Original Article

Repurposing N-acetylcysteine for management of non-acetaminophen induced acute liver failure: an evidence scan from a global health perspective

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Background: The World Health Organization (WHO)'s Essential Medicines List (EML) plays an important role in advocating for access to key treatments for conditions affecting people in all geographic settings. We applied our established drug repurposing methods to one EML agent, N-acetylcysteine (NAC), to identify additional uses of relevance to the global health community beyond its existing EML indication (acetaminophen toxicity).

Methods: We undertook a phenome-wide association study (PheWAS) of a variant in the glutathione synthetase (*GSS*) gene in approximately 35,000 patients to explore novel indications for use of NAC, which targets glutathione. We then evaluated the evidence regarding biologic plausibility, efficacy, and safety of NAC use in the new phenotype candidates.

Results: PheWAS of *GSS* variant R418Q revealed increased risk of several phenotypes related to non-acetaminophen induced acute liver failure (ALF), indicating that NAC may represent a therapeutic option for treating this condition. Evidence review identified practice guidelines, systematic reviews, clinical trials, retrospective cohorts and case series, and case reports. This evidence suggesting benefit of NAC use in this subset of ALF patients. The safety profile of NAC in this literature was also concordant with existing evidence on safety of this agent in acetaminophen-induced ALF.

Conclusions: This body of literature indicates efficacy and safety of NAC in non-acetaminophen induced ALF. Given the presence of NAC on the EML, this medication is likely to be available across a range of resource settings; promulgating its use in this novel subset of ALF can provide healthcare professionals and patients with a valuable and safe complement to supportive care for this disease.

Keywords: Acute liver failure (ALF); N-acetylcysteine (NAC); global health; health equity

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Introduction

Background

Equity in access to treatments for a broad range of diseases is an essential principle of achieving meaningful improvements in health around the globe (1). The World Health Organization (WHO) has Model Essential Medicines Lists (EMLs) (2), defining acceptable availability of almost 600 medicines from a global health perspective. Since medicine access is particularly challenging in low- and middle-income countries, the EMLs provide trustworthy guidance for governments and providers in prioritizing medicinal supplies based on their communities' needs (3). EML medicines are thus more likely to be available in countries with varying resources.

Rationale and knowledge gap

While the EML includes indications for each medication, there may be uses for those agents yet to be propagated. These medications represent an exciting opportunity for drug repurposing and expansion of our global therapeutic armamentarium for treating significant health conditions. Inspired by this idea within our institution's larger Drug Repurposing Program (4), we began an initiative to identify new therapeutic uses for these WHO-identified essential medicines—Project Repurposing Essential Medicines Internationally (Remedi).

Objective

Project Remedi's approach integrates several powerful data sources—the phenome-wide association study (PheWAS), the electronic health record (EHR), and systematic evaluation of primary evidence in the literature—to elucidate novel gene/disease associations corresponding with new uses of EML medicines. By uncovering new applications for widely available medications, we hope to increase the likelihood that humans affected by disease, regardless of country or setting, will have safe and effective treatments.

In previous work, we have demonstrated that the combination of PheWAS with thorough evidence review and synthesis can yield valuable and actionable insights regarding additional therapeutic uses of existing medicines (4-10). The current analysis applies these methods to one agent from the EML, N-acetylcysteine (NAC), currently listed for "exposure to or harmful effects of undetermined intent of analgesics, antipyretics, or NSAIDs (nonsteroidal anti-inflammatory drugs)". NAC provides an accessible source of the amino acid cysteine, which is readily used by the enzyme glutathione synthetase (*GSS*) to form glutathione, a key defender against oxidative stress (11). Since NAC has a known mechanism of action related to a specific protein target, making it appropriate for application of our methods, we explored potential new indications for its use.

Highlight box

Key findings

- Our established drug repurposing methods, combining a phenome-wide association study (PheWAS) with review and synthesis of the biomedical literature, indicated a role for use of N-acetylcysteine (NAC) in non-acetaminophen-induced acute liver failure (ALF).

What is known and what is new?

- NAC is currently included on the World Health Organization's Essential Medicine List for management of acetaminophen toxicity.
- Concordance between PheWAS data and evidence from the primary literature indicates that NAC has also shown therapeutic utility and reasonable safety in non-acetaminophen-induced ALF.

What is the implication, and what should change now?

- NAC is available across countries of varying resource settings. The evidence indicates that healthcare providers may consider use of NAC in non-acetaminophen-induced ALF as a complement to current care strategies—a valuable addition to global strategies for improving health and health equity.

Methods

Our established repurposing methods follow a multi-step approach to identify and assess the evidence for potential novel indications for an existing therapeutic agent. These include: (I) drug and gene/protein target selection; (II) PheWAS of relevant gene; (III) thorough literature review, including assessment of biologic plausibility, burden of disease and public health relevance, and clinical evidence; and (IV) evidence synthesis and dissemination (*Figure 1*).

As described above, for the purposes of this analysis we selected the enzyme *GSS* gene, which is directly affected by the therapeutic agent NAC.

PheWAS

We reviewed a set of data in which a PheWAS analysis was

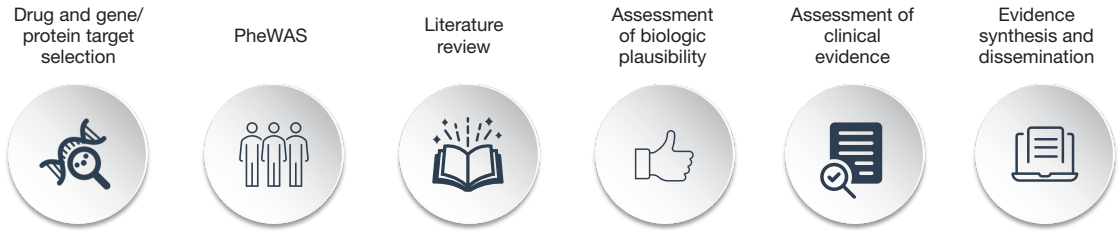

Figure 1 Overview of Project Remedi's Drug Repurposing Approach. PheWAS, phenome-wide association study.

performed. PheWAS can identify diseases (phenotypes) that are associated with a specific gene (12). Because the logic of PheWAS can be extended to predict phenotypic manifestations of pharmacological targeting of a given gene product in humans, we have established use of these methods for drug repurposing (4,5).

Our PheWAS analysis included approximately 35,000 patients at a large academic medical center and incorporated existing de-identified Illumina Infinium Exomechip genotype data and phenotypes extracted from our institution's Synthetic Derivative, a de-identified copy of EHRs (13). We focused on the glutathione synthetase gene *GSS*, as it is the primary target of NAC.

The Exomechip platform includes over 250,000 coding variants. Our PheWAS focused on a missense variant in *GSS*, R418Q (rs150141794), the only *GSS* single nucleotide polymorphism (SNP) in our existing dataset. Based on the structure of *GSS* (14), replacing the arginine at position 418 with a glutamine would potentially reduce the ability of the residue to form hydrogen bonds with the glutamate residue at position 455. These bonds help to anchor the end of the β-sheet and the final N-terminal loop; thus this variant may have effects on protein stability.

Statistical analysis

The PheWAS association calculations were performed in PLINK (version 1.9, https://www.cog-genomics.org/plink/1.9/) (15) using a logistic regression model; covariates included sex and age. This model was applied to calculate case and control genotype distributions and associated allelic P value and allelic odds ratio (OR).

Literature review and evidence synthesis

After identifying candidate indications for repurposed use of NAC, we next evaluated whether the established evidence was supportive of *GSS* involvement in these conditions. This included assessment of existing knowledge about the disease's biology involvement of *GSS* and any previous investigations exploring NAC for the novel phenotypes. Our review was conducted by a trained information scientist searching PubMed, Web of Science, and Google and hand searching references. Evidence was systemically extracted from relevant papers and prescribing information.

Ethical approval

As no personal health information identifiers are available in the Synthetic Derivative database and the genotype data was also deidentified (13), this study met criteria for non-human subjects research. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This project was reviewed and received a non-human subjects research determination from the Vanderbilt University Institutional Review Board (No. IRB #151121). Informed consent was not required given the use of a fully deidentified dataset and non-human subjects determination from the Institutional Review Board.

Results

PheWAS

As a GSS 'stimulator', NAC is known to have hepatoprotective effects in acetaminophen toxicity (16). Orienting to these *in vivo* effects, we explored hepatic phenotypes in our PheWAS results to identify potential new indications for NAC. In line with this orientation, a decreased risk of liver-related phenotypes would indicate that the variant is functioning like NAC, and an increased risk of these phenotypes would suggest that the variant is functioning more like an inhibitor of GSS.

In our data (*Table 1*), we observed an increased risk of a constellation of liver-related conditions such as esophageal

Table 1 Glutathione synthetase phenome-wide association study results, missense variant R418Q*

Phecode	Phenotype	Cases (n)	Controls (n)	OR	P	AFF_11 (n)	AFF_12 (n)
530.2	Esophageal bleeding (varices/hemorrhage)	394	18,594	5.9300	0.002337	0	5
261.2	Vitamin B-complex deficiencies	557	21,366	4.5910	0.00661	0	5
571.8**	Liver abscess and sequelae of chronic liver disease	598	22,795	4.2490	0.008865	0	5
573.7	Abnormal results of function study of liver	890	22,795	3.4230	0.01187	0	6
571	Chronic liver disease and cirrhosis	1,312	22,795	2.7070	0.02196	0	7
571.51**	Cirrhosis of liver without mention of alcohol	769	22,795	3.3010	0.02317	0	5
571.5**	Other chronic nonalcoholic liver disease	1,092	22,795	2.7880	0.0282	0	6
573.2	Liver replaced by transplant	368	22,795	4.1420	0.04077	0	3
571.81**	Portal hypertension	399	22,795	3.8190	0.04958	0	3

*, organized by increasing P value; **, within phecode hierarchy, these phecodes are embedded under the main code 571 "Chronic liver disease and cirrhosis". OR, odds ratio; AFF_11, two copies minor allele; AFF_12, one copy minor allele.

bleeding (OR 5.93, P=0.002), liver abscess and sequelae of chronic liver disease (OR 4.25, P=0.009), and abnormal results of function study of liver, a phenotype that is commonly included in a medical record when laboratory testing indicates elevated liver enzymes (OR 3.42, P=0.012). Of note, these phenotypes suggest that both acute and chronic liver disease are reflected in the underlying patient dataset.

In sum, these data indicate that the SNP is behaving *in vivo* like a *GSS* inhibitor (i.e., the opposite of the drug, NAC). Thus, the variety of liver phenotypes in our analysis illustrate with human data that decreased *GSS* is associated with a broad range of liver injury, as is true in acute liver failure (ALF).

Evidence synthesis: GSS in pathways leading to liver injury

After detecting the constellation of hepatic phenotypes in our data, we next explored the literature regarding involvement of glutathione and *GSS* in development of liver dysfunction. The evidence indicates that glutathione deficiency manifests largely through increased susceptibility to oxidative stress, playing an important role in the pathogenesis of various liver diseases (17). It is striking that even though glutathione is the most abundant human thiol, this abundance is rather precarious (18). In a well-nourished individual without *GSS* mutations, glutathione exists in concentrations adequate for detoxification at low levels (19). However, stores can be quickly depleted with significant toxin exposure or other physiologic insult (20). Glutathione efflux further affects cellular redox balance and progression of apoptosis (21).

Cysteine is a conditionally essential amino acid; endogenous synthesis is insufficient during periods of oxidative stress (22), thus explaining why glutathione levels drop substantially during inflammation and other endogenous and exogenous insults, and why NAC can have such a dramatic restorative effect when administered relatively early in the ALI cascade before effects become permanent. Further, the established use of NAC in acetaminophen toxicity is acknowledged to have the most dramatic clinical impact when administered as soon as possible—its ability to prevent and mitigate liver injury and failure in the acute phase led us to focus more specifically on other types of ALF as an indication for NAC (23), inspired by our PheWAS data suggesting a host of hepatic phenotypes associated with decreased GSS.

Briefly, various acute insults (e.g., medication adverse effects, hepatitis A virus, dengue virus, toxin ingestion, excess alcohol intake, heat stroke) directly deplete glutathione with relative rapidity (24-26). Decreased levels of glutathione both lead to progression of liver injury as well as dramatically impair the liver's ability to repair the damage caused by the initial insult. Each of the etiologies for ALF noted above 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 (27-39). NAC, through enhancing glutathione S-transferase activity, affects several

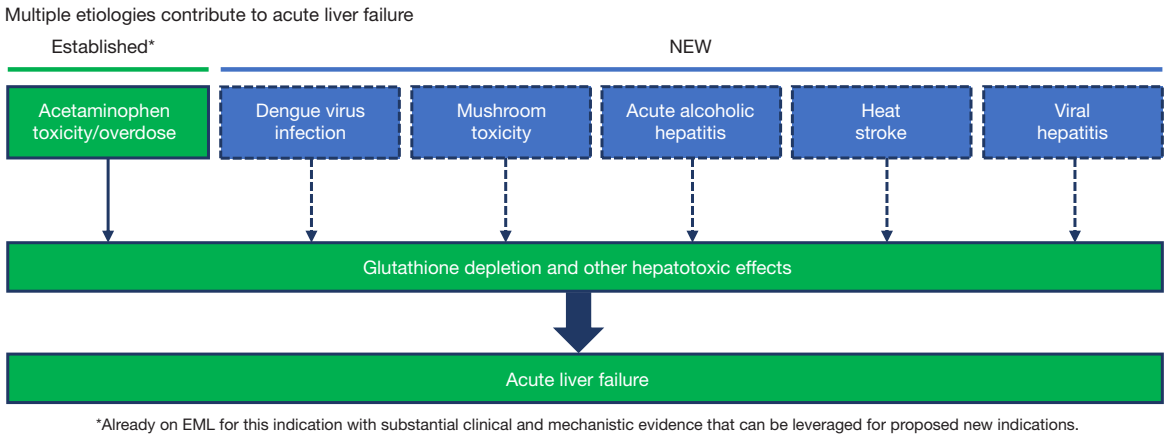

Figure 2 Activity of N-acetylcysteine in non-acetaminophen-induced acute liver failure. EML, Essential Medicines List.

of these mechanisms (16,24,40-42). In addition, NAC has antioxidative, anti-inflammatory, and vasodilatory effects (43), including mitochondrial pathways (26), which can help counteract the adverse effects of impaired liver perfusion and reducing hepatocytes apoptosis due to oxidative stress and immune-mediated injury.

The beneficial effect of NAC in acetaminophen toxicity is attributed specifically to its ability to replenish the liver with the cysteine needed for *de novo* synthesis of glutathione (44). Data also suggests that glutathione depletion also plays an important role in other types of ALF (*Figure 2*), though supportive care remains the primary option for this condition (45).

Evidence synthesis: public health relevance of ALF of various etiologies

While a relatively rare condition, ALF 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 (46,47). ALF affects all age groups, and the causes of ALF are heterogeneous. One of the most well-known and commonly reported is acetaminophen overdose (48). However, a range of other etiologies are described in the literature, associated with a variety of pathophysiologic insults.

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) (49). 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 (50). 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 (51), 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 (52). 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 (53). The WHO notes (49), "*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 4,100 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% (54). A 2015 report by the WHO notes that heat waves are an emerging public health problem as

climate change worsens (55), 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 (55).

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 (56,57).

ALF caused by excess alcohol intake is another serious condition, with estimated 30-day mortality of 30% (58). Its exact incidence is unknown, but some have estimated that its incidence in alcoholics may be up to 20% (59). 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 (60), suggesting that some regions may be at risk of increased prevalence of this type of ALF.

Evidence synthesis: NAC in non-acetaminophen induced ALF

We next reviewed the literature regarding use of NAC in non-acetaminophen induced ALF. Generally, we note a trend toward supporting evidence accrual over time; we observed increasing frequency of publications assessing use of NAC in non-acetaminophen induced liver failure, particularly within the last 10 years.

To inform assessment of therapeutic use of NAC among the various types of ALF, we organized our evidence synthesis by reporting multiple types of ALF, and then by delving specifically into various subtypes of ALF. In line with the heterogeneity of ALF, we identified reports describing NAC use across a broad range of ALF etiologies, suggesting the utility of this intervention across many ALF subtypes.

Practice guidelines

We identified three relevant guidelines. The American Association for the Study of Liver Diseases 2011 guideline notes NAC may improve survival in these patients and should be considered (61) and the 2017 European Association for the Study of the Liver guidelines suggest NAC treatment as standard care for both acetaminophen and non-acetaminophen related liver failure (62). The 2017 American Gastroenterological Association guidelines indicate existing data suggest potential benefit of NAC in non-acetaminophen related ALF but do not recommend use outside of trials, apart from ALF of indeterminate cause (63).

General non-acetaminophen-induced ALF

Eight systematic reviews (*Table 2*) (65,67-70,74,75,82) provide useful insights into the evolution of evidence. While the earlier analyses note potential utility of NAC based primarily on retrospective case reports and series, recent reviews included randomized controlled trials (RCTs) and concluded significant benefit in terms of transplant-free and post-transplantation survival. All noted that adverse effects in this population were consistent with known NAC effects.

In addition to the primary literature captured in these reviews, a 2021 retrospective analysis found improved transplant-free survival and reduced all-cause mortality with extended NAC treatment compared to 72 hours (66). Another retrospective analysis of pediatric data included 61 patients with non-acetaminophen induced liver injury etiologies were treated with NAC compared with 44 patients not receiving NAC; this analysis did not find significant differences in liver function values between the two groups (64).

Non-acetaminophen induced ALF subtypes

Table 3 summarizes data on a NAC use in a range of ALF subtypes. A 2015 meta-analysis analyzed treatment of acute alcoholic hepatitis requiring hospitalization (85), identifying 22 RCTs comprising a total of 2,621 patients and five different interventions. A network meta-analysis of this moderate quality evidence found that the use of corticosteroids in combination with NAC reduced short-term mortality.

A recent systematic review described eleven studies including patients with drug-induced acute liver injury and concluded the existing evidence suggests NAC improves transplant-free survival. The authors of this systematic review (86) noted a risk of bias in some studies they analyzed, making the positive effects on overall survival less conclusive. In addition to the data included in the systematic review, a 2021 randomized controlled trial evaluated the use of NAC in anti-tuberculosis drug induced liver injury and found significantly reduced length of stay,

Table 2 NAC in general non-acetaminophen-induced acute liver injury

Author, year	Design	Total N	Finding(s)	Directionality of efficacy effect
Karaarslan, 2022, (64)	Retrospective cohort	105 (61 receiving NAC)	No significant difference in liver function changes between the groups	=
Shrestha, 2021, (65)	Meta-analysis	11 studies; 1,117	Reduced mortality; reduced mean length of stay; reduced encephalopathy	↑
Bass, 2021, (66)	Retrospective cohort	53	Transplant-free survival greater and lower all-cause mortality at 3 weeks with >72 hours NAC *vs.* 72 hours NAC	↑
Jawaid, 2021, (67)	Meta-analysis	3 studies; 344	Improved transplant-free survival; no difference in length of stay	↑
Niu, 2021, (68)	Meta-analysis	2 studies; 60	No improvement in overall survival	=
Walayat, 2021, (69)	Meta-analysis	7 studies; 667	Improved odds of transplant-free survival and post-transplant survival	↑
Siu, 2020, (70)	Systematic review	2 studies; 183 adults/174 children	No difference in survival, transplant rate, or adverse events	=
Nabi, 2017, (71)	RCT	80	Improved survival; reduced length of stay	↑
Darweesh, 2017, (72)	Observational study	155	Improved transplant-free survival; reduced length of stay	↑
Reuben, 2016, (73)	Observational study	2,070	Increased off label use in the US; improved overall survival and transplant-free survival	*↑
Hu, 2015, (74)	Meta-analysis	616	Improved transplant-free survival and post-transplant survival; no difference on overall survival	↑
Sales, 2013, (75)	Systematic review	8 case reports; 3 studies	Suggest marginally improved transplant-free survival	↑
Squires, 2013, (76)	RCT	184	No difference in 1-year survival or length of stay; decreased 1-year transplant-free survival	↓
Lee, 2009, (77); Stravitz, 2013, (78); and Singh, 2013, (79)	RCT	173	Improved transplant-free survival and transplant rate	↑
Mumtaz, 2009, (80)	Prospective non-blinded study with historical controls	91	Reduced mortality	↑
Kortsalioudaki, 2008, (81)	Retrospective review	170	Improved 10-year survival and transplant-free survival; no difference in length of stay	*↑
Sklar, 2004, (82)	Systematic review	7 studies	Microvascular regional benefits seen; clinical outcomes not previously studied	*↑
Ben-Ari, 2000, (83)	Retrospective observational	7	Improved mean peak prothrombin time, serum factor V, aspartate aminotransferase and alanine aminotransferase levels	*↑
Harrison, 1991, (84)	Case series	8	Increased oxygen delivery and consumption	*↑

↑, increased efficacy; ↓, decreased efficacy; =, similar efficacy among groups; *↑, presumed positive effect. NAC, N-acetylcysteine; Total N, total number of patients; RCT, randomized controlled trial.

Table 3 Evidence describing use of NAC in non-acetaminophen-induced ALF subtypes

Author, year; target condition	Design	Total N	Finding(s)	Directionality of efficacy effect
Singh, 2015, (85); severe acute alcoholic hepatitis	Meta-analysis	2,621	Corticosteroids combined with NAC reduced short-term mortality	*↑
Sanabria-Cabrera, 2022, (86); drug induced acute liver injury	Systematic review	11 studies	Improved TFS; inconclusive difference in overall survival; possible hepatoprotective effect; adequate safety profile	*↑
Moosa, 2021, (87); drug induced acute liver injury	Randomized controlled trial	102	Reduced LOS; no difference in time to ALT reduction or in-hospital mortality; 5 patients experience adverse events due to NAC	↑ for secondary outcome
Borlak, 2018, (88); drug induced acute liver injury	Retrospective cohort	51	Combined NAC + prednisolone treatment resulted in significant improvements in ALT, AST, and INR within 2 weeks; treated patients resolved more rapidly than those treated with standard of care	↑
Shah, 2023, (89); suspected clozapine associated ALF	Case report	1	Aminotransferases continued to trend slightly upward; acute encephalopathy improved	*↑
Alanli, 2021, (90); amiodarone associated ALF	Case report	1	Liver enzymes improved after 72 hours of NAC	*↑
Carothers, 2020, (91); suspected remdesivir associated liver injury	Case series	2	Liver enzymes improved in both patients after NAC initiation; one patient fully recovered and one patient died of suspected septic shock	*↑
Liu, 2020, (92); mushroom toxicity	Systematic review	506	Mortality rate 11%; liver transplant rate 4.3%; adverse anaphylactic reactions to NAC occurred in 5%	*↑
Karvellas, 2016, (93); mushroom toxicity	Registry cohort	18	NAC used in nearly all patients (PTS 88% *vs.* TFS 80%)	No inference possible
Vanooteghem, 2014, (94); mushroom toxicity	Case series	4	All patients survived without need for liver transplant	*↑
Montanini, 1999, (95); mushroom toxicity	Case series	11	All patients survived, 1 with preceding liver disease required liver transplant	*↑
Dawra, 2021, (96); rodenticide ingestion	Case reports	3	Two patients fully recovered; one patient did not survive	*↑
Getsuwan, 2021, (97); cassia occidentalis seed ingestion	Case report	1	Liver function improved after initiation of NAC and patient fully recovered	*↑
Monzon, 2020, (98); heat stroke-associated liver injury	Case report	1	Improvements in AST, ALT, and total bilirubin	*↑
Will, 2019, (99); heat stroke-associated liver injury	Case report	1	Improved liver function; laboratory values returned to normal by 8 weeks	*↑
Aquilina, 2018, (100); heat stroke-associated liver injury	Case report	1	Improved liver function	*↑
Saleem, 2015, (101); viral hepatitis (A and E)—pediatric	Case series	40	Improved liver enzymes and prothrombin time	*↑

Table 3 *(continued)*

Table 3 *(continued)*

Author, year; target condition	Design	Total N	Finding(s)	Directionality of efficacy effect
Sotelo, 2009, (102); viral hepatitis A—pediatric	Case series	12	Improved liver function and coagulation parameters	*↑
Sriphongphankul, 2021, (103); dengue fever	Retrospective cohort	16 of 33 received NAC	Higher rate of ALF resolution and survival in NAC-treated group	*↑
Dissanayake, 2021, (104); dengue fever	Retrospective case series	40	Statistically significant reduction of ALT and AST with NAC infusion. No adverse events. One patient died	*↑
Lewis, 2020, (105); dengue fever	Case report	1	Progressed to ALF after starting NAC but improved soon after; patient fully recovered	*↑
Kularatne, 2018, (106); dengue fever	Retrospective case series	2 of 10 received NAC	Both cases fully recovered	*↑
Dalugama, 2018, (107); dengue fever	Case report	1	AST and ALT gradually declined; lactate normalized; serum creatinine reduced; discharged day 9	*↑
Dalugama, 2017, (108); dengue fever	Case report	1	Gradual reduction in AST and ALT, prothrombin time normalized; discharged day 5; patient fully recovered	*↑
Tan, 2016, (109); dengue fever—pediatric	Retrospective case series	2 of 4 received NAC	All cases fully recovered; no adverse effects of NAC	*↑
Habaragamuwa, 2014, (110); dengue fever	Case report	1	50% reduction in AST and ALT after 48 hours; patient fully recovered	*↑
Manoj, 2014, (111); dengue fever	Case report	1	After NAC, recombinant factor VIIa, and other aggressive support measures, patient fully recovered	*↑
Tan, 2013, (112); dengue fever	Retrospective case series	7 of 8 received NAC	All patients discharged within median of 13.5 days; ALT normalized by long term follow up; no adverse effects of NAC	*↑
Paramasivam, 2013, (113); dengue fever	Retrospective cohort	13 of 85 received NAC	Reduced time to ALT reduction; increased LOS (authors note patients given NAC were more severe)	*↑
Senanayake, 2013, (114); dengue fever—pediatric	Retrospective case series	7	Improved biochemical profiles from first dose onwards; all patients fully recovered	*↑
Gan, 2013, (115); dengue fever—pediatric	Case report	1	Discharged at day 25 with lingering left hemiparesis; no residual deficit at 2 months post illness	*↑
Abeysekera, 2012, (116); dengue fever	Case report	1	Discharged on day 10; patient fully recovered	*↑
Lim, 2012, (117); dengue fever—pediatric	Case report	1	Rapid decrease in AST and ALT; coagulation profile normalized; no adverse effects of NAC	*↑
Kumarasena, 2010, (118); dengue fever	Retrospective case series	8	No adverse effects attributed to NAC; 5 patients recovered; 3 with coma grades III–IV died; no adverse effects of NAC	*↑

↑, increased efficacy; *↑, presumed positive effect. NAC, N-acetylcysteine; Total N, total number of patients; TFS, transplant free survival; LOS, length of stay; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PTS, post-transplant survival; ALF, acute liver failure.

though there was no difference in mortality (87). Adverse reactions in five patients were consistent with known NAC effects. A 2018 retrospective cohort compared flupirtine-induced liver injury patients treated with NAC as well as prednisolone to those who were not and concluded the combined treatment resulted in significant improvements in laboratory parameters and faster recovery (88). We also identified one additional systematic review that included both acetaminophen-induced ALF as well as ALF associated with other drug injury in pediatric patients, comprising 25 articles; the synthesis in this review did not include substantive differentiation between the two types of ALF, and reached the conclusion that this literature is heterogenous and further research is warranted (119). A 2023 report describing a case of ALI suspected to be related to clozapine noted that acute encephalopathy improved with use of NAC and supportive care, though aminotransferases continued to trend upward (89). Improvement in liver function tests was observed in a 2021 case of amiodarone-associated ALI (90) and a 2020 report of two cases of suspected remdesivir-associated ALI (91).

Several reports also suggested potential utility in liver injury and failure due to toxin exposure. A systematic review examined the literature on use of NAC in mushroom induced ALF, identifying 13 studies comprising 506 patients, concluding that NAC appeared to be safe and beneficial in affected patients (92). One child with ALF after ingestion of Cassia occidentalis seeds showed improvement in liver function and fully recovered with use of NAC infusion (97). One series of ALF due to rodenticide ingestion suggested improvement of liver function with administration of NAC in two patients; a third patient did not survive (96).

In addition to its representation in the general studies, we identified three case reports suggesting improvement in liver function and other outcomes with use of intravenous (IV) NAC in patients with heat-related ALF (98-100).

We found two small retrospective case series of NAC use in children with ALF in acute viral hepatitis (101,102), reporting improvement of liver enzymes and coagulation parameters and satisfactory NAC tolerance.

Finally, data regarding NAC use in dengue comprises retrospective cohort studies, case series, and case reports and totaling 89 patients with dengue infection receiving NAC. Adverse effects were either not observed or consistent with known NAC effects. In one retrospective case series of 40 adults with severe dengue infection and liver injury, investigators noted significant improvement in liver function tests after NAC infusion, with no adverse events and one patient death (104). In a retrospective cohort focusing on 33 pediatric patients with dengue-associated ALF, 16 patients received NAC. Authors note a greater improvement in liver function and survival among the NAC-treated children (103). Data from additional small case series and case reports indicated gradual normalization of liver function tests in 26 patients (15 adults; 11 infants and children) receiving NAC in moderate to severe dengue illness (105-118).

NAC safety in non-acetaminophen-induced ALF

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 2,500 patients (studies represented in *Tables 2*,*3*). 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, toxin exposures, acute viral hepatitis, dengue fever) concordant with the established safety profile of this agent in its use for acetaminophen induced ALF.

The safety profile of NAC in acetaminophen toxicity has accrued over decades. The most common side effect includes nausea and vomiting, which is reported to occur in up to 23% of patients (120). Oral NAC is rarely associated with more severe side effects like angioedema (11,121). IV administration of NAC is also usually well-tolerated but is associated with a higher risk of adverse effects, the most commonly described include nausea and vomiting at a frequency of up to 9% (120) and anaphylactoid reactions (rash, pruritis, angioedema, bronchospasm) at a frequency of 8.2% (75% were cutaneous) (122). It is noted that hypersensitivity reactions may be managed by decreasing the infusion rate or discontinuing the infusion (121,123). Serious adverse reactions and fatalities are rare but have occurred with IV treatment (these patients also had a history of asthma) (124).

Evidence synthesis: NAC dosing and administration in non-acetaminophen induced ALF

The presence of NAC as a recommendation within practice guidance and systematic review of non-acetaminophen ALF is supportive of this medication as a potential complement to supportive care in these patients. However,

we acknowledge that the body of evidence we identified includes a preponderance of small and retrospective studies, and further rigorous evaluation would be very helpful in further elucidating the role that this pharmacologic agent can play in treating ALF of various etiologies.

As with any off-label use of a medication, clinical judgment of the totality of evidence combined with patient and clinical context remains the best approach for determining whether NAC is a reasonable option in a given patient. Here, we summarize the typical approach used for NAC dosing to inform its use when clinical judgment suggests it is warranted.

While the existing evidence base includes some variation, NAC approaches generally paralleled its use in acetaminophen toxicity. This literature suggests that IV NAC should be initiated as soon as ALF is detected, typically defined via presence of one of the precipitating conditions (e.g., acute viral hepatitis, heat stroke, dengue) combined with alterations in clinical status and liver function tests. The approach employed in the included reports was usually (I) 150 mg/kg administered over 1 hour; (II) 50 mg/kg over 4 hours; (III) 100 mg/kg over 16 hours; (IV) 100 mg/kg/day until up to 7 days after initiation, guided by clinical response.

To avoid fluid overload, diluent volume should be reduced when needed. Food and Drug Administration (FDA) prescribing information for IV NAC notes that half-life was increased by 80% in patients with hepatic impairment, though not deemed clinically meaningful (125). Guidance indicates that hypersensitivity reactions may be managed by decreasing the infusion rate or discontinuing the infusion altogether. Clinicians should weigh relative risk and benefit of use in pregnancy. The US Food and Drug Administration label for IV NAC indicates that acetylcysteine crosses the placenta and notes limited data on use during pregnancy, precluding formal assessment of risk (125). The label notes that no adverse developmental outcomes were observed in rats or rabbits (125).

Discussion

Key findings

Application of our established drug repurposing methods detected an indication for use of NAC in ALF that is concordant with the literature. In a PheWAS analysis, alterations in the *GSS* gene showed an association with a cluster of conditions related to acute liver injury and failure. Thorough review of the literature confirmed this finding, suggesting a therapeutic opportunity for NAC in non-acetaminophen-induced ALF.

This indication leverages a sound foundation of trial and observational evidence supporting the safety and utility of NAC in preventing further progression of ALF in adults and children. It also encompasses 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. 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.

While ALF remains relatively rare, it affects children and adults across the world and confers significant morbidity and mortality (46,47). 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, the current analysis indicates that PheWAS, the biomedical literature, and existing knowledge on the biological pathway for action of NAC on the liver align to suggest utility in non-acetaminophen-induced liver failure when clinician judgment finds it to be a reasonable strategy, expanding beyond the use of NAC for acetaminophen toxicity that is currently articulated in the WHO's EML.

Strengths and limitations

The current analysis leverages the methods and experience of an experienced drug repurposing team; the methods employed have been developed and refined for generation of a number of repurposing opportunities across a variety of therapeutic candidates and conditions, as well as identification of potential safety signals associated with various agents (4-10,126-128). Further, the notable concordance between the PheWAS results and the primary literature provides additional confidence in the strength and validity of the identified connection between NAC and ALF. Our findings are also concordant with recent discussions related to repurposing of NAC in various indications, including ALF (25,129,130).

We acknowledge that this evidence set does not involve large scale, pivotal efficacy trials, so is insufficient as an indication for inclusion in the WHO EML; however,

it might be useful in individual treatment decisions or for inclusion in other information summaries by health authorities. The literature also does not include head-to-head comparisons with other "active" interventions, precluding a more thorough and quantified estimate of the comparative effectiveness of NAC. We hope this analysis may inspire other researchers to undertake research to further contribute to the evidence supporting this treatment option.

Comparison with similar research

As described extensively in the preceding evidence synthesis, the biomedical literature includes a firm foundation of observational data elucidating the efficacy and safety of NAC in a variety of ALF etiologies ALF beyond liver injury induced by acetaminophen 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, suggesting that this intervention would provide a valuable addition to the supportive care provided to these patients. Further, published guidelines support this option, which may potentially serve as one of few treatments available in some countries.

Implications and actions needed

We propose the evidence presented here warrants consideration of NAC as a safe and viable treatment option as a complement to supportive care for non-acetaminophen related ALF; sharing the evidence surrounding this therapeutic strategy will provide critical guidance to health workers regarding standard dosing and administration of NAC as supplemental treatment.

Conclusions

For several decades the WHO EML has played a critical role in guiding the selection and financing of medicines in numerous countries worldwide. Knowing the impact the EML can have on medicines' availability will drive Project Remedi to continue to identify and validate new therapeutic uses for drugs listed. Project Remedi's overarching goal is to help increase the knowledge surrounding the medications on the WHO EML, as well as the access to safe, affordable, and effective treatments for diseases worldwide. Application of our drug repurposing methods, including PheWAS and thorough primary evidence assessment, identified a new use of NAC in non-acetaminophen induced ALF. Future work will continue to explore use of our methods to identify repurposing opportunities for medicines on the WHO EML, with the hope that we can add to the therapeutic strategies available to healthcare providers and patients in a broad range of resource settings and contribute to meaningful improvements in global health.

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Footnote

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-40/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-40/coif). R.N.J., L.A.Z., J.J.A., M.M.J., J.K.S.R., G.R.B., and J.M.P. report that this project was supported by NCATS funding received by their institution. G.R.B. is on the board of directors for Cumberland Pharmaceuticals, who produces an intravenous formulation of acetylcysteine. R.S.W. reports that Aurum has received two research grants from the German Ministry of Education and Research to

conduct clinical trials of NAC in patients with tuberculosis and he led parts of this research. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This project was reviewed and received a non-human subjects research determination from the Vanderbilt University Institutional Review Board (No. IRB #151121). Informed consent was not required given the use of a fully deidentified dataset and non-human subjects determination from the Institutional Review Board.

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