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Author manuscript

*Alcohol*. Author manuscript; available in PMC 2017 September 16.

Published in final edited form as:

*Alcohol*. 2016 September ; 55: 51–59. doi:10.1016/j.alcohol.2016.08.005.

## Alcohol and Lung Injury and Immunity

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### Abstract

Annually, excessive alcohol use accounts for more than \$220 billion in economic costs and 80,000 deaths, making excessive alcohol use the third leading lifestyle-related cause of death in the US. Patients with an alcohol-use disorder (AUD) also have an increased susceptibility to respiratory pathogens and lung injury, including a 2–4-fold increased risk of acute respiratory distress syndrome (ARDS). This review investigates some of the potential mechanisms by which alcohol causes lung injury and impairs lung immunity. In intoxicated individuals with burn injuries, activation of the gut-liver axis drives pulmonary inflammation, thereby negatively impacting morbidity and mortality. In the lung, the upper airway is the first checkpoint to fail in microbe clearance during alcohol-induced lung immune dysfunction. Brief and prolonged alcohol exposure drive different post-translational modifications of novel proteins that control cilia function. Proteomic approaches are needed to identify novel alcohol targets and post-translational modifications in airway cilia that are involved in alcohol-dependent signal transduction pathways. When the upper airway fails to clear inhaled pathogens, they enter the alveolar space where they are primarily cleared by alveolar macrophages (AM). With chronic alcohol ingestion, oxidative stress pathways in the AMs are stimulated, thereby impairing AM immune capacity and pathogen clearance. The epidemiology of pneumococcal pneumonia and AUDs is well established, as both increased predisposition and illness severity have been reported. AUD subjects have increased

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susceptibility to pneumococcal pneumonia infections, which may be due to the pro-inflammatory response of AMs, leading to increased oxidative stress.

### Keywords

alcohol; lung immunity; lung injury; gut-liver-lung axis; airway cilia; alveolar macrophage

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### Introduction

Alcohol-use disorders (AUDs) have long been linked to increased susceptibility to lung infections. In 1789, Dr. Benjamin Rush, the first surgeon general of the United States, observed that individuals with an affinity for alcohol had a higher incidence of pneumonia and tuberculosis (Rush, 1808). In 1885, Sir William Osler reported that alcohol is one of the greatest predisposing factors to the development of pneumonia (Osler, 1892). The Centers for Disease Control estimates that 80,000 annual deaths in the United States are attributed to excessive alcohol ingestion, making it the third leading lifestyle-related cause of death (Mokdad, Marks, Stroup, & Gerberding, 2004). In 2006, excessive alcohol ingestion was responsible for ~\$224 billion in healthcare costs, including emergency room and physician office visits (Bouchery, Harwood, Sacks, Simon, & Brewer, 2011). Compared to non-alcoholics, patients with a history of alcohol abuse are twice as likely to develop sepsis, and those with sepsis are twice as likely to develop acute respiratory syndrome (ARDS) (Jong, Hsiue, Chen, Chang, & Chen, 1995; Joshi & Guidot, 2007; Moss, 2005). Alcohol-induced lung injury and immune dysfunction contribute to a higher risk for developing respiratory infections, leading to increased morbidity and mortality in patients with a history of AUDs (Moss, 2005).

This critical review delves into some of the potential mechanisms by which alcohol causes lung injury and impairs lung immunity. With a burn injury, alcohol intoxication exacerbates the pulmonary response through the gut-liver-lung pro-inflammatory response. In the lung, prolonged alcohol exposure causes desensitization of cilia in the upper airway, making motility and pathogen clearance resistant to stimulation due to oxidant stress-related mechanisms. Chronic alcohol ingestion also induces oxidative stress within the microenvironment of the alveolar space, which impairs the capacity of alveolar macrophages to phagocytose and clear bacteria. Translational studies show that when alveolar macrophages are isolated from individuals with AUDs and are stimulated with pneumococcal infections, they exhibit increased pro-inflammatory cytokine production that may promote increased severity of illness. Collectively, these alcohol-associated alterations are likely contributors to deleterious outcomes in the setting of pulmonary infections among people with unhealthy alcohol consumption.

### **Alcohol intoxication exacerbates pulmonary response to remote injury: gut-liver-lung axis regulates pulmonary inflammation after intoxication and burn injury**

Alcohol intoxication increases both the risk and severity of accidental injury (Smith, Branas, & Miller, 1999; Tulloh & Collopy, 1994). Alcohol use is associated with increased complications and delays the recovery time after injuries such as lacerations (Curtis, Hlavin,

Brubaker, Kovacs, & Radek, 2014), fractures (Lauing, Roper, Nauer, & Callaci, 2012), and burns (Silver et al., 2008). Burns are a devastating injury affecting nearly 500,000 people in the US annually, resulting in 40,000 hospitalizations (ABA, 2012). Half of adult burn patients are intoxicated at the time of hospital admission and have increased morbidity, mortality, and socioeconomic costs, relative to their non-intoxicated counterparts (Grobmyer, Maniscalco, Purdue, & Hunt, 1996; Kelley & Lynch, 1992; Silver et al., 2008). Most intoxicated burn patients are considered binge drinkers as opposed to chronic alcoholics (Savola, Niemelä, & Hillbom, 2005), and present with an average blood alcohol content (BAC) of 150 mg/dL (Silver et al., 2008), which is associated with twice the infection risk, greater requirement for surgical procedures, longer stays in the intensive-care unit, and increased need for mechanical ventilation (Brezel, Kassenbrock, & Stein, 1988; Davis et al., 2013; Grobmyer et al., 1996; Silver et al., 2008).

In burn patients, compromised pulmonary function portends a poor prognosis and develops independently of the presence or absence of inhalation injury (Liffner, Bak, Reske, & Sjöberg, 2005), and likely contributes to the poorer outcomes associated with burn injury in AUD patients. The lungs may be particularly susceptible to damage due to their delicate architecture, numerous resident inflammatory cells, and high degree of vascularization. Experimental evidence suggests that the worsened clinical outcomes when alcohol precedes a burn are due to the ability of alcohol to fundamentally alter the pulmonary physiological response to a remote and indirect injury, causing a decrease in lung function (Shults et al., 2015). In a mouse model, a single dose of alcohol (1.1 g/kg) prior to a 15% total body surface area (TBSA) scald burn results in increased pulmonary edema (M. M. Chen, Bird, et al., 2013; M. M. Chen, O'Halloran, Ippolito, Choudhry, & Kovacs, 2015; M. M. Chen, Palmer, et al., 2013; M. M. Chen et al., 2014), neutrophil infiltration (Bird, Morgan, Ramirez, Yong, & Kovacs, 2010; Bird, Zahs, et al., 2010), and susceptibility to infection (Murdoch, Brown, Gamelli, & Kovacs, 2008) relative to either insult alone and despite no direct injury to the lung itself.

Alcohol exacerbates post-burn levels of systemic pro-inflammatory cytokines, such as interleukin-6 (IL-6) (M. M. Chen, Palmer, et al., 2013; Colantoni et al., 2000; Li, Akhtar, Kovacs, Gamelli, & Choudhry, 2011), which can quickly accumulate in the pulmonary vasculature (M. M. Chen, Bird, et al., 2013). Clinically, elevated IL-6 correlates with increased mortality risk in burn patients (Drost et al., 1993; F. L. Yeh, Lin, Shen, & Fang, 1999). Furthermore, the absence of the IL-6 gene or IL-6 blockade confers protection against the increased pulmonary inflammation of the combined insult of alcohol and burn (M. M. Chen, Bird, et al., 2013), suggesting a crucial role for IL-6 in driving this aberrant response. Therefore, the cellular source and impetus for IL-6 production may be key to understanding how alcohol modulates the pulmonary response to remote injury, resulting in subsequent alterations in lung vasculature, lung dysfunction, and susceptibility to infection.

The high baseline bacterial content of the intestines represents an enormous potential reservoir for systemic infections and sepsis after injury (Bahrami, Redl, Yao, & Schlag, 1996; Deitch, 2001; Hassoun et al., 2001). Animal studies demonstrate that post-burn intestinal permeability is exacerbated when intoxication precedes the injury (Choudhry, Fazal, Goto, Gamelli, & Sayeed, 2002; Kavanaugh et al., 2005), leading to greater

translocation of bacteria and bacterial products, such as lipopolysaccharide (LPS), into the lymphatic (Baron et al., 1994; Deitch, Maejima, & Berg, 1985; Zabs, Bird, Ramirez, Choudhry, & Kovacs, 2013) and portal (Deitch, 1990) systems. This occurs secondary to alcohol's potentiating effect on bradykinin signaling, thereby enhancing post-burn third spacing of fluid which, together with catecholamine-mediated splanchnic vasoconstriction, leads to ischemic injury in the bowel (M. M. Chen et al., 2015). Portal blood then carries the bacterial products to the body's largest tissue-fixed macrophage population, the Kupffer cells of the liver. Kupffer cells continuously sample portal blood for foreign antigens and orchestrate the hepatic response to injury (Wisse, 1974). Kupffer cells can become activated when LPS binds to toll-like receptor 4 (TLR4), an interaction dependent on its co-receptor, CD14 (Su et al., 2002). Even a single dose of alcohol may sensitize Kupffer cells to LPS via a variety of mechanisms, including changes in CD14 expression (Enomoto et al., 1998), lipid rafts (Dolganiuc, Bakis, Kodys, Mandrekar, & Szabo, 2006), and mitogen-activated protein kinases (MAPKs) (Kishore, Hill, McMullen, Frenkel, & Nagy, 2002; Kishore, McMullen, & Nagy, 2001), the functional consequence of which is increased TLR4 signaling and cytokine production. At low levels, cytokines, such as IL-6, are beneficial to hepatocyte survival, but exposure to levels above an acceptable threshold can be detrimental (Jin et al., 2006). When alcohol precedes a burn, there is both increased stimulus for and sensitivity to TLR4 signaling, leading to harmful levels of IL-6 relative to either insult alone. Accordingly, the combined insult has been shown to result in greater hepatic damage as evidenced by elevated serum transaminase levels, hepatic triglycerides, and liver-weight to bodyweight ratio (M. M. Chen et al., 2014, 2015; M. M. Chen, Palmer, et al., 2013). Using the same model of intoxication and burn in which mice are deficient in TLR4 but not TLR2, IL-6 production and organ damage are attenuated after alcohol intoxication and burn injury compared to wild-type mice (Bird, Zabs, et al., 2010).

The interaction between the intestinal microbiome and the liver is known as the gut-liver axis and is thought to regulate a myriad of human diseases (Compare et al., 2012; Seo & Shah, 2012; Szabo & Bala, 2010; Tabibian, O'Hara, & Larusso, 2012; Volta, Caio, Tovoli, & De Giorgio, 2013). Because alcohol can increase post-burn intestinal damage while simultaneously augmenting the hepatic IL-6 response to intestine-derived LPS (M. M. Chen et al., 2014), the gut-liver axis may play an especially prominent role in how alcohol drives post-burn pulmonary inflammation. Supporting this idea are findings that sterilization of the gut before intoxication and burn or pharmacologic restoration of intestinal permeability after injury decreases bacterial translocation and subsequent hepatic damage and IL-6 production (M. M. Chen et al., 2014). Interestingly, interrupting the crosstalk between the gut and liver after intoxication and burn corresponds to diminished pulmonary inflammation as well (M. M. Chen et al., 2014). Similarly, antecedent depletion of Kupffer cells leads to decreased systemic IL-6 and improved pulmonary parameters after intoxication and burn despite no effect on the alveolar macrophage (AM) population (M. M. Chen, O'Halloran, Shults, & Kovacs, in press), again highlighting the role of the gut-liver axis in driving pulmonary inflammation in this setting.

These findings do not exclude the importance of direct effects of alcohol on the lung, including impairment of AM phagocytosis (Karavitis, Murdoch, Deburghraeve, Ramirez, & Kovacs, 2012; Murdoch et al., 2008) and pulmonary neutrophil sequestration (Murdoch,

Karavitis, Deburghraeve, Ramirez, & Kovacs, 2011). Rather, they suggest that the full effects of alcohol on the pulmonary response to remote injury may be multifactorial and involve effects on multiple organ systems.

### **Alcohol-mediated ciliated airway dysfunction**

Ciliated airway cells clear inhaled particles from the lung, thus acting as the first line of defense against inhaled pathogens. During alcohol ingestion, these ciliated cells are uniquely exposed to vapor-phase alcohol during breathing. The high alcohol blood concentration in the bronchial circulation is directly exposed to the ciliated airways. This occurs because, during alcohol ingestion, alcohol is off-gassed from the bronchial circulation of the conducting airways into the exhaled breath, resulting in alcohol flux through the airway epithelium into the exhaled air (George, Hlastala, Souders, & Babb, 1996). Indeed, this is the mechanism for delivery of alcohol into the airways, which is the basis for the Breathalyzer™ test. Importantly, brief low-dose alcohol exposure has very different effects on airway cilia than prolonged high-dose alcohol exposure. These bimodal effects of alcohol on airway cilia function share related but different mechanisms.

Alcohol modifies airway cilia in two ways. Brief exposure to moderate concentrations of alcohol stimulates cilia to beat faster through a nitric oxide-dependent mechanism (Sisson, Pavlik, & Wyatt, 2009). Conversely, prolonged alcohol exposure causes desensitization of cilia, making motility resistant to stimulation, a process known as alcohol-induced ciliary dysfunction (AICD), through a mechanism related to oxidant stress (Simet, Pavlik, & Sisson, 2013a; Wyatt, Gentry-Nielsen, Pavlik, & Sisson, 2004). While the mechanisms of alcohol-driven cilia stimulation and AICD are known to involve dysregulation of key cilia kinases and phosphatases that regulate motility, the upstream triggers of these post-translational processes are unknown. One mechanism may be through post-translational modifications in key kinases and phosphatases that regulate the effects of alcohol on airway ciliary control. Specifically, studies have focused on alcohol's ability to modulate phosphorylation and *S*-nitrosylation of target molecular regulatory pathways in airway cilia, thereby providing insight into the differential effects of brief versus prolonged alcohol exposure on the ciliated airway epithelium.

Two approaches to explore protein changes in alcohol-exposed isolated bovine tracheal cilia were developed. 1) 2-dimensional gel analysis of ciliary proteins briefly exposed to modest concentrations of alcohol was performed. The alcohol-modified ciliary protein blots were probed with phospho-antibodies, and mass spectroscopy was used to detect unique alcohol-driven phosphorylated protein sites. 2) The formation of *S*-nitrosylated ciliary proteins was separately examined with mass spectroscopy to identify post-translationally modified ciliary proteins after prolonged alcohol exposure and experiments to mimic AICD.

### **Brief alcohol exposure increases phosphorylation of heat shock protein 90 (HSP90) in isolated demembrated bovine tracheal cilia**

Using the first approach, brief alcohol exposure (1 h with 100-mM ethanol) significantly stimulated serine/threonine phosphorylation of only 6 out of over 600 (1%) ciliary proteins. Most of the 6 were structural proteins, but conspicuous among that group was the striking

phosphorylation of HSP90. Functional experiments were performed to confirm that HSP90 is required for alcohol to stimulate cilia via a chaperone and translocation mechanism, likely involving intraflagellar transport (Simet, Pavlik, & Sisson, 2013b).

### **Prolonged alcohol exposure causes a 20-fold increase of S-nitrosylation of protein phosphatase 1 (PP1) in isolated demembrated bovine tracheal cilia**

With prolonged alcohol exposure (24 h with 100-mM ethanol), S-nitrosylation was decreased in 158 of 626 (25%) ciliary proteins but increased in 121 of 626 (19%) ciliary proteins. Of these proteins, 10 unique S-nitrosylation sites, corresponding to 6 unique proteins, demonstrated a >20-fold increase in S-nitrosylation by alcohol exposure. Four of these unique sites corresponded to different residues of PP1. Preliminary functional cilia experiments demonstrated that prolonged alcohol exposure of ciliated cells upregulated PP1 activity and blocked the cilia desensitization seen in AICD (Price, Pavlik, Sisson, & Wyatt, 2015).

### **Alcohol-induced alveolar macrophage (AM) oxidative stress and dysfunction**

When the upper airway fails to clear inhaled pathogens, they enter the alveolar space where they are primarily cleared by AMs. In the alveolar space, AM surveillance is the first line of defense in cellular immunity because the AMs ingest and clear pathogens as well as release cytokines and chemokines to recruit other immune cells (Aderem & Underhill, 1999). Although the molecular mechanisms are poorly understood, oxidative stress results in impaired phagocytosis and diminished pathogen clearance. Alcohol induces an oxidized microenvironment within the lung. In a sampling of the alveolar epithelial lining fluid (ELF) of otherwise healthy patients with a history of AUDs, chronic alcohol ingestion depleted the critical antioxidant glutathione (GSH) and caused corresponding oxidation of the GSH pool to glutathione disulfide (GSSG), resulting in oxidation of the GSH/GSSG redox potential (Liang, Yeligar, & Brown, 2012; Moss et al., 2000; F. L. Yeh et al., 1999). GSH and oxidation of the GSH/GSSG potential were similarly depleted in the exhaled breath condensate (EBC) of alcoholic subjects (M. Y. Yeh, Burnham, Moss, & Brown, 2008). Experimental animal models of chronic alcohol ingestion demonstrated similar oxidation of the lung microenvironment. GSH levels were abrogated in the lungs and bronchoalveolar lavage (BAL) fluid of ethanol-fed rats (Holguin, Moss, Brown, & Guidot, 1998) and mice (Yeligar, Harris, Hart, & Brown, 2014). Collectively, these studies indicate that chronic alcohol abuse alters GSH homeostasis in the lung, leading to an increasingly oxidized pulmonary microenvironment.

The AM is acutely affected by chronic alcohol ingestion and the oxidized lung microenvironment that results from alcohol abuse. Through multifactorial mechanisms, alcohol stimulates oxidative stress within the AM, resulting in impaired phagocytic capacity and decreased bacterial clearance. The mechanisms involved in alcohol-induced AM oxidative stress include altered GSH/GSSG redox status, decreased intracellular zinc, attenuated nuclear factor erythroid 2 [NF-E2]-related factor 2 (Nrf2), diminished granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor beta (GM-CSFR $\beta$ ), depleted peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), enhanced NADPH oxidases (Nox), and increased transforming growth factor beta-1 (TGF $\beta$ <sub>1</sub>). Experimental



manipulations of each of these mechanisms attenuated alcohol-induced oxidative stress and improved AM immune function.

AMs depend on the GSH in the ELF pool for cellular uptake and protection against the oxidative stress generated during immune responses (Liang, Harris, & Brown, 2014). During chronic alcohol ingestion, AMs themselves exhibit alterations in GSH/GSSG redox status. As observed in the ELF, AMs isolated from ethanol-fed mice had decreased GSH levels, increased GSSG, and increased oxidation of the GSH/GSSG redox potential. This was associated with compromised *in vitro* fluorescent *Staphylococcus aureus* (*S. aureus*) internalization and impaired *in vivo* clearance of *Klebsiella pneumoniae* (*K. pneumoniae*) (Yeligar et al., 2014). These studies demonstrated that alcohol-induced alterations in AM GSH/GSSG redox status resulted in impaired AM phagocytic capacity and bacterial clearance.

Zinc deficiency and down-regulation of Nrf2, GM-CSFR $\beta$ , and PPAR $\gamma$  are additional mechanisms that drive AM oxidative stress during chronic alcohol ingestion. AM isolated from alcoholic subjects had decreased intracellular zinc levels, and *ex vivo* zinc treatments restored AM capacity to bind and internalize *in vitro* fluorescent *S. aureus* (Mehta, Yeligar, Elon, Brown, & Guidot, 2013). Additionally, ethanol-fed female mice had decreased AM zinc levels, zinc transporter expression, and bacterial clearance (Konomi, Harris, Ping, Gauthier, & Brown, 2015). Nrf2, a zinc-dependent protein essential for antioxidant defenses, was also depleted by chronic alcohol ingestion in rat AMs (Staitieh, Fan, Neveu, & Guidot, 2015), causing impaired *in vivo* lung bacterial clearance of *K. pneumoniae* (Mehta et al., 2011). GM-CSFR $\beta$ , which initiates intracellular signaling cascades responsible for AM function including phagocytosis, was decreased in AM from ethanol-fed rats (Joshi et al., 2005, 2006; Joshi, Mehta, Jabber, Fan, & Guidot, 2009) and alcoholic subjects (Mehta et al., 2013) could be restored by GM-CSF treatments. Further, alcohol-induced AM depletions in PPAR $\gamma$ , which is associated with augmented oxidative stress, and treatment with PPAR $\gamma$  ligands reversed impaired phagocytic function and bacterial clearance capacity (Yeligar, Mehta, Harris, Brown, & Hart, 2015). Collectively, these studies indicate that diminutions in intracellular zinc, Nrf2, GM-CSFR $\beta$ , and PPAR $\gamma$  result in an oxidized lung redox status and subsequent AM dysfunction.

Reactive oxygen species (ROS) play important roles in disease pathogenesis due to their involvement in complex physiological processes (Thannickal & Fanburg, 2000). Nox proteins, which are membrane-associated enzymes that use NADPH as an electron donor to catalyze the reduction of molecular oxygen to superoxide and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) (D. I. Brown & Griendling, 2009), are major sources of ROS in the lungs under physiologic conditions (Piotrowski & Marczak, 2000). Nox isoforms Nox1, Nox2, and Nox4 are expressed in the lung, where Nox1 and Nox2 primarily produce superoxide and Nox4 primarily produces H<sub>2</sub>O<sub>2</sub> (Mittal et al., 2007; Polikandriotis et al., 2006). Additionally, TGF $\beta$ <sub>1</sub> up-regulates Nox4 expression (D. I. Brown & Griendling, 2009). Increased Nox1, Nox2, and Nox4 in ethanol-exposed mouse embryos (Dong, Sulik, & Chen, 2010), and ethanol-fed rat and mouse lungs (Polikandriotis et al., 2006; Wagner, Yeligar, Brown, & Hart, 2012), were found to be key sources of ROS production. AMs from ethanol-fed mice showed that increases in the expression of Nox1, Nox2, Nox4 (Yeligar, Harris, Hart, &

Brown, 2012), and TGF $\beta_1$  (S. D. Brown & Brown, 2012) enhanced oxidative stress and impaired AM phagocytosis. These studies demonstrated that alcohol-induced expression of Noxes and TGF $\beta_1$  are also associated with AM oxidative stress and phagocytic dysfunction.

Collectively, these studies demonstrate that chronic alcohol ingestion induces an oxidized microenvironment within the lung that subsequently induces AM derangements, as manifested in an impaired capacity to phagocytose and clear bacteria from the alveolar space. Alcohol stimulates oxidative stress through multiple, and potentially interactive, mechanisms including oxidation of the GSH/GSSG redox status, decreased intracellular zinc, attenuated Nrf2, diminished GM-CSFR $\beta$ , depleted PPAR $\gamma$ , enhanced Noxes, and increased TGF $\beta_1$ . Therefore, strategies to reverse any of these mechanisms for alcohol-induced exaggerated oxidative stress in the AM may improve lung immune function and susceptibility to developing respiratory infections in patients with a history of AUDs.

### **Unraveling the alcohol-pneumococcal pneumonia relationship: clues from translational research**

Worldwide, individuals with AUDs are disproportionately affected by *Streptococcus pneumoniae*, the most common etiologic agent in bacterial pneumonia. Among patients hospitalized with pneumococcal infections, up to 20–30% will meet criteria for an AUD (de Roux et al., 2006; Garcia-Vidal et al., 2010; Plevneshi et al., 2009; van der Poll & Opal, 2009). Further, pneumonia in the setting of AUDs is often associated with extra-pulmonary spread of disease, including bacteremia, sepsis, and septic shock (Garcia-Vidal et al., 2010; Gentile, Sparo, Mercapide, & Luna, 2003; Plevneshi et al., 2009; Shariatzadeh, Huang, Tyrrell, Johnson, & Marrie, 2005). Both pneumonia and sepsis are major risk factors for the development of ARDS; therefore, in patients with AUDs who develop pneumococcal pneumonia, respiratory failure (de Roux et al., 2006) and the development of ARDS (Moss, Bucher, Moore, Moore, & Parsons, 1996; Moss et al., 2003) are unfortunately common in US intensive-care units. In ARDS patients who have AUDs, clinical outcomes are frequently poorer (Clark et al., 2013; Moss et al., 1996; O'Brien et al., 2007), including increased mortality and requirement for persistent hospitalization. Notably, anti-pneumococcal vaccines in individuals with AUDs are problematic in that this population is less likely to receive preventive medical services (Merrick et al., 2008), and that an efficacious response to pneumococcal vaccination is less assured (Benin et al., 2003; Luján et al., 2013). Therefore, understanding the pathophysiologic mechanisms underlying increased severity of illness and poorer outcomes in the setting of pneumococcal pneumonia among those with AUDs represents a major clinical need.

AUDs have been associated with both pulmonary and systemic oxidative stress (M. Y. Yeh, Burnham, Moss, & Brown, 2007) that may contribute to poorer outcomes in the setting of pulmonary infections, including pneumococcal pneumonia. Specifically, oxidative stress has been associated with a myriad of deleterious effects on pulmonary immune system function, including poorer apoptotic cell clearance (Moon, Lee, Park, Chong, & Kang, 2010), induction of autophagy (Malaviya, Laskin, & Laskin, 2014), abnormalities in ciliary morphology and function (Sunil et al., 2013), and impaired AM phagocytosis (Mehta et al., 2013). GSH is the quantitatively most abundant pulmonary antioxidant, and abnormalities in



*GSH homeostasis*, favoring oxidation, have been consistently observed in the alveolar space in the setting of AUDs (Burnham, Brown, Halls, & Moss, 2003; M. Y. Yeh et al., 2007). Chronic alcohol exposure's relationship to oxidative stress in the systemic circulation (Burnham et al., 2012; Yang et al., 2010), liver (C. H. Chen, Pan, Chen, & Huang, 2011; Leung & Nieto, 2013; Sid, Verrax, & Calderon, 2013), gut (Abdelmegeed et al., 2013; Keshavarzian et al., 2009; S. M. Tang, Gabelaia, Gauthier, & Brown, 2009), and brain (Herrera et al., 2003), both in animals and humans, has also been noted. Importantly, pulmonary GSH homeostasis remains abnormal even after abstinence from alcohol (Burnham et al., 2003, 2012).

The precise impact of alcohol-associated oxidative stress on pulmonary innate immunity remains to be determined in humans, but may represent one modifiable factor that could positively influence outcomes in AUD patients with pneumococcal pneumonia. As noted above, AMs are responsible for initiating and regulating the pulmonary immune response in the setting of infection. When stimulated by pathogen-associated molecular peptides (PAMPs), AMs secrete a variety of pro-inflammatory chemokines and cytokines, including IL-6, IL-1 $\beta$ , and tumor necrosis factor (TNF)- $\alpha$ . Although these mediators play an important role in generating an immune response against invading pathogens (D. Tang, Kang, Coyne, Zeh, & Lotze, 2012), they have also been implicated in the pathogenesis of lung injury and ARDS (Meduri et al., 1995; Park et al., 2001). Since bacterial pneumonia is a common risk factor for the development of ARDS (Matthay, Ware, & Zimmerman, 2012), the marked lung inflammation, followed by progressive epithelial and endothelial damage, and subsequent neutrophil influx to the alveolar space (Williams & Chambers, 2014), are also thought to be related, in part, to PAMP activation of AMs (Aggarwal, King, & D'Alessio, 2014; Herold, Mayer, & Lohmeyer, 2011; Rosseau et al., 2000; Steinberg et al., 1994). Earlier investigations have supported an association between AUDs with diminished AM activation (Omidvari, Casey, Nelson, Olariu, & Shellito, 1998). However, in experiments with human BAL cells that are comprised of ~90% AMs, it was recently reported that AUDs appear to be associated with an activated, pro-inflammatory BAL cell phenotype with an exaggerated response to LPS (Gaydos et al., 2016; O'Halloran et al., 2016). Moreover, data indicated that the BAL cells' response may be partially driven by oxidative stress (Gaydos et al., 2016). Other pre-clinical investigations performed in models of chronic alcohol exposure further support a pro-inflammatory monocyte response to LPS stimulation *in vitro* (Mandrekar, Bala, Catalano, Kodys, & Szabo, 2009), as well as augmented BAL neutrophils in response to LPS exposure *in vivo* (Boé et al., 2010). Therefore, AMs may be activated in the setting of AUDs, and upon exposure to pathogens, AMs display an over-exuberant, pro-inflammatory response that contributes to the increased morbidity in pneumonia and the predisposition to develop ARDS.

Preliminary experiments in a small number of healthy subjects with AUDs and smoking-matched controls (n = 10 in each group) were performed to determine if exposure of BAL cells (~90% AMs) to heat-killed *S. pneumoniae* protein (ATCC #55143, strain JY2008) at doses ranging from 0–10  $\mu$ g over a 42-h time period would elicit a pro-inflammatory response, analogous to what was previously observed with LPS (Gaydos et al., 2016). BAL cell elaboration of IFN $\gamma$ , IL-6, and TNF $\alpha$  were increased among AUD subjects with the 10- $\mu$ g *S. pneumoniae* protein dose after 18 h in culture ( $p < 0.05$ ). Addition of 10-mM NAC

concurrent with *S. pneumoniae* protein diminished, but did not normalize AM pro-inflammatory cytokine secretion at 18 hours' culture time. In separate experiments, when NAC was added *after* BAL cells had been in culture with *S. pneumoniae* protein for 18 h, IL-6, TNF $\alpha$ , and IFN $\gamma$  secretions were less than in BAL cells cultured with *S. pneumoniae* protein, but without NAC, after 42 h in culture.

These data suggest that when BAL cells (primarily AMs) from individuals with AUDs are stimulated by pathogens, pro-inflammatory cytokine production is more robust. The over-exuberant response by AMs may have implications for the severity of illness among individuals with pulmonary infections. Modulation of AM oxidative stress represents a potential mechanism to restore appropriate immune cell function in the setting of pneumococcal infection.

## Conclusion

Patients with AUDs have enhanced susceptibility to lung injury and respiratory infections, which increase economic costs, morbidity, and mortality. There are several potential mechanisms by which alcohol causes lung injury and impairs lung immunity. Alcohol intoxication, combined with burn injuries, activates the gut-liver axis and drives pulmonary inflammation, promoting morbidity and mortality. Other mechanisms that activate the gut-liver axis may have similar results when superimposed on alcohol intoxication. During alcohol-induced lung immune dysfunction, the upper airway is the first checkpoint to fail in the clearance of respiratory pathogens due to differential post-translational modifications of novel proteins that control cilia function. Proteomic approaches are needed to identify novel alcohol targets and post-translational modifications in airway cilia for therapeutic interventions. When inhaled pathogens are not cleared in the upper airway, they enter the alveolar space, where they are phagocytized and cleared by AMs. With chronic alcohol ingestion, oxidative stress pathways in the AM are stimulated, thereby impairing AM immune capacity and pathogen clearance. AUDs increase both the predisposition and illness severity of pneumococcal pneumonia infections, which may be due to the pro-inflammatory and oxidative stress response of AMs.

These combined studies suggest that alcohol-induced gut leakiness and liver macrophage activation may drive cytokine expression, resulting in systemic oxidative stress and lung injury. This lung injury starts with the desensitization of the ciliated airway epithelium, causing impaired clearance of inhaled pathogens from the upper airway. Altered activation of alcoholic alveolar macrophages in the lower airway not only impairs bacterial phagocytosis and clearance, but may also induce the release of more cytokines into the circulation. Kupffer cells, resident liver macrophages, demonstrate up-regulation of pro-inflammatory transcription factors and pathways, including hypoxia inducible factor-1 alpha and activator protein-1 (Yeligar, Machida, & Kalra, 2010). Circulating cytokines may further perpetuate systemic oxidative stress that results from alcohol-use disorders. This cycle of systemic oxidative stress and the effects it may have on the gut-liver-lung axis have been summarized in Fig. 1.

Although macrophages are derived from monocytes, the ability of AMs to be recruited into the alveolar space suggests that they represent a population of phagocytes present in this microenvironment that are very different from the resident macrophages of other tissues. During alcohol use, the AM response to remote injury and systemic oxidative stress renders the host susceptible to infection due to an over-exuberant, pro-inflammatory response that perpetuates even further systemic oxidative stress. However, AMs exhibit an immunosuppressed phenotype. In fact, some studies suggest that alcohol compromises host defenses against bacterial pneumonia, such as *K. pneumoniae*, by suppressing the recruitment and bactericidal activity of polymorphonuclear leukocytes into the lung (Nelson et al., 1991) and attenuating lung expression of CXC chemokines bearing the Glu-Leu-Arg motif, which attracts T cells (Happel et al., 2007). There is high plasticity in AM activation that influences how they clear microbes and respond to pathogens. The molecular mechanisms by which AM activation affects their response, and their plasticity in range of responses to pathogens and clearance of microbes, warrant further study. The commonly accepted distinguishing factor between AM activation states centers around their ability to perform phagocytosis. In AMs isolated from human subjects with alcohol-use disorders, phagocytosis is only impaired by ~50% (Mehta et al., 2013; Yeligar et al., 2015), suggesting a heterogeneous AM population where some cells can phagocytize and clear bacteria from the alveolar space and others cannot.

Additionally, current tests that are commonly used to identify individuals with alcohol-use disorders and to categorize severity of consumption, including the Short Michigan Alcohol Screening Test and the Alcohol Use Disorders Identification Test (AUDIT), do not factor in other clinical variables that may affect the response of AMs to various stimuli, such as age, sex, race/ethnicity, or environmental effects of cigarette smoking, that are common among unhealthy alcohol consumers. Therefore, clinical investigations should carefully characterize these potential confounders to most accurately study the effect of alcohol on outcome variables since these confounders have the potential to contribute to the heterogeneity of human AM populations and phenotype plasticity. Further study in suitably powered populations is warranted to delineate and characterize heterogeneous AM populations and their phenotypes in individuals with alcohol-use disorders.

Focused proteomic approaches are needed to identify alcohol-driven post-translational modifications of key functional proteins that regulate airway host defenses. Such approaches will have broad applications in the identification of novel protein targets for alcohol in the lungs and other organs affected by alcohol exposure. These studies may well lead to the development of useful biomarkers of alcohol exposure and therapeutic approaches to correct impaired lung host defenses. Additionally, novel therapeutic strategies to abrogate alcohol-induced AM oxidative stress, such as treatments with NAC or GSH, could potentially restore pathogen clearance by AMs. Therapies that target oxidative stress as a means to normalize the immune response have potentially particular benefit in the AUD setting; *N*-acetylcysteine (NAC), a thiol precursor of GSH, represents one potential therapeutic option. NAC has been demonstrated to replenish intracellular GSH and to directly scavenge ROS at target cells. Small trials ( $n < 30$  subjects) of NAC in patients with ARDS have demonstrated that intravenous NAC was efficacious in increasing the number of organ failure-free days (days a patient was both alive and without organ failure) (Bernard et al., 1997; Soltan-Sharifi

et al., 2007), and had an excellent safety profile in the critically ill. Understanding the value of NAC to diminish *pulmonary oxidative stress* in the setting of *chronic alcohol exposure*, and its impact on AM activation, would help to determine whether antioxidant therapy might be useful as an adjunct for patients with pneumococcal pneumonia to ameliorate outcomes. AMs isolated from ethanol-fed rats also showed enhanced oxidation of the GSH/GSSG redox potential and impaired *in vitro* fluorescent *S. aureus* internalization that could be reversed with GSH treatments (L. A. Brown, Ping, Harris, & Gauthier, 2007). Further explorations into the molecular mechanisms of alcohol-mediated respiratory derangements are necessary for the discovery of novel therapeutic interventions to mitigate alcohol-induced lung injury and immune dysfunction.

## Acknowledgments

The section titled, "Alcohol intoxication exacerbates pulmonary response to remote injury: gut-liver-lung axis regulates pulmonary inflammation after intoxication and burn injury", was supported by NIH grants R01 GM115257 (EJK), R01 AA012034 (EJK), R21 AA023193 (EJK), T32 AA013527 (EJK), F30 AA022856 (MMC), and the Dr. Ralph and Marian C. Falk Medical Research Trust (EJK). The section titled, "Alcohol-mediated ciliated airway dysfunction", was supported by the NIH grants R01 AA008769 (JHS), F32 AA019859 (Samantha M. Simet), and F30 AA024676 (Michael E. Price). The section titled, "Alcohol-induced alveolar macrophage oxidative stress and dysfunction", was supported by the Emory Alcohol & Lung Biology Center P50 AA135757 (LAB), AHA SDG 13SDG13930003 (SMY), K99 AA021803 (SMY), and R00 AA021803 (SMY). The section titled, "Unraveling the alcohol-pneumococcal pneumonia relationship: clues from translational research", was supported by the R24 AA019661 (ELB) and the University of Colorado Department of Medicine Team Science Award (ELB). We would also like to extend our thanks to Brandy E. Wade, PhD for her contributions to the illustration depicted in Fig. 1.

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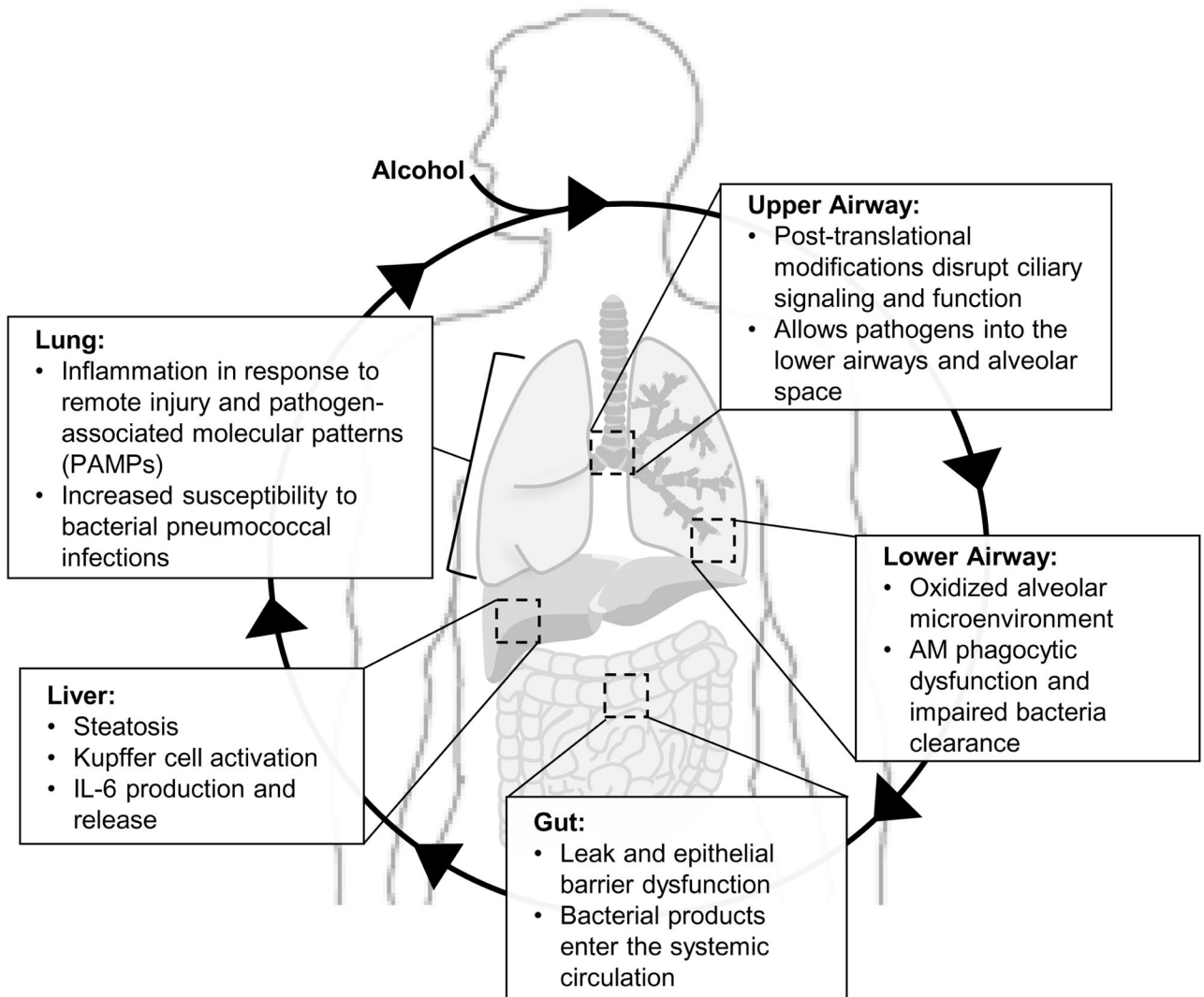
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### Highlights

- Mechanisms by which alcohol causes lung injury and immune dysfunction are reviewed.
- Gut-liver-lung axis regulates lung inflammation after intoxication and burn injury.
- Alcohol mediates ciliated airway dysfunction via post-translational modifications.
- Alcohol induces alveolar macrophage oxidative stress and phagocytic dysfunction.
- Translational research shows the link between alcohol and pneumococcal pneumonia.





**Fig. 1. Hypothetical schema summarizing alcohol-induced systemic oxidative stress**

During prolonged alcohol use, the ciliated airway epithelium of the upper airway undergoes post-translational modifications that disrupt ciliary signaling and function, allowing inhaled pathogens into the lower airways and alveolar space. The oxidized alveolar microenvironment in the lower airway alters alveolar macrophage activation, impairing phagocytosis and bacterial clearance. Alcohol-induced gut leak and epithelial barrier dysfunction in the gut cause bacterial products to enter the systemic circulation, leading to subsequent liver steatosis, Kupffer cell activation, and interleukin-6 (IL-6) production and release. Circulating bacterial products and chemokines exacerbate the lung inflammatory response to remote injury and pathogen-associated molecular patterns (PAMPs), increasing susceptibility to bacterial pneumococcal infections.