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Intravenous Glutathione: A Promising Therapy for the Alcoholic Liver Disease

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Abstract

Alcoholic liver disease (ALD) and sepsis are life-threatening conditions marked by severe oxidative stress. Chronic alcohol use triggers oxidative stress and inflammation that damages liver cells. Glutathione (GSH), a tripeptide consisting of gamma glutamyl cysteinyl glycine possesses a thiol group and participates in oxidation reduction reactions, acting as a principal cellular scavenger of free radicles. GSH is present in large concentrations in the liver, and its endogenous levels are depleted in ALD, exacerbating the condition. Intravenous GSH supplementation has shown promising results in improving liver function and reducing fibrosis markers in ALD patients. Intravenous GSH treatment has demonstrated the potential to reduce oxidative injury and mortality rates in patients with sepsis in the intensive care unit. The versatility of GSH in mitigating oxidative stress, inflammation, and tissue damage and proven safety and tolerability profile make it a valuable adjunct to current treatments. Further research is imperative to comprehensively unravel the therapeutic benefits of GSH injection adjunct to standard of care in patients with ALD and sepsis.

Keywords: *Glutathione, Alcoholic liver disease, Sepsis, Antioxidants, Intensive care unit, Intravenous.*

Introduction

Alcoholic liver disease (ALD) is highly prevalent globally and associated with significant morbidity and mortality. In 2017, the global prevalence of alcohol-associated compensated cirrhosis was estimated to be 23.6 million cases, while the prevalence of decompensated cirrhosis was reported to be 2.5 million cases.[1] This collective burden of alcohol-associated cirrhosis and liver cancer accounts for approximately 1% of all deaths worldwide, and it is projected to increase further.[1] Several studies conducted at various centres in India have consistently identified alcohol as the primary cause of ALD, accounting for a prevalence ranging from 30% to 70% of all reported cases of this condition.[2]

Alcohol use disorder is a major risk factor for sepsis and associated mortality.[3] Individuals with alcohol dependence have higher rates of sepsis (12.9% vs. 7.6%), organ failure (67.3% vs. 45.8%), septic shock (3.6% vs. 2.1%), and mortality (9.4% vs. 7.5%) than do those without alcohol dependence.[4] Alcoholic liver disease is an independent risk factor for sepsis morbidity and sepsis-associated death.[5] In the intensive care unit (ICU), ALD-related complications can pose life-threatening risks, including variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepato-pulmonary syndrome, severe infections, and septicemia.[6] Some patients may already have infections upon admission, which further contribute to the progression of alcoholic hepatitis (AH). In other cases, infections may develop after admission or after the initiation of corticosteroid treatment, leading to increased short-term mortality.[7] During hospital admission, patients diagnosed with alcoholic hepatitis often display signs of systemic inflammatory response syndrome (SIRS), even in the absence of an infection. Elevated levels of lipopolysaccharide in plasma have been linked to the progression of SIRS, leading to the development of multi-organ failure and an increased risk of mortality.[8,9]

Alcohol induced oxidative stress is the main contributor to the pathogenesis of ALD and hepatotoxicity.[10,11] Patients with ALD undergo antioxidant deficiency and glutathione (GSH) depletion.[12] Therefore, establishing an optimal therapeutic strategy for severe ALD requiring ICU admission remains a challenge. While abstinence, adequate nutrition, and corticosteroids are recommended as first-line therapies for ALD, their effectiveness may be limited.

Antioxidant therapy is of considerable interest as adjunct therapy for ALD patients.[10] Exogenous administration of GSH, glutathione esters or GSH precursors (glutamine or cysteine, N-acetyl-L-cysteine, alpha-lipoic acid) as intravenous infusion, orally, or as aerosol restores cellular GSH concentration and improves patient outcomes. Various clinical studies have shown the efficacy and safety of glutathione therapy adjunct to standard of care in patients with ALD and sepsis admitted to the intensive care unit (ICU). This review aims to collate the potential therapeutic benefits of glutathione therapy in the management of patients admitted to the ICU due to severe alcoholic liver disease (ALD) and sepsis.

Pathophysiology of Hepatic Disorders

ALD is a chronic condition that involves progressive deterioration of liver functions due to persistent oxidative injury, inflammation, infection, and degeneration of liver parenchyma.[13] ALD encompasses a wide range of diseases, starting from early alcoholic fatty liver (AFL) or hepatic steatosis to more severe fibrosis and cirrhosis accompanied by complications, such as ascites, portal hypertension, hepatic encephalopathy, and hepatocellular carcinoma (HCC) (table 1).[10] Acute-on-chronic liver failure (ACLF) is one of the major causes of early mortality in ALD patients, wherein persistent alcohol intake causes severe alcoholic hepatitis (AH) and death due to systemic inflammatory response syndrome, sepsis, and multiorgan failure. The natural trajectory of ALD is depicted in Fig 1.

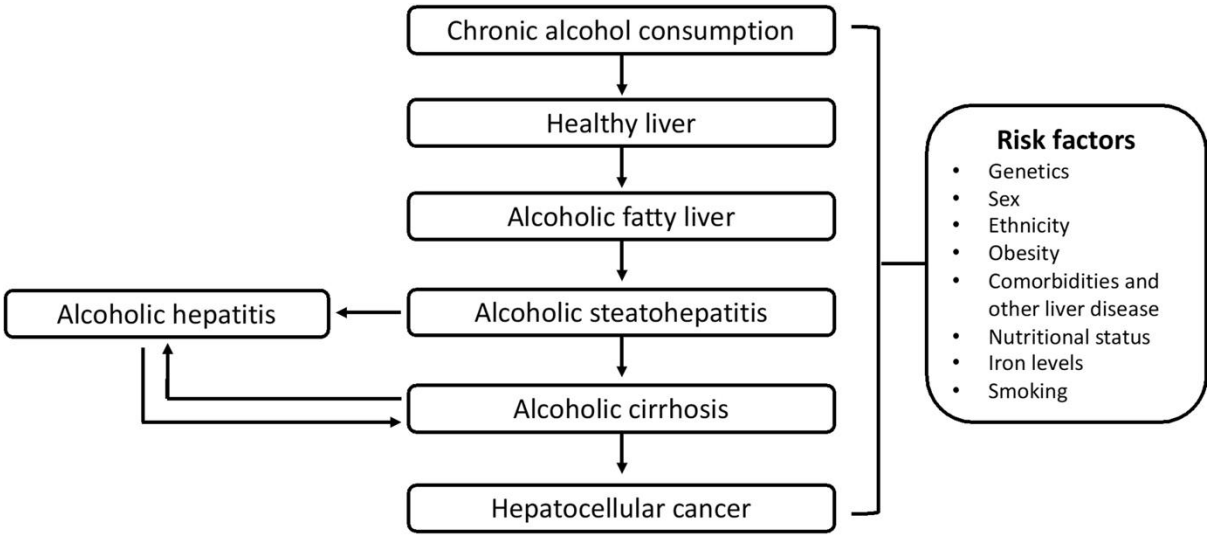

Fig 1: The natural trajectory of alcoholic liver disease

Table 1: Different stages of hepatic disorders

Steatosis and steatohepatitis	**Fibrosis**	**Cirrhosis**	**Decompensated cirrhosis and acute on chronic liver failure**	**Hepatocellular carcinoma**
-Histologically characterized by hepatocyte ballooning, inflammatory cell infiltrate (usually neutrophils), and Mallory bodies within hepatocytes (specific for ALD).[14, 15] -Clinically indicated by jaundice, canalicular cholestasis and intracellular bile.[14, 15]	-Chronic ethanol consumption initiates transformation of hepatic stellate cells (HSCs) and structural changes in the liver, such as loss of hepatocyte microvilli and sinusoidal endothelial fenestrae, leading to hepatic function decline.[14, 15] -HSCs undergo complex activation:[14, 15] - increased proliferation, contractility, and chemotaxis. - irregular extracellular matrix deposition characterizing fibrosis. - Inflammation -Excessive fibrogenic response[14, 15]	-Persistent inflammation and fibrogenesis replaces liver parenchyma with scar tissue, severely affecting vascular architecture.[14, 15] -Cirrhosis development progresses from **compensated** to **decompensated** portions of liver causing portal hypertension and/or liver failure.[14, 15]	major cause of morbidity and mortality in cirrhotic patients.[14, 15] Cirrhosis amplifies intrahepatic vasoconstriction and resistance, leading to portal hypertension.[14, 15] Systemic and splanchnic circulation raise NO, inducing vasodilation, reducing systemic resistance and activating the renin-angiotensin-aldosterone system (RAAS), causing hyperdynamic circulation.[14, 15]	Most concerning issue in ALD, primarily arising from alcoholic cirrhosis.[14, 15] Acetaldehyde is a crucial tumor trigger, being both a toxin and reactive mutagen, generating stable DNA adducts, mutations, exchanges, inhibiting DNA repair.[14, 15] Epigenetic modifications through alcohol alter DNA methylation, silencing tumor suppressor genes and activating oncogenes via hypomethylation.[14, 15]

a) Oxidative Stress: the key player in alcoholic liver disease

Alcohol intake triggers oxidative stress and impairs the intracellular antioxidant defense mechanisms.[16] In hepatocytes, alcohol dehydrogenase enzyme oxidizes alcohol into acetaldehyde and acetate. Both ROS and acetaldehyde are extremely toxic and carcinogenic agents. They can bind to DNA and proteins and induce structural and functional alterations. Acetaldehyde disrupts mitochondrial structure and impairs its functions, causing decreased ATP generation via the respiratory chain, and further production of ROS (Fig 2).[17,18]

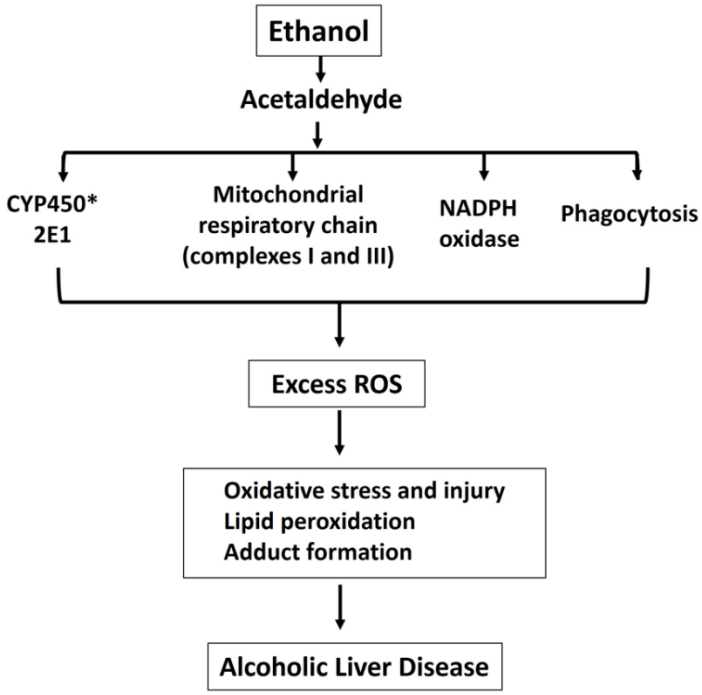

Fig 2: Role of oxidative stress and reactive oxygen species in alcoholic liver disease

b) Combating Oxidative Stress: a therapeutic approach to manage alcoholic liver disease

Oxidative stress plays a critical role in the progression and deterioration of ALD. Antioxidant molecules that enhance GSH levels have shown therapeutic promise for managing the early stages of ALD. Studies on ethanol-fed rodents have shown significant reductions in steatosis, ER stress, and mitochondrial damage with supplementation of S-adenosylmethionine or betaine.[19] However, further evidence is needed to determine the effectiveness of these compounds in different stages of ALD.[19]

The 2018 EASL (European Association for the Study of the Liver) clinical practice guidelines recommend intravenous use of N-acetylcysteine (NAC) for five days, adjunct to corticosteroid treatment in patients with severe alcoholic hepatitis (Grade B2).[9] A multicentre trial in patients with severe acute alcoholic hepatitis showed that intravenous administration of NAC in combination with standard glucocorticoid therapy for five days significantly reduced mortality in patients at one month (27%; 23 of 85 patients died) compared to the standard therapy alone (38%; 34 of 89 patients died).[20] Further studies with prospective data are required to support the efficacy of such combinations in ALD patients.[21]

Glutathione

GSH, known as L-glutamyl-L-cysteinyl-glycine, is a tripeptide that serve as a primary cellular

redox buffer to protect against oxidative stress.[22] It is present at high concentrations (1-10 mM) in mammalian cells, particularly in the liver.[22] The physiological functions of glutathione are summarized in table 2.

Table 2: Physiological roles of GSH

Function	Description
Antioxidant Defense	Protection of cellular macromolecules and organelles from both endogenous and exogenous reactive oxygen and nitrogen species (ROS/RNS) [55, 29] • Detoxification of hydroperoxides, peroxynitrites, and lipid peroxides. • Scavenging oxidant molecules, including superoxide anion, hydroxyl radical, nitric oxide, and carbon radicals. • Peroxide buffering by oxidation of GSH to GSSG utilizing glutathione peroxidases (Gpxs) and glutathione reductases (GRs)
Metabolic Detoxification	Detoxification of xenobiotics and exogenous compounds (heavy metals and persistent organic pollutants (POPs)) [55, 29]
Cell Cycle	Cell cycle regulation[55, 29]
Immune System	Modulation of the functioning of the immune system[55, 29]
Protection from Electrophilic Substrates	protection against electrophilic substrates by facilitating their conjugation and reducing peroxides along with glutathione S-transferase[55, 29]
Cofactor for Antioxidant Enzymes	• cofactor for several antioxidant enzymes[55, 29] • facilitates the recycling of vitamins C and E[55, 29]

a) Depletion of glutathione in various disease condition

GSH is oxidized into glutathione disulfide (GSSG); the oxidized form is reconverted into GSH by the NADPH-dependent enzyme glutathione reductase (GR). The ratio of GSH to GSSG determines redox status of cells and is often used as a marker of cellular toxicity. The depletion of GSH in chronic degenerative diseases and age-related decline in functions is associated with the progressive deterioration of mitochondrial function due to damage to mtDNA and structural proteins.

Patients diagnosed with ALD exhibit a strong correlation between the progression of ASH and a depletion in mitochondrial GSH (mGSH) levels by approximately 45-60%.[23] Another cause of mGSH depletion in individuals with chronic alcohol intake is disruption of the GSH transport across the inner mitochondrial membrane (table 3).[24, 25]

Table 3: Diseases Associated with GSH Depletion

Category	Description
Neurodegenerative disorders[26]	Alzheimer's, Parkinson's, and Huntington's diseases, amyotrophic lateral sclerosis, Friedreich's ataxia
Pulmonary disease [27]	Chronic obstructive pulmonary disease, asthma, and acute respiratory distress syndrome
Immune diseases[27]	Acquired immunodeficiency syndrome, autoimmune diseases
Cardiovascular diseases[28]	Hypertension, myocardial infarction, cholesterol oxidation
Chronic age-related diseases	Cataract, macular degeneration, hearing impairment, and glaucoma
Liver diseases[29]	Non-alcoholic fatty liver disease (NAFLD), Alcoholic liver disease, Hepatitis, other liver disorders
Cystic fibrosis[30]	Cystic fibrosis
Aging[31]	Age-related health conditions commonly seen in the older population

b) Therapeutic use of glutathione

Both direct treatment with GSH and the promotion of glutathione production through supplementation have been successfully employed in various diseases. These therapeutic approaches have demonstrated efficacy in conditions such as Parkinson's disease, various cancer types, emphysema, chronic obstructive pulmonary disease, nephropathy, lead poisoning, non-alcoholic fatty liver disease, alcoholic hepatitis, and COVID-19 among others. The clinical applications of GSH span a wide range of diseases, showcasing its versatility and effectiveness.

Clinical Efficacy of Glutathione Therapy in Hepatic Disorders and Sepsis

a) Hepatitis

Due to the significant role of oxidative stress in the advancement of ALD, the utilization of antioxidant agents as part of medical management has been suggested in various pre-clinical and clinical studies. While other antioxidants, such as N-acetylcysteine (NAC), can aid in restoring the reduced form of GSH, they are unable to compensate for the reduced de novo synthesis or the liver's secretion of GSH to other cells.[32] Intravenous administration of GSH has shown promising results in patients with chronic steatohepatitis leading to improved liver functions.[33]

In patients with chronic steatosis, high-dose intravenous GSH treatment resulted in a significant and sustained improvement in hepatic injury biomarkers, such as bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), gamma-glutamyl transferase (GGT) even months after the treatment was discontinued.[33] One study on Indian patients with acute hepatitis (n=84) showed that treatment with glutathione injection (600 mg) for 7 days significantly improved the levels of principle liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and GGT irrespective of aetiology and age group.[34] The two major causes of hepatitis in the study participants were alcohol use (34.5%) and viral infection (27.4%). Another study on patients with alcoholic hepatitis showed that intravenous GSH treatment at a dosage of 1200 mg per day led to a significant improvement in liver function indices ($p < 0.01$) without causing any adverse effects.[35] Furthermore, treatment of patients with chronic Hepatitis B infection with intravenous GSH (1200 mg) resulted in improved liver function and significant reduction in ALT, AST, total bilirubin, total bile acids levels ($p < 0.05$), and hepatic fibrosis, as indicated by decreased hyaluronic acid, collagen IV, laminin, and transforming growth factor-β1 ($p < 0.05$). Patients also showed significant improvement in levels of serum cytokines, such as tumour necrosis factor-α, interleukin-6, and interleukin-8 ($p < 0.05$).[36] These findings suggest that GSH treatment not only improves liver functions, but also inhibit inflammation and hepatic fibrosis in patients with chronic Hepatitis B.[36]

b) Hepatocellular carcinoma

The primary risk factors associated with the development and progression of hepatocellular carcinoma (HCC) include chronic infections caused by viral hepatitis, as well as alcoholic and non-alcoholic fatty liver disease, often accompanied by metabolic syndrome. In patients with advanced HCC (aHCC), hepatic arterial infusion chemotherapy (HAIC) prolongs the survival of patients,[37] but it can worsen liver damage, particularly in patients with liver cirrhosis (LC) due to depletion of hepatic GSH stores rendering hepatocytes more vulnerable to apoptosis.[38] A study conducted by Momiyama et al. investigated the effects of intravenous GSH (100 mg daily) on the hepatotoxicity of chemotherapy in patients with liver cirrhosis and advanced HCC over a two-year period.[39] The administration of intravenous GSH demonstrated a preventive effect on active fibrogenesis in liver

cirrhosis patients with advanced HCC.[39] The study emphasized that GSH might safeguard endothelial cells against oxidative injury through detoxification of free radicals and also inhibit the release of mediators from leukocytes and/or Kupffer cells, thus preventing the activation of hepatic stellate cells.[39]

c) Non-alcoholic fatty liver disease

Oral administration of GSH has demonstrated positive effects on hepatic metabolism and NAFLD. In a pilot study, NAFLD patients were orally administered GSH for a duration of four months.[40] The study observed significant reductions in blood ALT levels and triglyceride content after the treatment period.[40] While it has been suggested that exogenous GSH may be degraded into its amino acid constituents during digestion, many studies have shown that the administration of GSH precursors, such as serine and glycine, can effectively mitigate NAFLD in both animal models and humans.[41, 42]

d) Sepsis

Sepsis is characterized by GSH depletion, an imbalance in redox state and severe oxidative stress that impairs the host's response to infection and inflammation and may lead to organ failure and death.[43,44] Different stages of sepsis are accompanied by cytokine production, hormonal changes, nutritional imbalance, hyperglycaemia, and physical inactivity, further contributing to fluctuations in GSH levels among patients.[44,45] Therefore, treatment with GSH, thiol antioxidants and other GSH-replenishing agents may be useful than other therapies that target the overall immune functionality.[43]

To investigate the early stages of sepsis, a study measured hepatic GSH levels in a septic-sheep model.[46] After six hours, the animals developed hypotension, hypoxemia, and granulocytopenia that were closely accompanied by a significant reduction in intrahepatic GSH levels.[46] In critically ill children with limited nutritional support, a study showed significant decrease of approximately 60% in whole blood GSH levels within 48 hours of sepsis diagnosis.[47]

According to an observational study, MOF patients in the ICU exhibited significantly lower levels of total GSH compared to healthy volunteers or stable out-patients with COPD, with levels reaching only 60-70% of the healthy control levels.[48]

Intravenous administration of GSH at a dosage of 70 mg/kg/day to patients with septic shock within 24 hours demonstrated noteworthy protection against oxidative injury on days 3 and 5 of the treatment.[49] At Day 5, a significant reduction in peroxidative indices was observed.[49] The GSH treatment exhibited a 50% reduction in mortality by day 10 compared to untreated patients ($p < 0.01$).[49] Moreover, by Day 10, the clinical scores, including acute physiology and chronic health evaluation II (APACHE II) and logistic organ dysfunction score (LOD), were significantly lower compared to baseline values ($p < 0.01$) and the control group values ($p < 0.05$).[49] Notably, patients receiving high doses of intravenous GSH therapy reported no adverse effects in any of the clinical trials.[49]

Pharmacokinetics and Dosing Regimen of Glutathione

Clinical studies have demonstrated that GSH can be administered to patients via different routes, viz. oral, intravenous, subcutaneous, or aerosols with doses ranging from 250-1,000 mg. In humans, the absorption and bioavailability of GSH via oral route might be hindered due to hydrolysing effects of gamma-glutamyl transferase enzyme present in the human gastrointestinal tract.[50] Pharmacokinetic investigations revealed that GSH at a loading dose of 1.69 g/kg and a maintenance dosage of 5.70 g/hr/kg are needed to reach 1 mM GSH which is a minimum requirement of extracellular concentration to suppress significantly the intracellular ROS.[35] Studies based on oral

supplementation of GSH did not measure plasma GSH levels, and hence it remains unknown whether therapeutic effect is achieved following oral intake of GSH.[51,52] Intravenous glutathione, on the other hand has shown protective effects against oxidative stress mediated damage in septic shock patients.[49]

In patients with acute hepatitis due to alcohol use or hepatitis infection, administration of glutathione injection (600 mg) for 7 days was tolerated well and significantly improved liver enzymes. [34] In small-scale study involving 9 patients with Parkinson's disease who received intravenous GSH (600 mg, twice daily) and assessed over a period of 30 days,[53] showed improvement in clinical outcomes with a 42% decline in clinical disability caused by Parkinson's disease.[53] The therapeutic effect of GSH reportedly lasted for 2-4 months.[53] In 2009, Milla et al. assessed the use of intravenous GSH (1500 mg/mL) in managing neurotoxicity caused by oxaliplatin infusion in 27 colorectal cancer patients.[51] They observed a significant decrease in neurotoxicity compared to the placebo group, without any adverse events. [51]

Recently, a case series examined the treatment of two patients with cough dyspnoea associated with COVID-19-related pneumonia using oral and intravenous GSH (2 g).[54] Both patients reported improvement in dyspnoea within one hour of administration. The repeated use of 2 g of oral and intravenous GSH proved effective in providing additional relief from respiratory symptoms.[54] The study proposed that oral and intravenous GSH could serve as a new treatment approach to inhibit NF-κB and regulate "cytokine storm syndrome" in patients with COVID-19-derived pneumonia.[54]

Summary

Restoring GSH homeostasis in patients with ALD is of utmost importance due to its regulatory functions, involvement as a cofactor in enzymatic reactions, and participation in hepatic detoxification mechanisms. Intravenous glutathione (GSH) has emerged as a promising therapeutic approach for sepsis and ALD patients admitted in ICU as it restores GSH levels in the lungs, enhances the functions of immune cells, and regulates pro-inflammatory cytokines and free radicals. Administration of glutathione injection 600 mg twice daily for a week has shown significant improvement in liver functions and patient recovery. Intravenous GSH supplementation is safe, well-tolerated, and does not interfere with ongoing standard of therapy. GSH injections are widely available, cost-effective, and have a good safety profile and should be considered as an adjunctive therapy for patients admitted in the ICU with manifestations of alcoholic liver disease and sepsis.

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