 13% of patients. The difference between the drug-related adverse events was not statistically significant and no deaths were reported
- The remaining body of clinical trial literature is comprised of prospective, non-randomized, observational trials.(83,85,93,94) Nevertheless, the data from these studies support the RCTs above showing that both oral and IV NAC are safe and well tolerated. Case reports have also described other rarer features of anaphylactoid reactions like ECG abnormalities(102), status epilepticus(103), and a serum sickness-like illness(104), however these are not commonly reported in larger trials.

Table 2: Adverse event summary for various NAC formulations

Drug (route)	Population	Indication	Adverse event (and frequency, if reported)	Reference
CETYLEV (oral effervescent tablet)	Adults and children, though pediatric approval is not based on adequate or well-controlled studies	Acetaminophen overdose	<ul style="list-style-type: none"> - Allergic reaction - Nausea and vomiting (up to 30% of patients) - Rash (with or without fever) - GI problems - May aggravate vomiting as a symptom of acetaminophen overdose - May aggravate vomiting and increase risk of upper GI hemorrhage in at risk patients (those with esophageal varices, peptic ulcers) - Hypersensitivity reactions, including generalized urticaria 	U.S package insert(91)
ACETADOTE (IV)	Adults	Acetaminophen overdose	<ul style="list-style-type: none"> - Pruritis (4.3%) - Urticaria/ facial flushing (6.1%) - Respiratory symptoms (1.9%) - Edema (1.6%) 	U.S package insert(27)
	Children	Acetaminophen overdose	<ul style="list-style-type: none"> - Urticaria/ facial flushing (7.6%) - Pruritis (4.1%) - Respiratory symptoms (2.2%) - Edema (1.2%) 	
	Geriatric	Acetaminophen overdose	<ul style="list-style-type: none"> - Clinical studies do not provide sufficient number of geriatric subjects to determine whether the elderly respond differently - There are not adequate and well-controlled studies in pregnant women, but limited case reports do not include any adverse maternal, fetal, or neonatal outcomes 	
Acetylcysteine 200 mg/mL injection (IV)	Adults and children	Acetaminophen overdose	<ul style="list-style-type: none"> - The most common AEs are nausea, vomiting, flushing, and skin rash - Less commonly, more serious anaphylactoid reactions have been reported (angioedema, bronchospasm, hypotension, tachycardia, or hypertension) - AEs usually occur between 15 and 60 min after start of infusion (many 	Europe/UK package insert(105)

			<p>symptoms are relieved by ceasing infusion)</p> <ul style="list-style-type: none"> - Other reported AEs include: infection site reaction, pruritus, cough, chest tightness or pain, puffy eyes, sweating, malaise, raised temperature, vasodilation, blurred vision, bradycardia, facial or eye pain, syncope, acidosis, thrombocytopenia, respiratory or cardiac arrest, stridor, anxiety, extravasation, arthropathy, arthralgia, deterioration of liver function, generalized seizure, cyanosis, lowered blood urea - Fatalities are very rare - Hypokalemia and ECG changes have been noted in patients with acetaminophen overdose, monitoring of plasma potassium concentration is recommended 	
Acetylcysteine solution, USP (inhaled)	Adults and children	Chronic or acute bronchopulmonary disease, pulmonary complications of cystic fibrosis, and other conditions associated with abnormal, viscid, or inspissated mucous secretions	<ul style="list-style-type: none"> - Stomatitis, nausea, vomiting, fever, rhinorrhea, drowsiness, clamminess, chest tightness and bronchoconstriction. - Clinically overt bronchospasm occurs infrequently and unpredictably even in patients with asthmatic bronchitis or bronchitis complicating bronchial asthma 	Package insert(106)
		Acetaminophen overdose	<ul style="list-style-type: none"> - Oral administration of the large doses needed to treat acetaminophen overdose may result in nausea, vomiting, and other GI disorders - Rash, with or without fever, has been reported but rarely 	
Parvolex (200 mg/ml concentrate solution for infusion)	Adults and children	Acetaminophen overdose	<ul style="list-style-type: none"> - Swelling of the face, lips or tongue - Wheezing, difficulty breathing - Irritation at the injection site - Skin rash, itching - Flushing - Low blood pressure resulting in dizziness - Rapid heartbeat or increased blood pressure (rarely) - Other rare side effects include coughing, noisy breathing, respiratory arrest, chest tightness or pain, puffy eyes, blurred vision, sweating, raised temperature, liver problems, slow heartbeat, fainting or collapsing, reduction in blood platelets 	Package insert(107)

Identification of variation in safety that may relate to health systems and patient factors

- Studies using IV NAC for acetaminophen overdose have shown that females(86) and those with a history of asthma or atrophy(87) are particularly susceptible to anaphylactoid reactions.
- The package insert for CETYLEV (oral, effervescent NAC tablets) states that it may aggravate vomiting as a symptom of acetaminophen overdose and may aggravate vomiting and increase risk of upper GI hemorrhage in at risk patients (those with esophageal varices, peptic ulcers).(91)

- Reduced clearance of NAC in seven patients affected by chronic liver disease as compared with six healthy controls, suggesting that it is possible that cirrhotic patients may be at increased risk of hypersensitivity reactions.(26)
- As NAC is a nitrogenous substance, a theoretical risk of hepatic encephalopathy (HE) is noted in some NAC package inserts, which further note that there is no clinical data suggesting that acetylcysteine influences on hepatic failure.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

NAC is already on the EML, with a widespread availability in most countries of the world at very low cost. The current application is not a request to add a medication for which pricing would be needed, as there would be no change to the existing pricing data expected from adding this new use of NAC. Considering one of the more extreme outcomes of ALF, liver transplantation has varied costs and availability in different settings; in the United States, for example, a recent report noted that the average liver transplant was billed at over \$800,000 per patient(108); while it is likely that the US is on the upper end of the global spectrum of costs for this procedure,(109) the resources required for transplant and follow-up are likely intensive in most settings, compounded further by the limited availability of organs for transplant. The estimated cost for NAC is US\$70. Given the extremely low NAC price per dose and the potential for averting significant downstream outcomes such as need for liver transplantation, its use would have substantial cost effectiveness.

12. Summary of regulatory status and market availability of the medicine.

NAC is approved by many health authorities for prevention of liver injury in acetaminophen overdose or as a mucolytic. To our knowledge, no health authority currently has NAC formally listed for a liver indication outside of acetaminophen overdose despite it being used in this setting. The lack of financial incentives for the pharma manufacturing industry to pursue new regulatory approvals for a medication that is no longer proprietary likely prevents this from happening. Examples of NAC approval for use in various countries are as follows:

Regulatory Agency	Indication
US Food and Drug Administration (FDA)	<ul style="list-style-type: none"> - To prevent or lessen liver injury after acetaminophen overdose - Mucolytic in patients with cystic fibrosis (or other conditions associated with abnormal or viscid mucous secretions)
European Medicines Agency (EMA)	<ul style="list-style-type: none"> - To prevent or lessen liver injury after acetaminophen overdose - Mucolytic in patients with cystic fibrosis (or other conditions associated with abnormal or viscid mucous secretions)
Australian Government, Department of Health, Therapeutic Goods Administration	<ul style="list-style-type: none"> - To prevent or lessen liver injury after acetaminophen overdose - Mucolytic in patients with cystic fibrosis (or other conditions associated with abnormal or viscid mucous secretions)

Japanese Pharmaceuticals and Medical Devices Agency	<ul style="list-style-type: none"> - To prevent or lessen liver injury after acetaminophen overdose - Mucolytic in patients with cystic fibrosis (or other conditions associated with abnormal or viscid mucous secretions)
Health Canada	<ul style="list-style-type: none"> - To prevent or lessen liver injury after acetaminophen overdose - Mucolytic in patients with cystic fibrosis (or other conditions associated with abnormal or viscid mucous secretions)

Further, there is widespread market availability of NAC and multiple generic manufacturers including Fresenius Kabi, Auro Medics Pharma, Cadila Healthcare, Zydus Pharmaceuticals, Roxane Laboratories Inc., Sagent Pharmaceuticals, and Pfizer, among many others in various countries. Given that NAC is in widespread use globally as an acetaminophen overdose antidote and as a mucolytic, it is anticipated that the currently proposed expanded use for this agent would leverage the existing supply chains established in various regions.

13. Availability of pharmacopeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopoeia). Summary of available data on comparative cost and cost-effectiveness of the medicine.

Acetylcysteine is included in several pharmacopeial standards, including the British Pharmacopoeia; the United States Pharmacopoeia; and the European Pharmacopoeia.

Literature summaries: non-acetaminophen acute liver failure, organized by precipitating exposure/condition

LITERATURE SUMMARY: Evidence describing use of NAC in general non-acetaminophen-induced acute liver injury

First author, year country	Design	Condition	Sample size	NAC dose, frequency, duration, route of administration; <i>comparator</i>	Findings	Outcome
Hu, 2015(4)	Meta-analysis	Non-acetaminophen induced acute liver failure	4 clinical trials (total n 331 NAC, 285 control)	NAC as administered in original clinical trials, compared to control arm	<p>No statistical difference was identified between NAC group and control group for overall survival [236/331 (71%) vs 191/285 (67%); 95% CI 1.16 (0.81-1.67); P=0.42].</p> <p>There were significant differences between NAC group and control group regarding the survival with native liver [112/273 (41%) vs 68/226 (30%); 95% CI 1.61 (1.11-2.34); P=0.01] and post-transplantation survival [78/91 (85.7%) vs 50/70 (71.4%); 95% CI 2.44 (1.11-5.37); P=0.03].</p> <p>Side effects included nausea, vomiting, and diarrhea or constipation; rarer effects included rashes, fever, headache, drowsiness, low blood pressure, and elevated serum transaminase levels in a patient with cystic fibrosis.</p> <p>No hepatotoxic effects observed at the dose used for acetaminophen toxicity.</p>	Positive effect
Sales, 2013(3)	Systematic review	Non-acetaminophen induced acute liver failure	11 articles included (8 case reports, 2 retrospective trials, 1 RCT)	NAC as administered in original report	<p>The 2 retrospective studies suggested survival benefit in adults and children; RCT suggested benefit in terms of transplant-free survival.</p> <p>Oral and IV NAC well tolerated.</p> <p>Authors concluded marginal benefit of NAC</p>	Suggests positive effect
Sklar 2004(2)	Systematic review	Non-acetaminophen	7 studies	NAC as administered in original report	Investigators commented: "All of the studies found were small and do not provide conclusive evidence that	Suggests positive effect related to

		induced acute liver failure			acetylcysteine benefits this subgroup of patients. Microvascular regional benefits were seen, but clinical outcomes have not been studied."	microvascular regional benefit
Nabi, 2017(45)	Randomized study	Non-acetaminophen-induced liver failure (etiology included undetermined, hepatitis E, other drugs and toxins, Wilson disease, autoimmune disease, CMV, HSV)	80	IV NAC initial loading dose of 150 mg/kg over 1 hour, followed by 12.5 mg/kg/h for 4 hours and continuous infusion of 6.25 mg/kg/h for remaining 67 hours. Control patients received 5% dextrose infusion for 72 hours.	Incidence of renal failure was not significantly different between the two groups. Mannitol for increased ICP was used more often in the control group as compared with the NAC group (92.5 vs 75%, p=0.037). Among the patients who survived, mean hospital length of stay was shorter in the NAC group (8.241 ± 2.115 vs 10.737 ± 3.106, p=0.002). A total of 32 of 80 (40%) patients died with ALF complications; 11 (27.5%) patients belonged to the NAC group and 21 (52.5%) patients to the control group (chi-square = 5.208; P = 0.023) and the mean time to death from diagnosis was 9.3 days. More patients (72.5%) survived in the NAC group than in the control group (47.5%) (p=0.025) Stratification by etiology suggested that patients with drug-induced ALF showed improved outcomes.. No adverse effects attributable to NAC were observed.	Positive effect
Lee, 2009(71), Stravitz, 2013(73) and Singh, 2013(72) USA	RCT	Non-acetaminophen-induced liver failure Majority fell into 4 etiologies: drug-induced liver injury (n=45), autoimmune hepatitis (n=26), hepatitis B (n=37) and indeterminate (n=41)	173	NAC infusion in 5% dextrose: an initial loading dose of 150 mg/kg/h of NAC over 1 hour, followed by 12.5 mg/kg/h for 4 hours, then continuous infusions of 6.25 mg/kg NAC for the remaining 67 hours (3 days total) (81 assigned, 48 completed 72h trial, 33 received less than full treatment because of death, withdrawal of support, transplantation, or side effects of drugs (4 thought to be due to NAC specifically))	Transplant-free survival was significantly better for NAC patients (40%) than for those given placebo (27%; 1-sided P = .043). The transplantation rate was lower in the NAC group but was not significantly different between groups (32% vs 45%; P = .093). Adverse effects: Nausea and vomiting occurred significantly more frequently in the NAC group (14% vs 4%; P=0.031).	Positive effect

				Subjects in the placebo group received infusion of 5% dextrose only (92 assigned, 58 completed 72h trial, 34 received less than full treatment)	<p>Treatment group and day of study in models including bilirubin or ALT were predictors of transplantation or death (maximum $p < 0.03$). Those patients with early coma grade who were treated with NAC showed significant improvement in bilirubin and ALT levels when compared to the other three groups (maximum $p < 0.02$ for NAC 1-2 vs. the 3 other treatments) when predicting death or transplantation. Treatment group, day of study, and bilirubin were predictors of transplantation (maximum $p < 0.03$) in ALF patients.</p> <p>Stepwise multivariate logistic regression analysis identified only NAC administration and lower IL-17 concentrations as independent predictors of transplant-free survival. In patients with detectable IL-17 concentrations on admission, 78% of those who received NAC vs. 44% of those who received placebo had undetectable levels by day 3-5 ($P = 0.042$), and the mean decrease in IL-17 concentrations between admission and late samples was significantly greater in patients who received NAC vs. placebo ($P = 0.045$).</p>	
Squires, 2013(110) USA	Double-blind, placebo-controlled RCT	Pediatric acute liver failure not believed to be caused by acetaminophen (discharge diagnoses included autoimmune, infection, metabolic disorders, and other conditions; 1 patient had acetaminophen overdose and approximately	184	<p>150 mg/kg/d NAC infusion in 5% dextrose infused over 24 hours for up to 7 consecutive days (92 subjects)</p> <p>92 received placebo (dextrose and water alone)</p>	<p>The 1-year survival did not differ significantly ($p=0.19$) between the NAC (73%) and placebo (82%) treatment groups.</p> <p>*The 1-year transplant-free survival was significantly lower ($p=0.03$) in those who received NAC (35%) than those who received placebo (53%).</p> <p>There were no significant differences between treatment arms for hospital or ICU length of stay, organ systems failing, or highest recorded grade of HE.</p> <p>Metabolic disease was more common in the NAC arm (13 NAC vs 5 placebo) with</p>	Reduced efficacy?

		60% had unknown cause)			Wilson disease (7 NAC vs 3 placebo) being more common in the NAC arm than the placebo arm.	
Darweesh 2017(74) Egypt	Prospective and retrospective observational study	Non-acetaminophen-induced liver acute liver failure	155	<p>IV NAC 150 mg/kg in 100 ml dextrose 5% over 30 min, then 70 mg/kg in 500 ml dextrose 5% over 4 hr., then 70 mg/kg in 500 ml dextrose 5% over 16 hr., then continuous infusion over 24 hr. of 150 mg/kg in 500 ml dextrose 5% until up to two consecutive normalized INRs were obtained.</p> <p>Control group included those who did not receive NAC</p>	<p>The incidence of transplant-free survival was 96.4% (n=82) in the NAC-treated group (p<0.01 compared with control group); among the 3 remaining patients, 2 received a liver transplant and 1 died. These 3 patients did not receive the full dose of NAC, two due to a severe allergic reaction to NAC (both were transplanted)</p> <p>In the control group, 17 (23.3%) recovered; among the remaining 53 patients, 37 (53.3%) received a liver transplant and 16 (23.3%) died.</p> <p>NAC treated patients had significantly shorter hospital stays (p<0.001), less encephalopathy (p=0.02), and less bleeding (p<0.01) as compared with control patients.</p> <p>Control patients had higher incidence of ICU admission (p=0.01) and increased incidence of abnormal creatine and electrolytes (p=0.002 and p<0.01, respectively).</p> <p>Bilirubin was significantly increased among controls (p=0.02); AST and INR were significantly increased among NAC-treated patients (p<0.001 for both). ALT was not significantly different between the groups.</p>	Positive effect

					Adverse events attributed to NAC included prolonged cholestasis in 82; bilirubin showed a steady but slow decrease over 2-3 months; patients not treated with NAC did not develop this sign. Fever and allergic reaction were observed in 3 patients and dyspepsia in 11 patients. No bronchospasm was observed.	
Reuben, 2016(46) US	Prospective observational	Acute liver failure of all causes except previous liver transplant; ~46% acetaminophen toxicity, the rest due to heterogeneous causes	2070	NAC protocol varied from site to site; not detailed	Two time periods, 1998-2005, 2006-2013 Use of NAC increased in the 2 nd time period (69.3% vs 48.9% in the first time period, $p < 0.001$) in patients with ALF not due to acetaminophen toxicity Overall survival and transplant free survival increased during the 16 year period Other changes in the 2 nd vs. 1 st period included reduced RBC and plasma infusion, mechanical ventilation, and use of vasopressors.	Suggests positive effect + significant off label use in the US
Mumtaz, 2009(76) Pakistan	Prospective non-blinded study with historical controls	Acute liver failure not caused by acetaminophen (majority were due to hepatitis E or B virus, but some due to antituberculosis treatment)	91	Oral NAC dose of 140 mg/kg followed by 70 mg/kg, for a total of 17 doses 4 hours apart within 6 hours of admission (47 subjects prospectively enrolled) 44 subjects received standard care only (historical controls from hospital database)	A total of 34 (37.36%) patients survived; 22 (47%) in group 1 (NAC group) and 12 (27%) in group 2 (controls) ($P = 0.05$), indicating NAC causes a significant reduction in mortality. (<i>no liver specific outcome measures</i>) On multivariable regression analysis, patients not given NAC (odds ratio [OR] = 10.3, 95% confidence interval [CI] = 1.6–65.7), along with age older than 40 years, patients requiring mechanical ventilation, and interval between jaundice and hepatic encephalopathy were independent predictors of mortality.	Presumed positive effect

Kortsalioudaki, 2008(75) UK	Retrospective review	Pediatric acute liver failure not believed to be caused by liver failure	170	Continuous IV infusion NAC 100 mg/kg/24 hours until INR normalization, death, or liver transplant. Median duration 5 days (range 1-77) Compared with historical group receiving supportive care without NAC	Length of hospital stay, length of ICU stay, and incidence of death without liver transplant were not significantly different between the two groups. The 10 year actuarial survival was 50% in the supportive care group and 75% in the NAC treated group (n=0.009). Survival with native liver was observed in 13 (22%) of the supportive care group and 48 (43%) of the NAC-treated group. Death after transplantation occurred in 15 (39%) of the supportive care group as compared with 8 (16%) of the NAC treated group (p=0.02). Among NAC-treated patients, side effects were noted in 8 (10.8%), including rash (n=3) resolving with no treatment; bradycardia (n=2) or tachycardia (n=1) attributed to underlying disease; dizziness and peripheral edema (n=1) with NAC tolerated at lower dose; and bronchospasm and florid maculopapular rash attributed as an allergic reaction to NAC requiring discontinuation.	Presumed positive effect
Ben-Ari, 2000(77)	Retrospective observational	Acute liver failure not caused by acetaminophen	7	NAC administered at presentation	Clinically, 3 patients who initially had grade O/II encephalopathy, did not progress, and have fully recovered. The mean peak prothrombin time, serum factor V, aspartate aminotransferase and alanine aminotransferase levels, all significantly improved. Four patients (57%) have recovered fully (1 patient, although fully recovered, died later from an unrelated cause). Two patients required orthotopic liver transplantation and 1 patient died. N-acetylcysteine administration may have prevented progression to grade III/IV encephalopathy and improved serum coagulation factors.	Presumed positive effect
Harrison 1991(78) UK	Case series	Acute liver failure	12 due to acetaminophen and 8 due	NAC was given in a dose of 150 mg per kilogram of body weight in 250 ml of 5 percent dextrose over a period of 15 minutes and then in a dose of	Positive effects in patients with non acetaminophen induced liver failure were similar to those observed in the acetaminophen group.	Presumed positive effect

			to other causes	50 mg per kilogram in 500 ml of 5 percent dextrose over a period of 4 hours		
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LITERATURE SUMMARY: Evidence describing use of NAC in heatstroke-associated acute liver injury

First author, year country	Design	Condition	Sample size	NAC dose, frequency, duration, route of administration; comparator	Findings	Outcome
Monzon 2020(47) US	Case report	Heatstroke-associated ALF	1	NAC IV initiated hospital day 2 for ALI. NAC was infused at 15,000 mg IV over one hour, followed by 5000 mg IV over four hours, then 10,000 mg IV over 16 h without continuation of therapy.	24-year-old unresponsive male without significant past medical history presented to the emergency department with heat stroke; his initial temperature was 107.4 °F. During his hospital course, he developed ALI with significant elevation in aspartate aminotransferase, alanine aminotransferase, and total bilirubin. These laboratory findings peaked by hospital day two, but improved prior to discharge on hospital day five and throughout his follow up clinic visits. His treatment course included cooling measures, supportive care, supplemental oxygen and airway management, seizure control, and intravenous NAC therapy.	Suggest positive effect
Will 2019(49) US	Case report	Heatstroke associated ALF	1	Starting hospital day 3, loading dose of NAC at 150 mg/kg was given over one hour. NAC therapy was continued at a dose of 12.5 mg/kg/hr for four hours with steady clinical improvement. Following stabilization, he was transferred back to the military treatment facility, where he completed a 72-hour total course of NAC continued at 6.25 mg/kg/hr.	27-year-old basic combat trainee presented with altered mental status, renal insufficiency, rhabdomyolysis, and a core temp of 107.9 °F after collapsing during a run, leading to the diagnosis of heat stroke. While the patient's azotemia and creatinine kinase levels rapidly improved with aggressive intravenous hydration, transaminases continued to increase to nearly 155 times the upper limit of normal. Further laboratory evaluation revealed coagulopathy and thrombocytopenia suggestive of acute liver failure (ALF). Liver function improved on NAC; patient discharged after 3 days of NAC and laboratory values returned to normal by 8 weeks.	Suggests positive effect

Aquilina 2018(48) Malta	Case report	Heatstroke associated ALF	1	NAC dose not reported; initiated day 6 and continued until day 29	31 year old collapsed during a race, had ALF at admission and liver function continued to deteriorate. Liver transplant considered NAC discontinued at day 29 due to improvement in liver function; discharged on day 31.	Suggests positive effect
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LITERATURE SUMMARY: Evidence describing use of NAC in alcohol poisoning-associated acute liver injury

First author, year country	Design	Condition	Sample size	NAC dose, frequency, duration, route of administration; <i>comparator</i>	Findings	Outcome
Singh 2015(50)	Systematic review and meta analysis	Severe acute alcoholic hepatitis	22 RCTs, 2621 patients, 5 interventions	NAC as used in original reports	in a direct meta-analysis, only corticosteroids decreased risk of short-term mortality. In a network meta-analysis, moderate quality evidence supported the use of corticosteroids alone (relative risk [RR], 0.54; 95% credible interval [CrI], 0.39-0.73) or in combination with pentoxifylline (RR, 0.53; 95% CrI, 0.36-0.78) or NAC (RR, 0.15; 95% CI, 0.05-0.39), to reduce short-term mortality; low quality evidence showed that pentoxifylline also decreased short-term mortality (RR, 0.70; 95% CrI, 0.50-0.97). The addition of NAC, but not pentoxifylline, to corticosteroids may be superior to corticosteroids alone for reducing short-term mortality.	Positive effect with corticosteroids

LITERATURE SUMMARY: Evidence describing use of NAC in mushroom toxin-induced acute liver injury

First author, year country	Design	Condition	Sample size	NAC dose, frequency, duration, route of administration; <i>comparator</i>	Findings	Outcome
Liu 2020(51)	Systematic review	Mushroom poisoning	13 studies, 506 patients	Not detailed; all studies included NAC intervention	The mortality rate (including liver transplant patients) of amatoxin-poisoning patients with NAC treatment was 11% (57/506), and the mortality rate (excluding transplant patients) 7.9% (40/506) and a liver transplantation rate of	Positive effect

					<p>4.3% (22/506). Transaminase concentrations generally peaked around 3 days after ingestion, prothrombin time/International Normalized Ratio (PT/INR) generally worsened during the first 3-4 days after ingestion before returning to normal four to 7 days after ingestion, and Factor V levels normalized in about 4-5 days after ingestion in patients treated with NAC. Renal failure was reported in 3% (3/101) and acute kidney injury was reported in 19% (5/27). Gastrointestinal bleeding occurred in 21% (15/71). Anaphylactoid reactions were the principle adverse reaction to NAC treatment in amatoxin-poisoning patients with an incidence of 5% (4/73).</p> <p>Authors concluded that NAC appears to be beneficial and safe.</p>	
Karvellas 2016(79) North America	Registry cohort	Mushroom-induced ALF and ALI	18, 13 with ALF	Not detailed	N-acetylcysteine used in nearly all patients 88% of nonspontaneous survivors and 80% of spontaneous survivors.	No efficacy inferences possible; significant off label use.
Vanooteghem 2014(80) Belgium	Case series	Mushroom-induced ALF	4	Not detailed	All patients survived without need for liver transplant.	Suggests positive effect
Montaninia 1999(81) Italy	Case series	Mushroom-induced ALF	11	Not detailed, notes "high dose"	All patients survived, 1 with preceding liver disease required liver transplant	Suggests positive effect

LITERATURE SUMMARY: Evidence describing use of NAC in virus-associated acute liver injury (hepatitis A, hepatitis B, dengue fever)

First author, year country	Design	Condition	Sample size	NAC dose, frequency, duration, route of administration; comparator	Findings	Outcome
Saleem 2015(52) Pakistan	Case series	Children age 1 month to 16 years with ALF and acute viral hepatitis	40	Not detailed	There was significant statistical difference in liver enzymes and prothrombin time on admission comparing at discharge in	Suggests positive effect

					children received NAC ($p < 0.001$). Fifteen (38%) children died.	
Sotelo 2009(53) Mexico	Case series	Children with acute viral hepatitis and acute hepatic failure	12 (10 with hepatitis A)	All received oral NAC, six patients for a week and the remaining six for 9-36 days. Treatment was not ceased until patients showed clinical and laboratory improvement.	Significant improvement in liver function and coagulation parameters compared with initial values. Investigators note good tolerance to medication and satisfactory clinical course	Suggests positive effect
Arboviral infections						
Paramasivam 2013(55) Malaysia	Retrospective cohort	Dengue fever with moderate or severe hepatitis	13 of 85 treated with NAC	NAC administered over 1 hour followed by maintenance until AST < 300 mmol/L (NAC dose not detailed) Mean (SD) duration of NAC administration was 2.4 (2.9) days. Comparison group: those not treated with NAC	7 patients had moderate hepatitis (AST 300-9999 mmol/l) and 6 had severe hepatitis (AST>1000 mmol/l). Time to ALT reduction to < 300 mmol/l was 3.8 days in patients receiving NAC compared with those who did not receive NAC (4.7 days, $p=0.003$). Length of hospital stay was significantly longer in those receiving NAC vs. those not receiving NAC (6.0 vs. 4.7 days, $p=0.009$). Authors note that NAC was given to patients who were more ill.	Positive effect
Tan 2013(57) Malaysia	Retrospective case series	Severe dengue fever by WHO 2009 classifications	7 of 8 treated with NAC	IV NAC infusion 100-150 mg/kg/day for a minimum of 5 days	The maximum grade of hepatic encephalopathy was grade III in five patients and grade II in three patients, all occurring within one to four days of admission. All patients discharged well after a median of 13.5 (5, 35) hospital days; all seven patients with longer term follow up had normalization of ALT. No adverse effects of NAC observed	Presumed positive effect
Kumarasena, 2010(58) Sri Lanka	Retrospective case series	Dengue-associate acute liver failure in the setting of severe disease (six patients had dengue shock syndrome)	8	Intravenous NAC at 150 mg/kg loading dose over 15 min followed by 12.5 mg/kg/h for 4 hours, then 6.25 mg/kg/h for up to 72 hours All received other supportive management	All five patients with hepatic encephalopathy coma grades I-II recovered completely and were well at follow-up after at least 2 months, whereas the three patients with coma grades III-IV died. No patients had adverse effects attributable to NAC.	Presumed positive effect

Senanayake 2013(59) Sri Lanka	Retrospective case series	Dengue-associated acute liver failure (pediatric : age 6 months – 12 years)	7	IV NAC 100 mg/kg over 24 hours, continued up to 72 hours in patients with hepatic encephalopathy at the end of the first dose	Following the first dose of NAC (100 mg/kg over 24 hours) four patients showed rapid clinical improvement of encephalopathy. Remaining three responded after second (2) and third (1) doses. In all seven patients, biochemical profiles showed improvement from first dose onwards. No side effects of NAC were noted. All seven made complete recovery without residual hepatic or neuro-developmental damage.	Presumed positive effect
Kularatne, 2018(60) Sri Lanka	Retrospective case series	Dengue-associated acute liver failure in adults (age 22 and age 39)	2 of 10 received NAC	IV NAC (in one case, at 150 mg/hour, duration not noted; NAC regimen details not provided for 2 nd patient)	Case 1: discharged at day 12 with near normal liver transaminases; follow-up at 21 days indicated normal liver biochemistry Case 2: symptoms resolved within the next few days	Presumed positive effect
Tan 2016(61) Singapore	Retrospective case series	Dengue-associated liver failure in pediatrics (age 5 months to 6 years)	2 of 4 received NAC	IV NAC (100 mg/kg/day) for 1 week	All patients recovered fully. No adverse effects of NAC observed.	Presumed positive effect
Lewis 2019(62) US	Case report	Dengue shock syndrome (age 23)	1	NAC (details not given)	Exchange student arrived from India 3 days before hospital admission, treated with platelets, NAC, and other supportive care. Progressed to acute liver failure including hepatic encephalopathy and was listed for liver transplant. 24 hours after listing, liver tests began to improve and mental status normalized over the next 48 hours, along with resolution of fever and tachycardia. Patient was delisted.	Presumed positive effect
Dalugama 2018(56) Sri Lanka	Case report	Dengue fever with acute liver failure and acute kidney injury (age 43)	1	IV NAC 100 mg/hour for five days	Transaminases gradually declined, lactate normalized, serum creatinine reduced and normalized, urine output gradually increased and CVVHD was terminated after 138 hours of dialysis. Discharged on 9 th day after admission.	Presumed positive effect
Dalugama, 2017(63) Sri Lanka	Case report	Dengue fever (age 53)	1	Intravenous NAC at a rate of 100 mg/hour (in addition to packed cells transfusion) until discharge (day 5)	Gradual reduction in AST and ALT, prothrombin time and activated partial thromboplastin time normalized. On day 5 of admission AST and ALT were less than 200 U/L and NAC infusion was terminated and patient discharged. Patient was in good in health with normal liver enzymes, clotting profile, and albumin	Presumed positive effect

					at follow up visits on day 7 and 2 weeks later.	
Habaragamuwa 2014(54) Sri Lanka	Case report	Dengue associated severe hepatitis (age 54)	1	Intravenous NAC at 100 mg/kg/day infusion for 5 days	Prior to NAC treatment, liver enzymes reached peak values of AST 16261 U/L and ALT 4545 U/L, prothrombin time/international normalized ratio (PT/INR) 1.7, and total bilirubin 5.9 mg/dl on 4 th day of admission (7 th day of illness). NAC administration produced marked improvement in liver enzyme values, and AST and ALT levels dropped by more than half by 48 hours of treatment. On the 9 th day of admission liver function revealed AST 300 U/L, ALT 223 U/L and PT/INR 1.2. During follow up visit at 2 weeks after discharge, patient had normal liver profile and no evidence of chronic liver disease.	Presumed positive effect
Manoj 2014(67) Sri Lanka	Case report	Dengue hemorrhagic fever with acute liver failure and massive bleeding (age 37)	1	IV NAC for 72 hours (dose not detailed) along with recombinant factor VIIa and other supportive therapies	Patient was admitted after 3 days of illness and moved to ICU after developing agitation and drowsiness 36 hours after admission, with intubation around day 5-6 of illness. Transaminases showed a marked rise (AST 12500 U/L and ALT: 2700 U/L, bilirubin 1.8) in seventh day of illness; massive hematemesis on day 8 and CVP rise at 9 th day required furosemide. Transaminases gradually declined over next several days. Patient was extubated after 7 days of ventilatory support and discharged after a total hospital stay of 18 days (discharge AST 96 U/L, ALT 109 U/L, bilirubin 16.8 mg/dL).	Presumed positive effect
Abeysekera 2012(64) Sri Lanka	Case report	Dengue fever with hepatic encephalopathy (age 52)	1	IV NAC initiated on day 6 of fever, just after admission, 150 mg/kg in 100 ml normal saline over 1 hr., 50 mg/kg in 500 ml normal saline over 24 hrs. for 3 days	Patient had complete recovery and was discharged home 10 days after admission with all parameters returning to normal levels.	Presumed positive effect
Lim 2011(65) Singapore	Case report	Dengue fever (pediatric age 6)	1	Intravenous NAC at 100 mg/kg/day as a continuous infusion over 24h for 6 days	Rapid decrease in liver transaminases: AST dropped to 5991 U/l and ALT 1789 U/l after 3 days; AST to 1044 U/l and ALT to 635 U/l, respectively, after 6 days.	Presumed positive effect

					Coagulation profile normalized: PT improved to 18.0 s and INR 1.54 after 6 days. Over the course of treatment with NAC, there were no adverse effects such as dysrhythmias, bronchospasm, dizziness, vomiting and rashes.	
Gan 2013(66) Malaysia	Case report	Post-dengue fever shock syndrome with fulminant liver failure (pediatric age 8 months)	1	IV NAC 10 mg/kg/hr.	Infant with severe dengue given paracetamol; developed fulminant liver failure with encephalopathy, gastrointestinal hemorrhage, and severe coagulopathy. Serum paracetamol was 0.1 mmol/l above the treatment nomogram at 20 hours after last dose of paracetamol. Patient received supportive care (transfusion, IV vitamin K) and NAC; discharged at day 25 with lingering left hemiparesis. No residual neurological deficit at two months after initial illness.	Presumed positive effect

Key: ALF acute liver failure; ALI acute lung injury; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARDS acute respiratory distress syndrome; AST = aspartate aminotransferase; AVH acute viral hepatitis; CABG coronary artery bypass grafting; COPD chronic obstructive pulmonary disease; CVVHD continuous veno-venous hemodialysis; DF dengue fever; DIH drug induced hepatotoxicity; GGT gamma-glutamyl transferase; HCV = hepatitis C virus; ICU intensive care unit; IFN = interferon; G-CSF granulocyte colony stimulating factor; ; INR international normalized ratio; MAP mean arterial pressure; MEGX = monoethylglycinexylidide; MET metformin; NAC = N-acetylcysteine; NAFLD nonalcoholic fatty liver disease; PPC postoperative pulmonary complications; PT prothrombin time; RCT = randomized controlled trial; SMT standard medical therapy; TB tuberculosis

14. Comprehensive reference list and in-text citations.

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Appendix 2: Evidence describing hepatic effects of N- acetylcysteine in other conditions (excluding acetaminophen toxicity)

First author, year country	Design	Condition	Sample size	NAC dose, frequency, duration, route of administration; comparator	Findings	Outcome
Other infections						
Grant, 2000(111) UK	Double blind, multicenter RCT	Chronic hepatitis C	147	Oral NAC 600 mg 3 times/day for 6 months (1800 mg/day) 73 received 3MU IFN-alpha 3 times/week by subcutaneous injection + NAC 3 times/day and 74 received IFN 3 times/week + placebo 3 times/day	No significant difference in sustained virological response; Changes in serum ALT levels correlated with virological outcome in 97% (n = 139) of cases; in 5 patients, serum ALT remained normal despite virologic relapse during 6 month post-treatment window (paper does not report treatment group data for these individuals).	no effect on virologic response
Neri, 2000(112) Italy	RCT	Chronic hepatitis C	77	Participants were treated with IFN (intramuscular 6,000,000 MU 3 times each week for 6 months) + NAC (2400 mg/day in two doses when fasting) (n=38) or with IFN alone (n=39)	No significant difference in viremia values between the two groups. 7 patients from the IFN only group and 6 patients from the IFN+NAC group had no evidence of relapse within 10 months after finishing therapy and were excluded from further analysis. Patients treated with IFN alone relapsed earlier than patients treated with NAC + IFN (22 vs. 31 weeks, p<0.05). Three cases of breakthrough occurred in the IFN only group and no cases in the IFN+NAC group. Oxidase-reductase balance was significantly higher during treatment in the IFN group as compared with the IFN+NAC group (p<0.05), which authors note suggests the presence of oxidative stress in patients treated with IFN alone. The difference waned over time after cessation of treatment. No adverse events requiring cessation of either treatment.	Positive effect on HCV relapse and measures of oxidative stress no difference in efficacy (ALT, liver biopsy or ultrasound)

Gunduz, 2003(113) Turkey	Placebo controlled RCT	Acute viral hepatitis A or B (hospitalized patients)	41	Oral NAC 200 mg 3x daily (600 mg/day) until discharge 21 received placebo tablets and 20 received NAC	NAC administration did not significantly affect the time necessary for ALT and total bilirubin values to normalize (100 U/L and 2mg/dl, respectively) or duration of hospitalization "NAC was not harmful for AVH patients" (given that hospital duration and time to normalization of ALT and total bilirubin did not get longer with use of NAC; no adverse effects noted)	no effect on time to normalization of ALT or total bilirubin; or duration of hospitalization
Look, 1999(114) Germany	Prospective, randomized pilot trial	Chronic hepatitis C	24	NAC effervescent tablets, 1800 mg/day for 24 weeks 8 received IFN alone, 8 received IFN + NAC + sodium selenite, and 8 received IFN + NAC + sodium selenite + vitamin E544	NAC administration did not significantly affect the response rate (normalization of ALT and negative HCV RNA). No significant improvement in liver histology or recurrence rates.	no effect on normalization of ALT or negative HCV RNA
Furtado 2017(115) Portugal	Case report	Acute HBV and coagulopathy with non-immune hemolytic anemia (age 41 years)	1	NAC for 5 days (protocol not detailed), along with entecavir, folic acid, and vitamin K	Bilirubin and INR normalized progressively during hospital stay.	Presumed positive effect
Prevention and treatment of non-acetaminophen drug-induced acute liver injury and failure						
Baniasadi, 2010(116) Iran	Open-label, RCT	Newly diagnosed, treatment naïve, pulmonary tuberculosis patients beginning anti-TB drug regimen	60	600 mg NAC taken orally twice a day 32 received standard anti-TB drug therapy and 28 received standard drug therapy + NAC	Hepatotoxicity occurred in 12 control patients (37.5%) and none of the patients treated with NAC. After 1 and 2 weeks of treatment, mean ± SD values of AST and ALT were significantly higher in controls (week 1: 99.44±150.11, 65.78±88.64 and week 2: 57.22±75.81, 58.09±86.18) than those treated with NAC (week 1: 27.68±13.79, 20.96±11.95, and week 2: 27.32±13.11, 21.53±9.56).	Positive effect
Cheng 2016(117) Taiwan	Case control	Patients receiving at least 5 months of an anti-TB drug course	279	NAC 1200 mg/day plus anti-TB regimen (n=82) Anti-TB regimen only (n=297)	11 patients (13.4%) were diagnosed with drug-induced hepatotoxicity (DIH) in the NAC group and 72 patients (24.2%) developed DIH in the comparison group (p<0.05).	Positive effect

					<p>The mean duration of treatment before the onset of hepatotoxicity was 28.6±14.9 days in NAC group, as compared with 17.4±11.3 days in the comparison group (p<0.01).</p> <p>Liver function normalized 9.4 ±6.7 days after stopping the anti-TB drugs in NAC group compared with 19.2±11.5 days in the comparison group (p<0.01).</p>	
Non-viral hepatitis						
Oliveira, 2019(118) Brazil	Open-label, multicenter RCT	Non-alcoholic steatohepatitis	53	<p>1200 mg/day of NAC taken orally for 48 weeks in combination with metformin and/or ursodeoxycholic acid</p> <p>26 received metformin + NAC + UDCA, 14 received metformin + NAC, 13 received metformin + UDCA</p>	<p>Significant improvements in the steatosis degree (P=0.014), ballooning (0.027) and, consequently, in the NAFLD Activity Score (NAS) (P=0.005), and in the ALT levels at the end of the treatment only in the metformin + NAC group</p> <p>No significant evidence of modification in the liver fibrosis in any group (via baseline and post-treatment liver biopsies)</p>	Positive effect
Singh, 2018(119) India	Open-label, randomized controlled pilot study	Severe alcoholic hepatitis	57	<p>Intravenous NAC for 5 days (day 1: NAC at 150, 50, and 100 mg/kg in 250, 500, and 1000 mL of 5% glucose solution over 30 minutes, 4 hours, and 16 hours, respectively; days 2–5: 100 mg/kg/day in 1000 mL of 5% glucose solution) in addition to standard medical therapy and G-CSF</p> <p>20 received standard medical therapy (SMT), 18 received SMT + granulocyte colony-stimulating factor (G-CSF), and 19 received SMT+ G-CSF + NAC</p>	<p>Both G-CSF and SMT+G-CSF + NAC improved 90-day survival compared to standard medical therapy, but no significant difference between this combination and G-CSF alone</p> <p>*There was a significant increase in ALP on day 6 compared with day 0 in the SMT+G-CSF+NAC group and the G-CSF group; no significant increase in ALP in the SMT alone group.</p> <p>There was significant improvement in the clinical severity scores on day 6 compared with day 0 in G-CSF group but not in the SMT+G-CSF+NAC and the SMT group.</p>	<p>No effect</p> <p>potential liver-related safety issue</p>
Hepatic surgical procedure (resection, transplant, biliary bypass)						

Kakaei 2020(120) Iran	RCT	Biliary bypass for obstructive jaundice	30	IV NAC 200 mg/kg/hour first 8 hours after surgery, then 100 mg/kg/hour for 40 hours Control participants received no infusion	The NAC group, as compared with control patients, had significantly greater decline of ALT (p=0.02), AST (p=0.01), ALP (p=0.01), GGT (p=0.04), total bilirubin (p=0.02), direct bilirubin (p=0.01). No significant differences in decline of INR or creatinine or of hospital stay duration, ICU admission, or ICU length of stay were observed. No adverse events due to NAC were observed	Positive effect
Li 2018(121) China	RCT	Liver transplantation	60 (42 included in analysis)	Atomization inhalation of 3 mL NAC (10%) for 30 minutes before surgery and 3 hours after reperfusion Control patients received atomization inhalation of 3 ml sterile water for the same periods of time.	Postoperative pulmonary complication as per broad clinical definitions (atelectasis, pneumothorax, pleural effusion, ALI, ARDS, pneumonia) were similar between the two groups. As measured by the Melbourne Group Scale Version 2 score, there was a significantly higher incidence of PPCs in the control group as compared with the NAC group (73% vs. 40%, p=0.032). 30 participants developed at least one respiratory infection within 1 month postoperatively. Among these patients, isolated bacterial infection was observed in 2 (11%) of 18 patients in the control group and 8 (67%) of 12 patients in the NAC group (p=0.019), while investigators note that more refractory infectious etiologies including fungal, combined, or unknown infection comprised the major pneumonia causes in the control group but not the NAC group. 18 of the 22 control patients developed and combined more than 3 kinds of coexisting pulmonary complications within 1 month postoperatively, an incidence higher than that of the NAC group (82% vs. 50%, p=0.028). NAC group had significantly shorter ICU (p=0.026) and hospital stay (p=0.029) and hospitalization costs (p=0.020). 12 month mortality related to pulmonary disease was significantly lower in the NAC group (p=0.012).	Positive effect

					No side effects related to NAC inhalation were observed.	
Aliakbarian, 2017(122) Iran	Double-blind RCT	Orthotopic liver transplant	115	After donor organ retrieval, 2000 mg NAC was added to 2 liters of UW solution and perfused through the mesenteric vein (49 patients) In 66 patients, standard UW solution was used	No significant difference between the groups regarding time to hepatic artery reperfusion, hospital stay, vascular complications, inotrope requirement before and after portal declamping, and blood gas analysis. (<i>no liver specific measures</i>) *Hypotension after portal reperfusion was significantly more common in experimental group compared with control group ($P = .005$). Retransplant and in-hospital mortality were comparable between the groups.	no effect
Grendar, 2016(123) Canada	Open-label, RCT (No blinding was performed)	Post-hepatic resection	206	NAC infusion: 150 mg/kg of NAC in 200 ml of 5% glucose over 45 min upon arrival in the post anesthesia recovery room, then 50 mg/kg of NAC in 500 ml of 5% glucose over 4 hr., followed by 100 mg/kg in 1000 ml of 5% glucose over the next 16 hr.; followed by 100 mg/kg in 1000 ml of 5% glucose per day over the next 3 days, which was administered in six infusions of 50 mg/kg in 500 ml of 5% glucose, given over 12 hr. each + standard care (98 patients) 108 patients received the usual postoperative management without NAC	No significant differences were noted in overall complications (32.7% and 45.7%, $P = 0.06$) or hepatic failure (3.6% and 5.4%, $P = 0.537$) between treatment groups. No significant difference between groups in biochemical markers of liver function except INR (1.24 without NAC and 1.35 with NAC) and creatinine (88.8 $\mu\text{mol/L}$ without NAC and 72.6 $\mu\text{mol/L}$ with NAC). *There was significantly more delirium within the NAC group (2.7% and 9.8%, $P < 0.05$) that caused early trial termination. Study had issues with randomization and there were disproportional females in the NAC group	no effect potential safety issue highlighted
Donadon 2016(124) Italy	Double-blind RCT	Hepatic resection using	48	IV NAC 150 mg/kg as a bolus for 1 hour before surgery, then continuous	Morbidity was not significantly different between the 3 groups.	Positive effect

		Pringle maneuver		<p>infusion of 50 mg/kg/h during the procedure</p> <p>Compared to two other regimens: Methylprednisolone (MET) 500 mg in 250 ml glucose 5% as bolus 1 hr. before surgery then continuous infusion OR Placebo infusion (glucose 5%)</p>	<p>Comparing across the 3 groups, ALT at postoperative day 1 was significantly lower in both the MET and NAC groups vs placebo (p=0.039), and significantly lower in the NAC group as compared with the MET group (p=0.021). At postoperative day 3, the 3-group difference was not significant, but the NAC group ALT was lower than the MET group (p=0.041).</p> <p>Similarly, the NAC group had lower bilirubin as compared with the MET group (p=0.03) at postop day 1; the 3 group levels were not significantly different and no significant differences at day 3 in bilirubin were observed.</p>	
D'Amico, 2013(125) Italy	RCT	First liver transplant for chronic liver disease patients	140	<p>15 minute NAC infusion (30 mg/kg) 1 hour before the start of organ retrieval and a locoregional infusion (150 mg/kg of estimated liver weight for a maximum dose 300 mg) in the portal vein just before cross-clamping (69 patients)</p> <p>71 patients assigned to standard protocol without NAC</p>	<p>The NAC harvesting protocol significantly improves graft survival (graft survival rates at 3 and 12 months were 93% and 90%, respectively, in the NAC group and 82% and 70%, respectively, in the control group ($P = 0.02$)).</p> <p>Post-op day 15 AST levels were 31 U/L (range = 15-150 U/L) in the study group and 38 U/L (range = 13-326 U/L) in the control group ($P = 0.02$). No significant differences in any other liver specific measures.</p> <p>The incidence of postoperative complications was lower in the NAC group (23%) versus the control group (51%, $P < 0.01$).</p>	Positive effect
Robinson 2013(126) UK	Retrospective cohort	Liver resection	88	<p>IV NAC (10,000 mg/24 hr. in 250 ml 5% dextrose) starting at time of parenchymal transaction and continuing for 3 days postoperatively or until a fall in ALT in patients operated on by one surgeon</p> <p>Comparison group: patients resected by</p>	<p>NAC was associated with lower postoperative ALT as compared with control (p=0.019); no significant differences in serum bilirubin or prothrombin time were observed between the two groups.</p> <p>Grade A post-hepatectomy liver failure was more common in the NAC group as compared with controls (31.8% vs 9.1%, p=0.025); incidence of no liver failure or grades B/C post hepatectomy liver failure were not significantly different between the NAC and</p>	No effect

				surgeons not using NAC as part of their perioperative regimen	control groups. No statistically significant difference in incidence of clinically important complications between the two treatment groups.	
Regueira, 1997(127) Spain	Retrospective clinical study	Liver transplant	62	Donor received IV of 6g of NAC at least an hour before extraction (25 patients) In 37 transplants, the donor did not receive any specific treatment	Grafts that received NAC presented less cytolysis and less elevation of transaminases (AST maximum was 353.56 UI/L in NAC group vs 825.97 UI/L in controls); (first day post-transplant ALT 250.16 UI/L in NAC group vs 440.54 UI/L in controls); bile production and synthetic function were also better. Prothrombin time was significantly superior in the first 5 days in the NAC group compared to controls (P=.0062) Patients in the NAC groups experienced acute rejection significantly less than controls (p=.0309)	Presumed positive effect
Other operative procedures; not a complete list						
El Hamamsy 2019(128) Egypt	Double-blind, placebo controlled RCT	Patients requiring ICU admission and total parenteral nutrition for at least 5 days after colon surgery	60	IV bolus NAC (100 mg/kg dissolved in 5% dextrose) infused over 15 minutes then continuous infusion 50 mg/kg/day starting 1 hour before induction of anesthesia and continuing for 48 hours after the operation Comparison group received infusion of dextrose 5% at equal volume and rate as the NAC group	Most clinical and laboratory parameters did not differ significantly between the two groups, including MAP, heart rate, temperature, respiratory rate, total leukocyte count, platelets, serum creatinine, BUN, serum sodium, serum potassium, TNF- α , and MDA. Mean postoperative serum ALT was significantly lower in the NAC-treated group as compared with the control group (22.6 \pm 9.9 vs. 31.1 \pm 17.8, p=0.028). Investigators note mild adverse effects of NAC in 2 patients (6.6%), including hypotension and tachycardia.	Positive effect
Onk, 2018(129) Turkey	Prospective, randomized study	COPD patients having coronary artery	70	900 mg/day of NAC for 7 days until the day of surgery (35 patients)	NAC pre-treatment has a stabilizing effect on NH ₃ and nitrogen metabolism in COPD patients undergoing CABG (postoperative 24th hour, and postoperative 48th hour)	Positive effect

		bypass grafting surgery		35 patients received standard care only	<p>(respectively, 39.0±8.8 vs. 55.4±19.6 and 40.1±8.4 vs. 53.2±20.2 mcg/dl).</p> <p>Patients with COPD who were started on N-acetylcysteine before surgery tend to have lower lactic acid levels (1.7±0.9 vs. 2.1±1.2 and 1.2±0.5 vs. 1.8±1.4 mmol/L; p<0.01), authors infer that this indicates a protective effect of N-acetylcysteine against renal and hepatic tissue damage</p> <p>Serum AST, ALT, ALP levels demonstrated no significant difference between the 2 groups at any of the 4 measurement time points (preoperative, during cardiopulmonary bypass, 24th postoperative hour, and 48th postoperative hour) (p>0.05)</p>	
Belgaumkar, 2016(130) UK	Single blinded, RCT	Laparoscopic sleeve gastrectomy	20	<p>NAC infusion at a standard 150 mg/kg in 200 ml 5% dextrose over 15 min at induction of anesthesia followed by an infusion of 50 mg/kg in 500 ml of 5% dextrose during surgical retraction of the liver for a max of 4 hours (10 subjects)</p> <p>10 control subjects received standard anesthetic medication alone</p>	<p>NAC did not reduce intraoperative liver injury</p> <p>No significant differences between liver enzymes, rates of complications, length of stay, white cell count, or liver injury scores: The trial was not powered to detect differences in clinical outcomes.</p> <p>Authors comment: "The major drawback of the study was a lack of a standardized, reproducible toxic insult to the liver during intraoperative liver retraction with the Nathanson liver retractor. The pressure applied to liver varied from patient to patient depending on their body habitus, intraabdominal dimensions and size and texture of the liver. There are presently no routine clinical methods of measuring tissue oxygen tension or pressure within the liver. This lack of uniformity lead the investigators to conclude that a major study redesign would be required to reach a robust conclusion."</p>	no effect
Septic shock						

Rank, 2000(131) Germany	Prospective, double-blind, placebo controlled RCT	Septic shock patients within 24 hours after onset of sepsis	60	<p>NAC infusion of 150 mg/kg in 250 mL of 5% dextrose over a period of 15 mins, followed by a continuous infusion of 12.5 mg/kg/hr. over 90 mins (30 patients)</p> <p>(30 control patients received 5% dextrose only)</p>	<p>After NAC, a significant increase in absolute liver blood flow index (2.7 vs. 3.3 L/min/m²; p = .01) and cardiac index (5.0 vs. 5.7 L/min/m²; p = .02) was observed.</p> <p>After NAC, microsomal liver function improved, evidenced by a significant increase in MEGX (p = .04). Liver blood flow index and MEGX correlated significantly (r(s) = .57; p < or = .01).</p>	Positive effect
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Appendix 3: Summary of adverse events reported in systematic reviews, by indication

Indication	Number of participants (studies)	Patient characteristics	Major adverse event(s) reported	Frequency
Acetaminophen overdose(83)	1058 (8 prospective trials of IV NAC)	Adult and pediatric patients, males and females	Anaphylactoid reactions including:	Up to 48% in prospective studies
			Nausea and vomiting	From 4.5% to 70.4%
			Cutaneous (rash, flushing, pruritis)	From 3.6% to 32%
			Bronchospasm	From 4 to 18%
			Hypotension	15.7% (only reported in one small study with 27 patients)
			Chest pain	6.5% (only reported in one small study of 11 patients)
			Decrease in INR	One study(132) reported the effect in 100% of patients (of 87)
Acetaminophen overdose(85)	6455 (1 retrospective medical review of patients treated with IV NAC at 34 Canadian hospitals)	Adult patients, males and females	Anaphylactoid reactions including:	8.2%
			Cutaneous only (rash, flushing, pruritis)	6.2%
			Systemic only	.5%
			Both cutaneous and systemic	1.5%
			Respiratory effects and/or hypotension	2%
Acetaminophen overdose(82)	503 (multi-center, retrospective chart review of patients treated with oral or IV NAC)	Adult patients, males and females	No serious adverse events reported. Nausea and vomiting were mild and the most common.	23% oral versus 9% IV
			Anaphylactoid reactions	2% oral versus 6% IV
Psychiatric and neurological disorders(93)	~1300 (16 controlled studies of patients treated with oral and IV NAC)	Adult and pediatric patients, males and females	Largest rate of AEs was seen in an open-label cannabis study (24 patients)(133)	63% reported at least one AE
			Abdominal discomfort	20.8%
			Muscle pains/aches	20.8%

			Insomnia	16.6%
			Headache, nasal congestion, nausea, weight decrease, restlessness, or dizziness	12.5%
Idiopathic pulmonary fibrosis(95)	1003 (12 RCTs of patients treated with oral or inhaled NAC reported safety)	Adult patients, males and females	Most commonly reported AEs were cough, dyspnea, bacterial pneumonia, diarrhea, headache, edema, abdominal pain	No trial reported a significantly increased risk of adverse events among patients treated with NAC.
Contrast neuropathy(96)	1776 (15, prospective, case-controlled studies of patients treated with oral and IV NAC)	Adult patients, males and females	No major treatment-related adverse events were reported.	No trial reported a significantly increased risk of adverse events among patients treated with NAC.
Chronic bronchitis(134)	2,540 (11 randomized, controlled trials of patients treated with oral NAC)	Adult patients, males, and females	6 trials reported GI adverse effects	No trial reported a significant increase in adverse events among patients treated with NAC.

<p>Acute liver failure not caused by acetaminophen overdose(75)</p>	<p>170 (1 retrospective case-controlled medical record review, IV NAC administered to 111 compared to 59 who did not receive NAC)</p>	<p>Pediatric patients, males and females</p>	<p>Adverse effects included rash, cardiac reactions which were not attributed to drug administration (3 children), mild dizziness and peripheral edema (1 child), and bronchospasm (1 child) which was attributed to an allergic reaction (NAC was immediately stopped)</p>	<p>Adverse events were reported in 11% of patients but there was not a significant increase in adverse events among patients treated with NAC.</p>
<p>Psychiatric conditions(135)</p>	<p>765 (12 randomized, controlled trials of oral NAC)</p>	<p>Pediatric patients, males and females</p>	<p>Mild adverse effects were reported including constipation (16.1%), increased appetite (16.1%), fatigue (12.9%), nervousness (12.9%), daytime sleepiness (12.9%) in ASD studies, headache and aggressive behavior in nail biting, and headache (Tourette's syndrome)</p>	<p>No trial reported a significantly increased risk of adverse events among patients treated with NAC.</p>