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The alcoholic lung: epidemiology, pathophysiology, and potential therapies

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Joshi PC, Guidot DM. The alcoholic lung: epidemiology, pathophysiology, and potential therapies. *Am J Physiol Lung Cell Mol Physiol* 292: L813–L823, 2007. First published January 12, 2007; doi:10.1152/ajplung.00348.2006.—Epidemiological evidence gathered only in the past decade reveals that alcohol abuse independently increases the risk of developing the acute respiratory distress syndrome by as much as three- to fourfold. Experimental models and clinical studies are beginning to elucidate the mechanisms underlying this previously unrecognized association and are revealing for the first time that chronic alcohol abuse causes discrete changes, particularly within the alveolar epithelium, that render the lung susceptible to acute edematous injury in response to sepsis, trauma, and other inflammatory insults. Recent studies in relevant animal models as well as in human subjects are identifying common mechanisms by which alcohol abuse targets both the alveolar epithelium and the alveolar macrophage, such that the risks for acute lung injury and pulmonary infections are inextricably linked. Specifically, chronic alcohol ingestion decreases the levels of the antioxidant glutathione within the alveolar space by as much as 80–90%, and, as a consequence, impairs alveolar epithelial surfactant production and barrier integrity, decreases alveolar macrophage function, and renders the lung susceptible to oxidant-mediated injury. These changes are often subclinical and may not manifest as detectable lung impairment until challenged by an acute insult such as sepsis or trauma. However, even otherwise healthy alcoholics have evidence of severe oxidant stress in the alveolar space that correlates with alveolar epithelial and macrophage dysfunction. This review focuses on the epidemiology and the pathophysiology of alcohol-induced lung dysfunction and discusses potential new treatments suggested by recent experimental findings.

acute respiratory distress syndrome; epidemiology

ALCOHOLIC BEVERAGES OF VARIOUS KINDS have been used and abused by humans for thousands of years. In many cultures, both ancient and modern, the consumption of beer, wine, and spirits is a part of religious ceremonies, social events, and simple daily living. Although many religious and social groups have proscribed its use, and temperance movements have arisen at various times in virtually every society, alcohol ingestion has proven to be an enduring human custom. Unfortunately, a significant proportion of individuals who consume alcohol on a regular basis develop patterns of alcohol abuse or even frank physical dependence, and the long-term health consequences of excessive alcohol use can be devastating. Many of the medical complications of alcohol abuse, including hepatitis, cirrhosis, pancreatitis, cardiomyopathy, peripheral neuropathy, and dementia, are well known to both the general public and to the medical community (45). By contrast, the ravages of alcohol abuse have been viewed as relatively sparing the lung. For example, there has not been described an “alcoholic pneumopathy” or “alcoholic pneumonitis” analogous to the aforementioned complications of chronic alcohol abuse. The notable exception is the link between alcohol abuse and pulmonary infections. More than two centuries ago, the first Surgeon General of the United States, Benjamin Rush,

noted that pneumonia and tuberculosis were infectious complications more commonly encountered in people who drank alcohol, and, a century later, William Osler cited alcohol abuse as the major risk factor for pneumonia (59). However, this risk has largely been attributed to alterations in immune function and/or structural/functional defects in the upper airway such as colonization of the oropharynx with gram-negative bacteria and the obvious risk of aspiration during inebriation. In fact, until relatively recently it had been generally assumed that chronic alcohol abuse had no effect on the lung parenchyma itself as there is no epidemiological evidence to implicate it as an independent risk factor for common pulmonary disorders such as bronchogenic carcinoma, asthma, emphysema, or interstitial lung disease.

Our understanding of the effects of alcohol abuse on the lung itself was changed when a novel epidemiological finding published in 1996 revealed for the first time that alcohol abuse independently increased the risk for developing the acute respiratory distress syndrome (ARDS) in critically ill individuals (54). Remarkably, this association and its impact had been missed even though independent risk factors for ARDS had been vigorously sought, and, even a decade later, it is not recognized routinely by the medical community.

This initial epidemiological observation inspired experimental and clinical studies that have led to an explosive growth in our understanding of the relationship between chronic alcohol abuse and pulmonary disease. This review summarizes the past

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decade of research on alcohol abuse and acute lung injury and synthesizes the novel findings in this area with previous and ongoing studies of alcohol abuse and pulmonary host defense. Specifically, it is becoming increasingly clear that alcohol abuse, even in otherwise healthy individuals, causes significant oxidant stress within the alveolar space and impairs both alveolar epithelial and alveolar macrophage function via common pathophysiological mechanisms. Therefore, this review will attempt to integrate the parallel but often independent findings on immune dysfunction and susceptibility to acute lung injury in the "alcoholic lung" into a common pathophysiological scheme. Finally, this review will discuss recent experimental findings that raise the possibility that novel therapies, targeted at the alveolar epithelial and macrophage dysfunction in alcoholic individuals, could limit the incidence and/or severity of respiratory failure when they present with serious lung infections and/or other critical illnesses that place them at high risk for developing ARDS.

General background on alcohol abuse and toxicity. Worldwide, alcohol is the most frequently abused drug (45). In the United States, one-half of the general population regularly consumes alcohol, and 15–20 million individuals are alcoholics (5, 28). The National Institute on Alcohol Abuse and Alcoholism has estimated that alcohol-related problems cost our society more than \$185 billion per year (32). Among persons admitted to general hospitals, 20–40% have alcohol-related problems (3). A more recent report published by the Centers for Disease Control and Prevention conservatively estimated that in the year 2001, there were ~76,000 alcohol-attributable deaths and more than 2.3 million years of potential life lost due to alcohol abuse in the United States alone (1). The majority of these deaths were attributed to chronic conditions such as cirrhosis and to alcohol-related acute trauma, particularly automobile accidents. However, as we discuss in the context of acute lung injury, these estimates failed to include a large number of cases in which a causative role for alcohol abuse was unrecognized.

Alcohol abuse causes a myriad of serious health consequences. Perhaps for obvious reasons, much of the medical attention has focused on alcohol-mediated pathophysiology within the gastrointestinal system. Following ingestion, alcohol is rapidly absorbed by the gastric and small intestinal mucosa and is metabolized primarily in the liver by alcohol dehydrogenase, a cytosolic enzyme with multiple isoforms that vary in their affinities for alcohol binding (43, 44). Only the liver and the gastric mucosa have the high-affinity isoform, and, therefore, alcohol metabolism by alcohol dehydrogenase in tissues other than the liver and the stomach is limited (43, 44). Alcohol can also be metabolized in microsomes via the cytochrome *P*-450 component CYP2E1 (44). This enzyme complex has a lower affinity for alcohol than the hepatic alcohol dehydrogenase enzyme and therefore may not contribute significantly to overall alcohol metabolism following occasional use. However, in the context of chronic use, the CYP2E1 enzyme metabolizes a significant percentage of ingested alcohol. Alcohol metabolism in the liver forms acetaldehyde and free radicals that have been implicated as direct causes of hepatocyte injury (43, 44). As many as 35% of heavy drinkers develop alcoholic hepatitis, and one-half of these develop frank cirrhosis (43, 44). Another prominent target of alcohol abuse within the gastrointestinal tract is the pancreas.

An association between alcohol abuse and pancreatic injury was reported as early as 1878 (23), and alcoholic pancreatitis has become a well-recognized clinical entity since then, and although less common than alcoholic hepatitis, can cause significant morbidity and mortality in affected individuals. Alcohol consumption has diverse deleterious effects elsewhere throughout the gastrointestinal tract including gastroesophageal reflux, damage to the gastric mucosa, and malabsorption of nutrients in the small intestine (11).

Beyond the gastrointestinal system, alcohol abuse has diverse targets. For example, it impacts the endocrine system by disrupting the actions of hormones such as cortisol, testosterone, growth hormone, and prolactin, and it interferes with glucose and lipid metabolism (20). Although much attention in recent years has been paid to the salutary effects of moderate alcohol consumption on the cardiovascular system, alcohol abuse can lead to significant morbidity and mortality from cardiomyopathy and vascular disease (80). Furthermore, alcohol abuse is clearly associated with certain cancers, such as esophageal and gastric carcinoma, and causes osteoporosis, myopathy, dementia, and peripheral neuropathy (45). Therefore, one could argue that alcohol abuse is a truly systemic disorder in which the clinical manifestations may vary depending on the individual affected. As this review focuses on the effects of alcohol abuse on the lung, readers are directed to several excellent reviews of the medical complications of alcohol abuse that have been only briefly mentioned here (45, 57).

Epidemiological evidence linking alcohol abuse and acute lung injury. Until recently, there was little evidence that chronic alcohol ingestion had any significant effects on the pulmonary parenchyma. The lack of a clinical syndrome such as alcoholic pneumonitis or alcoholic pneumopathy, analogous to other organ-specific disease states, suggested that other than an increased susceptibility to pneumonia, the lung was relatively spared from the consequences of chronic alcohol abuse. However, as long as 40 years ago, it had been speculated that chronic alcohol abuse might affect the lung parenchyma (16). In 1996, a seminal study demonstrated that chronic alcohol abuse independently increased the incidence of ARDS in critically ill patients at risk for the syndrome (54). This study analyzed the hospital courses of 351 critically ill patients admitted to an urban county hospital with a known risk factor for ARDS such as sepsis, trauma, gastric aspiration, or multiple blood transfusions. Patients with a known history of alcohol abuse had a 43% chance of developing ARDS compared with a 22% chance in patients who did not have a diagnosis of alcohol abuse. Within the largest subgroup of patients, in those with sepsis as a risk factor for ARDS, the incidence in the patients with known alcohol abuse was 52% compared with only 20% in the patients without a known history of alcohol abuse. Multivariate analysis determined that a history of alcohol abuse increased the risk of ARDS independently of the severity of illness, liver disease, or other factors that can be associated with alcohol abuse. A subsequent multicenter, prospective evaluation of 220 patients with septic shock confirmed an association between alcohol abuse and ARDS (56). In that study, the incidence of ARDS was 70% (46/66 patients) in septic patients with a history of alcohol abuse compared with only 31% (47/154) in septic patients without a history of alcohol abuse. After adjusting for a variety of factors including source of infection and severity of illness, the relative risk of

developing ARDS attributed to alcohol abuse was 3.7 (95% confidence interval, 1.83–7.71). Remarkably, in both the original and the follow-up study by these investigators (54, 56), ~50% of the patients who developed ARDS had a significant history of alcohol abuse. Other investigators have confirmed these findings, including the observation that prior alcohol abuse approximately doubles the risk of ARDS in patients who undergo thoracic surgery for lung cancer (42). Together, these recent studies demonstrate a previously unrecognized association between alcohol abuse and acute lung injury.

In addition to increasing the risk of ARDS in critically ill patients, alcohol abuse clearly increases the risk for many of the acute illnesses that lead to ARDS. Alcohol intoxication has long been recognized as a major risk factor for serious trauma requiring admission to specialized trauma centers (40, 66, 67). Furthermore, alcohol abuse is a major risk factor for aspiration of gastric contents as well as severe upper gastrointestinal bleeding from gastritis and esophageal varices that requires massive blood transfusions. Therefore, chronic alcohol abuse increases the risk of developing the acute insults, specifically sepsis, trauma, pneumonia, pancreatitis, aspiration, and massive blood transfusions, that can lead to ARDS.

The association between alcohol abuse and pneumonia merits specific discussion as severe pneumonia with or without associated sepsis is a major risk factor for ARDS; in fact, in the aforementioned study (56), pneumonia was the source of sepsis in 60% of the alcoholic subjects and was the most common source of sepsis in the nonalcoholic subjects (35%). Therefore, it is clear that the risks of pneumonia and ARDS are inextricably linked in the general population and that this link is even greater in the context of alcohol abuse. Alcohol abuse is classically recognized as an important risk factor for bacterial pneumonias (22), and several recent excellent reviews (26, 31, 83) address this topic. Alcoholic patients with pneumonia are more likely to be infected with either serious gram-negative pathogens such as *Klebsiella pneumoniae* (37) or to develop bacteremia and shock from even typical pathogens, most notably *Streptococcus pneumoniae* (62). For example, a recent study found that among 1,300 Spanish adults who were hospitalized for pneumonia, a history of alcohol abuse was associated with pneumococcal infection (18). Furthermore, both current and recovering alcoholics were more likely to develop pneumococcal pneumonia, suggesting that the effects of alcohol abuse on innate immune responses within the lung do not readily resolve with abstinence. Overall, the decreased ability to prevent and/or contain infection within the airways means that alcohol abuse greatly increases the severity of pneumonia in many cases, and, in the notable case of pneumococcal pneumonia, can lead to a clinical entity that has been termed the alcoholic leukopenic pneumococcal sepsis (ALPS) syndrome (62). Because sepsis due to bacterial pneumonia is among the most common causes of ARDS, there is a vicious feed-forward cycle in which alcoholics are more likely to develop severe pneumonia and sepsis, which alone carry a high mortality, but then these risks are compounded by the three- to fourfold increased susceptibility to developing ARDS as a consequence.

In addition, alcohol abuse may worsen the outcome in patients who develop ARDS, even if they do not succumb to the acute lung injury per se. In the prospective epidemiological study in patients with septic shock discussed above (56), the

effects of chronic alcohol abuse on other organ systems were assessed by comparing the daily aggregate sequential organ failure assessment scores in alcoholic and nonalcoholic patients. Based on this standardized scoring system to grade multiple organ dysfunction in critically ill patients, alcoholic patients with ARDS also had more severe nonpulmonary organ dysfunction compared with nonalcoholics with ARDS (56). In parallel, at least two studies implicate alcohol abuse in the frequency and severity of ventilator-associated pneumonia (VAP) in trauma patients (10, 75). Therefore, chronic alcohol abuse also increases the risk of multiple organ failure (MOF) and VAP, complications that exacerbate the morbidity and mortality associated with ARDS.

Some of the potential mechanisms to explain the overlapping risks for pneumonia and acute lung injury become apparent when one examines the deleterious effects of alcohol abuse on the entire airway from the mouth to the alveolus. Chronic alcohol abuse impairs salivary secretion, promotes gingivitis, and increases colonization of the mouth and pharynx with gram-negative bacteria (24, 31). In parallel, acute intoxication can impair consciousness and decrease the gag reflex. The result is that alcoholics are more likely to aspirate virulent organisms into the lower airways. Within the trachea and conducting airways, the primary defense against invading pathogens is mucociliary clearance. In experimental models, alcohol has been shown to impair this function (79). Within the lower airways, the primary innate immune defenses depend on the phagocytic functions of alveolar macrophages and their interaction with secreted factors, including surfactant proteins. There is abundant evidence showing that alcohol abuse impairs alveolar macrophage innate immune functions. In experimental models, alcohol ingestion decreases phagocytosis as well as proinflammatory cytokine and chemokine production and increases the severity of lung infection from diverse organisms including *S. pneumoniae*, *K. pneumoniae*, *Mycobacterium tuberculosis*, and *Pneumocystis carinii* (6, 16, 17, 50, 51, 70, 82, 84). Interestingly, alcohol has also been shown to decrease the ability of surfactant to facilitate macrophage phagocytosis and killing of *S. pneumoniae* in vitro (68), which only exacerbates the impaired innate immune response to infections in the alveolar space. Consistent with these experimental findings, alveolar macrophages isolated from alcoholic subjects have impaired immune function including decreased secretion of tumor necrosis factor- α (58). In addition, the coordinated adaptive immune response to infection that must be initiated by the alveolar macrophage is also dampened as impaired alveolar macrophage chemokine production decreases neutrophil recruitment to the alveolar space in response to bacterial infection (12, 65).

Together, these observations reveal that chronic alcohol abuse sequentially amplifies an individual's risk for ARDS and its complications. Specifically, alcoholics are 1) at increased risk for serious illnesses that lead to ARDS, particularly severe pneumonia with or without sepsis, 2) independently at increased risk for ARDS, and, finally, 3) at higher risk for subsequent complications such as MOF and VAP. We will now turn our attention to the more recently identified effects on the alveolar epithelium that provide new insights into the link between alcohol abuse and ARDS and that suggest novel therapeutic targets.

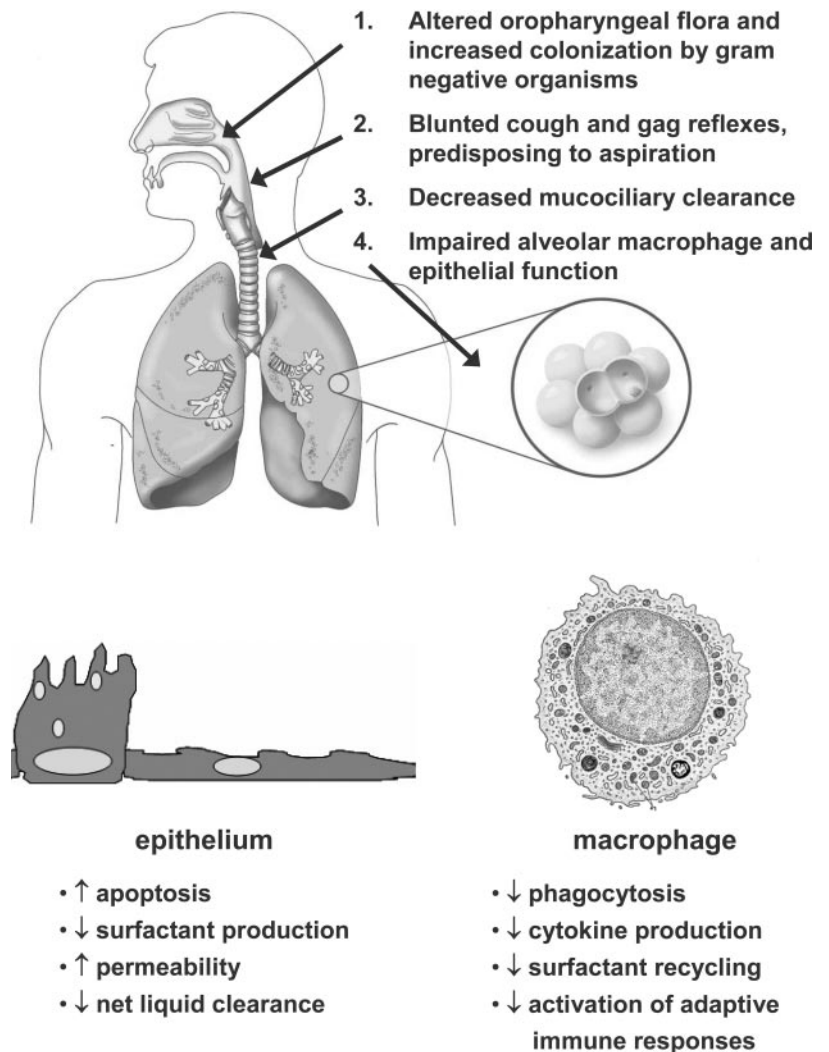
Mechanisms of alcohol-induced alveolar epithelial dysfunction. Experimental studies examining the potential mechanisms underlying alcohol abuse and acute lung injury have focused primarily on alveolar epithelial function, as damage to this barrier is one of the hallmarks of ARDS. Chronic alcohol ingestion for 6 wk in rats alone causes no evidence of respiratory distress. However, when alveolar epithelial function is examined more closely, it turns out that alcohol ingestion produces a wide array of defects that render the lung susceptible to acute edematous injury in response to endotoxemia and/or sepsis. To summarize some of these studies, chronic alcohol ingestion 1) impairs surfactant production and increases oxidant-mediated necrosis in alveolar epithelial cells (29, 33); 2) increases oxidant- and cytokine-mediated apoptosis in alveolar epithelial cells in vitro and in vivo (13, 14); 3) increases protein leak across the alveolar barrier and decreases alveolar liquid clearance in vivo (30); 4) increases activation of metalloproteinases and degrades the alveolar matrix during endotoxemia (47); 5) renders the lung intrinsically susceptible to injury during endotoxin-mediated acute inflammation (33, 47); 6) decreases functional surfactant in the alveoli and increases respiratory failure during sepsis in vivo in the cecal ligation and perforation model (74); and 7) increases

the expression and activation of transforming growth factor- β within the alveolar space where it can increase epithelial permeability (8).

Figure 1 illustrates some of the abnormalities discussed thus far that characterize the alcoholic lung phenotype. It is important to emphasize that even in otherwise healthy-appearing individuals, alcohol abuse can target any or all of these airway defenses and increase the susceptibility to serious lung infections and acute lung injury. Many of the identified mechanisms underlying alcohol-induced impairments in host defense by the upper airway and the alveolar macrophage have already been discussed. In terms of the more recently identified mechanisms by which alcohol abuse disrupts alveolar epithelial function, three merit discussion here.

The "glutathione story." Extensive evidence implicates depletion of the antioxidant glutathione in the pathogenesis of alcohol-mediated disease, particularly in the liver and in the lung, but in other target tissues as well. Glutathione is a tripeptide synthesized primarily by the liver. It is utilized in multiple important pathways including detoxification of peroxides, conjugation to xenobiotics and other toxic molecules to facilitate their excretion, and control of oxidant-mediated induction of inflammatory cytokines (41, 44, 52). Glutathione

Fig. 1. Proposed schema by which chronic alcohol abuse impairs airways defenses against microbial invasion and infection and amplifies the risk for serious pneumonias as well as their complications, including sepsis and acute lung injury. Even otherwise healthy-appearing alcoholics can become colonized in the oropharynx with virulent gram-negative bacteria, and, because of decreased mucociliary clearance of aspirated pharyngeal organisms, their lower airways are frequently challenged with relatively large numbers of infectious organisms. Within the alveolar space, alcohol-induced defects in macrophage immune function interfere with bacterial phagocytosis and clearance as well as activation of a robust adaptive immune response, all of which favors bacterial infection and dissemination. The situation is further exacerbated by the defects in alveolar epithelial function that render the alcoholic more likely to develop acute respiratory distress syndrome, either from local inflammation or from systemic inflammation if the pathogen gains access to the circulation and causes sepsis.



depletion precedes the development of the typical histological changes of alcohol-mediated hepatotoxicity (44), and hepatic tissue glutathione levels are decreased in chronic alcoholics whether or not there is evidence of cirrhosis (36). In experimental animal models, alcohol administration decreases glutathione synthesis and increases glutathione turnover independently of glutathione oxidation (44). In addition, alcohol treatment decreases glutathione transferase and glutathione peroxidase activity (44). Acetaldehyde may decrease glutathione levels by binding to cysteine or glutathione itself, although at least one study suggests that the alcohol-induced suppression of hepatic glutathione levels cannot be accounted for by acetaldehyde or alcohol levels alone (69). However, the precise mechanisms by which alcohol decreases glutathione levels in the liver are not known. Nevertheless, the fundamental causative role of glutathione depletion in alcohol-mediated liver disease has been shown in several laboratories in that dietary supplementation with glutathione precursors prevents the development of hepatic steatosis and injury in experimental animals (27).

Therefore, it is not surprising that a fundamental aspect of the alcoholic lung in both experimental models and in clinical studies is evidence of chronic oxidative stress and depletion of glutathione within the alveolar air space. Experimentally, alcohol ingestion in rats significantly decreases levels of glutathione in the type II alveolar epithelial cells by more than 90% and in the alveolar epithelial lining fluid by ~80% (33). The importance of alcohol-mediated glutathione depletion in altered lung cell function was first substantiated by the demonstration that isolated lungs from rats whose alcohol/water mixture was supplemented with glutathione precursors were less susceptible to endotoxin-mediated edema formation (33). Multiple subsequent studies have demonstrated that glutathione supplementation of the experimental diet prevents alcohol-mediated defects in alveolar epithelial function; specifically, dietary supplementation with glutathione precursors decreases cytokine- and/or oxidant-induced apoptosis (13, 14, 29, 30, 47, 74), preserves surfactant synthesis and secretion (13, 14, 29, 30, 47, 74), restores barrier function both in vivo and in vitro (13, 14, 29, 30, 47, 74), prevents activation of matrix metalloproteinases during endotoxemia (13, 14, 29, 30, 47, 74), and maintains surfactant composition as well as limits acute lung injury during sepsis in vivo (13, 14, 29, 30, 47, 74). These experimental observations were made even more exciting by the recognition that otherwise healthy subjects (normal nutritional indices and no clinical evidence of lung or liver disease) with a history of alcohol abuse have dramatically decreased levels of glutathione in their lung lavage fluid compared with non-alcoholic control subjects (55). In that study, as in the animal model, the glutathione concentrations were corrected for dilution during the lavage procedure and therefore represent the actual concentrations within the alveolar epithelial lining fluid in vivo. Furthermore, the relative degree of glutathione deficiency in the epithelial lining fluid in human subjects with chronic alcohol abuse compared with non-alcoholic subjects was virtually identical to that observed in the experimental model (33) and in some cases approximated only 10% of the glutathione levels in control subjects. This previously unrecognized deficiency in a critical antioxidant in the lungs of alcoholics reflects a significant vulnerability to oxidative stress in the lungs of these individuals that is consistent with their

increased susceptibility to ARDS in response to acute oxidative stresses such as sepsis or trauma.

Further investigation provided additional insights into alcohol-mediated glutathione deficiency and consequent susceptibility to acute lung injury. Although earlier studies suggested that the lung does not metabolize significant amounts of alcohol through alcohol dehydrogenase, metabolism through the cytochrome *P*-450 system in the lung is significant (48). Local alcohol metabolism within the lung may be sufficient to exert significant oxidative stress, as alcohol-fed animals and alcoholic humans have increased levels of oxidized glutathione, and not simply glutathione depletion, in their lung lavage fluid (33, 55). These findings suggest that chronic oxidative stress leads to glutathione consumption and depletion, which then leaves the alveolar space relatively unprotected and vulnerable to acute oxidative stresses such as sepsis or trauma. Within cells, there are distinct mitochondrial and cytosolic pools of glutathione. Although chronic alcohol ingestion depletes both the mitochondrial and cytosolic glutathione pools, it appears that the mitochondrial levels may be more critically involved in the pathophysiology of alcohol-mediated alveolar epithelial dysfunction (13, 14, 29, 30). Specifically, supplementing the diets of alcohol-fed rats with *N*-acetylcysteine, the only clinically approved glutathione precursor, prevents alcohol-mediated depletion of the alveolar epithelial cell cytosolic glutathione pool. However, *N*-acetylcysteine failed to prevent alcohol-mediated depletion of the mitochondrial glutathione pool and did not prevent alcohol-mediated derangements in surfactant synthesis or enhanced susceptibility to oxidant-induced apoptosis (13, 14, 29, 30). In contrast, supplementing the diets of alcohol-fed rats with procysteine, a glutathione precursor that prevents depletion of both mitochondrial and cytosolic glutathione pools, abrogated alcohol-induced derangements in alveolar epithelial cell function in vitro (13, 14, 29, 30). Importantly, procysteine supplementation also eliminated alcohol-mediated susceptibility to surfactant dysfunction and hypoxemia in an experimental model of sepsis-induced lung injury in vivo (74). Although it is unknown why procysteine, but not *N*-acetylcysteine (which is such an effective treatment for acetaminophen toxicity), restores and/or maintains both the cytosolic and mitochondrial glutathione pools during chronic alcohol ingestion, these and related studies nonetheless implicate mitochondrial glutathione depletion as a fundamental feature of alcohol-induced lung dysfunction. These findings parallel multiple studies implicating mitochondrial glutathione depletion in alcohol-induced liver injury (21, 27, 46) and strengthen the evidence that mitochondrial dysfunction is a common mechanism by which alcohol abuse leads to tissue injury. Furthermore, these findings have enormous clinical relevance as they argue that *N*-acetylcysteine, which is the only glutathione precursor in current clinical use, may have limited efficacy as a treatment for the alcoholic lung, particularly in the acute setting.

The role of angiotensin II in alcohol-mediated oxidant stress. As noted, the mechanisms by which alcohol abuse leads to oxidative stress in target tissues remain poorly understood, likely because multiple sources of reactive oxygen and reactive nitrogen species are perturbed by alcohol. One prominent mechanism receiving considerable attention is the renin-angiotensin system (RAS) and its active product, angiotensin II. Angiotensin II is a pluripotent vasoactive peptide increased in

patients with ARDS (76). Angiotensin II is formed by the sequential conversion of angiotensinogen to angiotensin I and then to angiotensin II, the latter conversion primarily by the angiotensin converting enzyme (ACE). Intriguingly, mice deficient in ACE have less lung injury following acid aspiration or sepsis (35), and at least one clinical study suggests that individuals who express the ACE allele associated with increased enzyme activity are at higher risk of ARDS (49). In contrast, ACE2 is a more recently identified negative modulator of the RAS that inactivates angiotensin II; experimentally, treatment with recombinant ACE2 also protects mice from lung injury (35). Chronic alcohol ingestion increases plasma levels of angiotensin II in rats (78), and it has been postulated that activation of the RAS may explain the association between alcohol abuse and hypertension in humans (77, 78). Although a mechanism is not known, it has been shown that acetaldehyde, the primary metabolite of alcohol, can convert angiotensinogen to angiotensin I in rat plasma *in vitro* (71). The biological effects of angiotensin II depend on its interaction with specific angiotensin II receptors, and at least seven subtypes have been identified. Of the angiotensin II receptors, the type 1 receptor (AT1) and the type 2 receptor (AT2) have been best characterized. The majority of the well-known effects of angiotensin II, such as vasoconstriction, sodium retention, and tissue hypertrophy and hyperplasia, are mediated via the AT1 receptor (4, 15). By contrast, the AT2 receptor is present in few tissues during adulthood, whereas it is abundantly expressed during embryogenesis and in response to injury (4, 73). Stimulation of the AT2 receptor inhibits cell proliferation and leads to apoptosis, actions directly opposed to the proliferative responses that often follow AT1 activation (19, 25, 53, 73). Experimentally, chronic alcohol ingestion markedly increases the relative expression of the AT2 receptor within the alveolar epithelium and in parallel renders these cells susceptible to apoptosis when exposed to oxidative stress or proinflammatory cytokines (7). Importantly, selective inhibition of the AT2 receptor completely inhibits angiotensin II- and TNF- α -induced apoptosis in alveolar epithelial cells isolated from alcohol-fed rats (7). Therefore, chronic alcohol ingestion shifts the angiotensin II receptor phenotype within the alveolar epithelium to one characterized by predominant AT2 receptor subtype expression, which in turn appears to mediate epithelial cell apoptosis in response to diverse inflammatory stimuli. Although it is not yet known why this phenotypic shift in angiotensin II receptor expression occurs in the lung, one explanation is offered by recent evidence that alcohol-induced oxidative stress in the lung is mediated in large part by angiotensin II and specifically through activation of the AT1 receptor (9). Angiotensin II appears to activate NADPH oxidase expression and subsequent production of superoxide within the lung (63). Therefore, the relative shift in AT1 vs. AT2 receptor expression in the alcoholic lung epithelium could be a compensatory response by the lung epithelium to decrease oxidative stress caused by the AT1-mediated activation of NADPH oxidase, but this is speculative at present. Although selective AT2 receptor blockers have not yet been tested clinically (as opposed to AT1 receptor blockers in widespread use to treat a variety of cardiovascular diseases), these experimental findings suggest that selective AT2 receptor blockade could potentially prevent or at least

limit alveolar epithelial cell death in the alcoholic lung during acute inflammatory stresses, and this is discussed further in the final section of this review.

Impaired GM-CSF signaling in the alcoholic lung. Granulocyte/macrophage colony-stimulating factor or GM-CSF is a 23-kDa glycosylated monomeric peptide secreted by multiple cell types, including the alveolar epithelial type II cell (72). It was first identified in mouse lung cell-conditioned medium and was named for its ability to stimulate the growth of granulocytes and macrophages from cultured hematopoietic progenitor cells. The cloning of this protein permitted a variety of *in vitro* and *in vivo* studies to characterize its functions, and subsequently it was found to stimulate the production of eosinophils, erythrocytes, megakaryocytes, and dendritic cells in addition to granulocytes and macrophages. GM-CSF has been widely used clinically to improve bone marrow recovery following chemotherapy. However, targeted deletion of the GM-CSF gene in mice surprisingly had no effect on the hematopoietic system but rather produced an unexpected lung-specific phenotype that was essentially identical to pulmonary alveolar proteinosis (PAP) (34). PAP is characterized by alveolar macrophage immune dysfunction and impaired surfactant phospholipid recycling, leading to opportunistic infections and accumulation of surfactant phospholipid and protein ("proteinosis") in the alveolar air space. Although the alcoholic lung is not as severely affected as the lung in PAP, the functional defects in the alveolar macrophage in these two conditions are similar.

Our laboratory recently reported for the first time the impact of chronic alcohol ingestion on GM-CSF-dependent alveolar epithelial cell and macrophage function. Recombinant GM-CSF delivered via the upper airway restored alveolar epithelial barrier function and fluid transport in alcohol-fed rats, even during endotoxemia (60). Importantly, although that study showed that GM-CSF treatment decreased endotoxin-mediated lung injury even in control-fed rats, the magnitude of the efficacious response was clearly greater in the alcohol-fed rats. The efficacy of recombinant GM-CSF turned out to be more than a serendipitous finding, as these initial observations led to the discovery that chronic alcohol ingestion decreases the expression of GM-CSF receptors in the airway epithelium and macrophages and in turn dampens intracellular signaling to the GM-CSF master transcription factor, PU.1. As a consequence, GM-CSF-dependent functions in each cell type are impaired (see Fig. 2 for illustration of this effect on the alveolar macrophage). Remarkably, and to date via unknown mechanisms, recombinant GM-CSF treatment restores GM-CSF receptor expression and signaling and normalizes both alveolar epithelial barrier function (38) and alveolar macrophage immune function (39). These findings are exciting as they provide novel insights into a previously unrecognized and common mechanism by which alcohol abuse impairs both the epithelial barrier and the innate immune capacity within the alveolar space, which would then translate to the increased susceptibility to both acute alveolar epithelial injury (as in ARDS) and pneumonia. At present, we do not yet know whether the dampening in GM-CSF signaling is directly related to angiotensin II activation and/or oxidant stress, but future studies should elucidate their relationship.

Potential novel therapies for the alcoholic lung. The overall survival of patients with ARDS has increased since the original

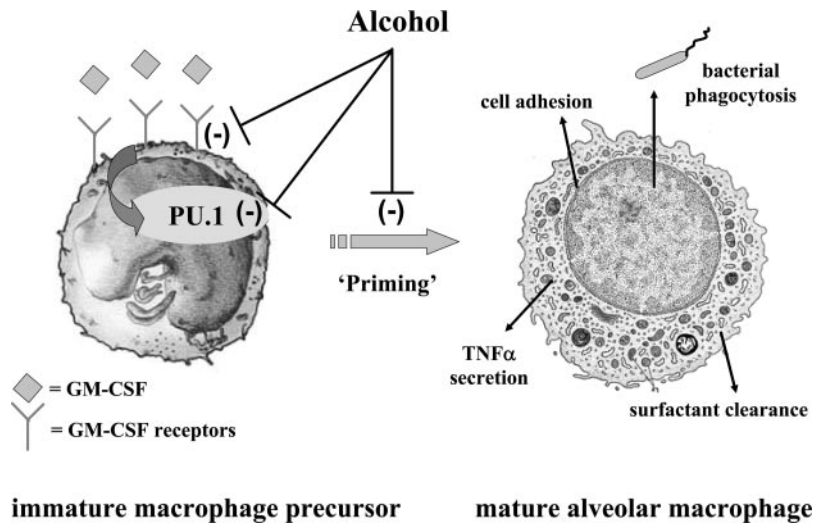


Fig. 2. Proposed mechanisms by which alcohol abuse inhibits alveolar macrophage maturation and innate immune functions that are critical to respond to pathogens within the alveolar space. In an experimental model, although chronic alcohol ingestion has no effect on granulocyte/macrophage colony-stimulating factor (GM-CSF) protein levels in the alveolar space, it decreases the cell surface expression of the GM-CSF receptor in alveolar macrophages. In parallel, chronic alcohol ingestion decreases the expression and nuclear binding of the GM-CSF master transcription factor, PU.1. As a consequence, GM-CSF priming and maturation of the precursor cell into a fully functional alveolar macrophage is inhibited. Importantly, recombinant GM-CSF treatment delivered to the airway in alcohol-fed rats rapidly (within 48 h) restores GM-CSF receptor expression, PU.1 expression and nuclear binding, and innate immune function in the alveolar macrophage (39). This same pathophysiological sequence, including rapid resolution in response to recombinant GM-CSF treatment, also underlies alcohol-mediated alveolar epithelial barrier dysfunction in the same experimental model (38).

description of the syndrome in 1967 due to incremental improvements in their care in the intensive care unit (ICU); most notable are the benefits of lung-protective ventilatory strategies designed to limit shear stresses to the already damaged lung (2). However, even with current “best ICU care,” the mortality from ARDS is unacceptably high at ~30–40%. Furthermore, no pharmacological treatments have been identified to date that significantly decrease ARDS mortality. Therefore, the search for effective treatments is clearly a high priority. This challenge is daunting, particularly in patients with alcohol abuse in whom acute stresses such as sepsis or trauma are superimposed upon chronic underlying alveolar epithelial and macrophage dysfunction. In the previous section, three fundamental mechanisms by which alcohol abuse disrupts normal airway epithelial and immune function were highlighted. These mechanisms not only provide new insights into the pathophysiology of the alcoholic lung but they suggest possible targets for novel therapeutic interventions. In this final section, we will extend the previous examination of these mechanisms and discuss the rationale for, as well as the potential challenges raised by, the development of glutathione replacement, angiotensin II blockade, and/or recombinant GM-CSF as therapies that could decrease the incidence of pneumonia and/or acute lung injury in susceptible individuals.

Glutathione replacement would seem to be an obvious choice in view of the extensive evidence implicating glutathione depletion in the pathophysiology of alcohol-induced liver and lung dysfunction in animal models as well as the observation that even healthy-appearing alcoholics have profound glutathione depletion within the alveolar space. Unfortunately, although dietary glutathione supplementation is effective in animal models, this approach requires chronic and concurrent ingestion with the alcohol to prevent oxidative damage and dysfunction. In fact, in at least one experimental study that examined a rescue or postingestion protocol, alveolar epithelial cell dysfunction in rats persisted for at least a week after alcohol abstinence followed by dietary treatment with *N*-acetylcysteine (29), which is the only clinically available glutathione precursor. In contrast, dietary supplementation with procysteine, which as discussed earlier restores both the mitochondrial and cytosolic glutathione pool, restored alveolar

epithelial function during a week of abstinence in alcohol-fed rats (29). Therefore, any clinically useful glutathione replacement strategy must not only target both cellular pools but will require time to reverse the alcoholic lung phenotype. Therefore, it may have little or no efficacy as monotherapy in the acute setting. In contrast, chronic dietary supplementation with glutathione precursors in otherwise healthy alcoholics before acute inflammatory stresses could potentially limit the glutathione depletion and oxidative lung dysfunction secondary to chronic alcohol abuse. If the findings in animal models translate to humans, then experimental evidence would argue that an alcoholic subject who ingested adequate doses of glutathione supplements on a regular basis might never develop the alcoholic lung phenotype and therefore would significantly decrease their risk of acute lung injury and possibly even pneumonia. However, there are understandable concerns about developing and testing such treatments in the context of alcohol abuse, as this approach would not alter the devastating complications of alcohol intoxication and abuse on public safety and could distract from the primary treatment goal of abstinence. In parallel, such a therapeutic approach runs the risk of creating the false impression that glutathione supplements are an antidote to the ravages of alcohol abuse and make excessive alcohol use “safer.”

Analogous to glutathione supplementation, angiotensin II inhibition could be an effective means to limit the development of alcohol-induced oxidative stress and tissue dysfunction if taken concurrently, and chronically, with alcohol. Furthermore, as ACE inhibitors as well as AT1 receptor blockers (that commonly go by the term angiotensin receptor blockers or ARBs) are in widespread clinical use to treat cardiovascular and renal disease, they could potentially be employed in preventing the alcoholic lung phenotype. As discussed earlier, experimental evidence strongly suggests that alcohol-induced oxidative stress and consequent lung dysfunction are mediated in large part through angiotensin II via activation of the AT1 receptor. If these experimental studies ultimately proved to be relevant in the clinical situation, then chronic treatment with ACE inhibitors or ARBs could potentially decrease the pulmonary complications of alcohol abuse. In this regard, the rationale for targeting angiotensin II would be similar to that

employed in patients with other chronic conditions such as congestive heart failure and kidney disease. However, the same concerns regarding the potential ethical issues discussed above in terms of glutathione supplementation would also apply to chronic angiotensin II inhibition in the context of alcohol abuse. Moreover, in the acute setting such as when a patient with alcohol abuse presents with major trauma or a serious infection, ACE inhibition or blockade of the AT1 receptor would likely exacerbate hemodynamic collapse. In contrast, blockade of the AT2 receptor has some theoretical advantages. As discussed earlier, in experimental animals, chronic alcohol ingestion switches the phenotype of the alveolar epithelium to favor AT2 receptor expression, which renders these cells more susceptible to apoptosis in response to acute inflammatory stresses (7). Therefore, acute blockade of the AT2 receptor in critically ill patients with underlying alcohol abuse could potentially improve alveolar epithelial cell viability and decrease alveolar protein leak and edema. At present, there have been very few experimental models that have used selective AT2 receptor blockers, and these agents have never been tested in humans. If further evidence for a mechanistic role of the AT2 receptor in the alcoholic lung and/or other pathophysiological conditions arises, one could imagine that the development and testing of such agents in clinical studies would ensue, just as AT1 receptor blockers were developed for clinical use when their efficacy in experimental models of cardiovascular disease was established.

Perhaps the most attractive candidate for treating the alcoholic lung phenotype in the acute setting is suggested by the recent experimental findings on GM-CSF signaling in the alcoholic lung described previously. GM-CSF treatment is already used clinically to accelerate bone marrow recovery following chemotherapy, and, therefore, its safety profile even in seriously ill patients has been established. Interestingly, although GM-CSF is better known for its effects on stimulating the bone marrow, a major site of its production is actually in the airway epithelium where, through paracrine actions, it is absolutely required for alveolar macrophage maturation, and where through autocrine actions, it also appears to play a prominent role in maintaining the normally tight epithelial barrier. As discussed previously, recombinant GM-CSF delivered intranasally to the airway restores alveolar epithelial barrier function and decreases endotoxin-mediated lung injury in an experimental model of chronic alcohol ingestion (60). In fact, this strategy has already been examined in human subjects at risk for ARDS, although not in the context of known alcohol abuse. Specifically, a phase II clinical trial of 18 patients with septic shock demonstrated that patients who received recombinant GM-CSF treatment ($n = 10$) appeared to have less severe lung injury than placebo-treated patients ($n = 8$) (64). Furthermore, alveolar macrophages from septic patients given recombinant GM-CSF treatment had improved function *in vitro*, including respiratory burst, compared with macrophages from placebo-treated septic patients (64). Currently, a National Institutes of Health-sponsored multicenter clinical trial is investigating the potential efficacy of GM-CSF treatment in patients with established ARDS (alcohol abuse as a potential factor is not being assessed) to determine if this therapy can improve outcome (Dr. Theodore Standiford, personal commu-

nication). Therefore, the experimental findings and the widespread use of GM-CSF in other clinical settings support the rationale and feasibility of testing the efficacy of GM-CSF in a highly vulnerable group such as alcoholics with septic shock, where the incidence of ARDS is ~70%. Such a strategy might also augment alveolar macrophage immune functions and improve the outcome in alcoholics with severe community-acquired or nosocomial pneumonia, as the aforementioned experimental findings argue that alveolar macrophage immune function in the alcoholic lung is also rapidly restored by recombinant GM-CSF treatment (39).

Whether any of these therapeutic strategies will prove to be effective in decreasing the consequences of alcohol abuse on acute pulmonary diseases is at present unknown. In light of the complex pathophysiology, one must be understandably cautious. In fact, it is likely (in our opinion) that combination therapies will be required to treat acute lung injury, particularly in the highly vulnerable subset of patients with chronic alcohol abuse. Furthermore, more investigation is required in both experimental models and clinical studies to identify additional candidate therapies. As just one final example, interest in zinc deficiency has recently emerged. Even apparently well-nourished people with a history of chronic alcohol abuse may be deficient in micronutrients such as zinc, which is known to be essential for epithelial integrity (81), and zinc deficiency and oxidative stress appear to be interdependent (61). Therefore, the traditional regimen of empiric thiamine and folate treatment of alcoholics at the time of hospital admission might one day be expanded to include zinc and additional agents such as glutathione and GM-CSF. Figure 3 shows a schematic representation of the novel therapies for the alcoholic lung that have been discussed. As shown, strategies to prevent and/or minimize the development of the alcoholic lung phenotype would require chronic administration before the development of critical illnesses and might offer little or no benefit in the acute setting. However, this is the same for many chronic preventive therapies such as anti-hypertensives and lipid-lowering agents. In contrast, it is plausible to develop and test novel treatments such as recombinant GM-CSF or selective blockers of the AT2 receptor that might be effective even in the acute setting. Such strategies could theoretically reverse or at least mitigate the chronic effects of alcohol abuse on alveolar epithelial and macrophage function and decrease the morbidity and/or mortality of pneumonia and ARDS in these patients.

Any discussion of potential novel therapies for the alcoholic lung should emphasize the following: although alcohol abuse increases the susceptibility to pulmonary diseases such as pneumonia and ARDS, the pathophysiology of these acute illnesses appears to be essentially the same in non-alcoholic and alcoholic subjects. Therefore, treatment strategies ultimately shown to be effective for the alcoholic lung phenotype could be applied to the non-alcoholic population as well. In fact, any strategy that proves to be efficacious for the alcoholic lung would be predicted to be even more effective in less vulnerable individuals. Finally, the fundamental mechanisms by which alcohol abuse renders the lung susceptible to injury, including chronic oxidative stress, may be common to other chronic health conditions such as malnutrition and human immunodeficiency virus-1 infection. Therefore, anything we learn from studies of the alcoholic lung has important implications beyond the context of alcohol abuse alone.

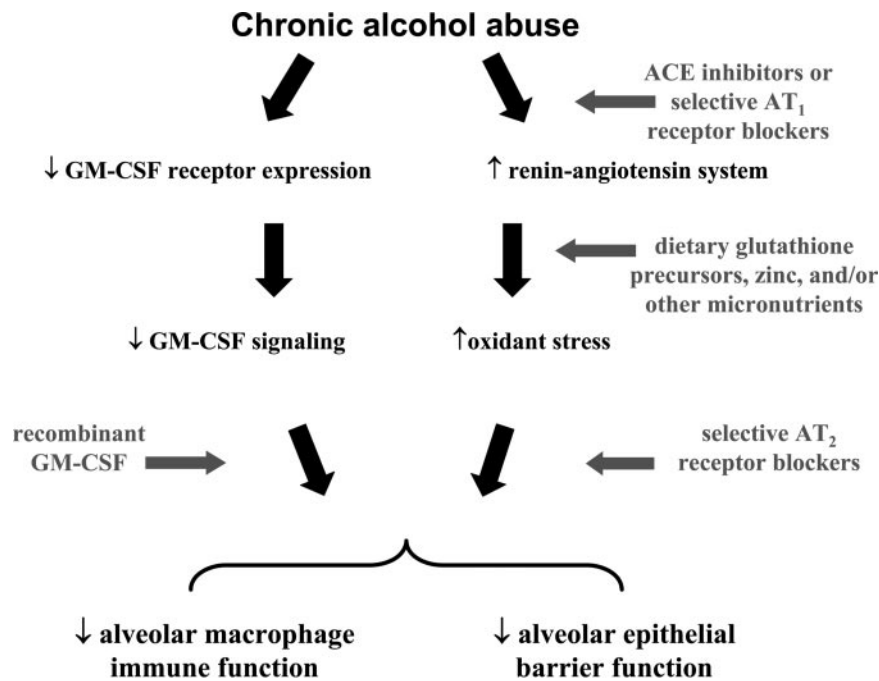


Fig. 3. Hypothetical pathophysiological sequence by which alcohol abuse causes oxidant stress and subsequent defects in alveolar epithelial and macrophage function and the potential therapeutic strategies that this sequence suggests. Experimental evidence from animal models implicates activation of the renin-angiotensin system (RAS), which, through the actions of its active product, angiotensin II, causes chronic oxidant stress and subsequent glutathione depletion within the lung. In these same experimental models, chronic blockade of angiotensin II [either angiotensin converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor (AT₁) receptor blockers] prevents glutathione depletion and subsequent lung dysfunction. In addition, although chronic dietary supplementation with procysteine, a glutathione precursor, has no apparent effect on the upstream RAS activation, it also prevents glutathione depletion and subsequent lung dysfunction. A second mechanism by which alcohol abuse impairs both alveolar epithelial and macrophage function appears to be through dampening of GM-CSF-dependent priming of these cells. Remarkably, treatment with recombinant GM-CSF *in vivo* restores alveolar epithelial and macrophage functions in alcohol-fed animals within 48 h and confers resistance to endotoxin-mediated lung injury. Whether GM-CSF signaling and RAS (and subsequent oxidant stress) represent separate or interconnected pathophysiological targets for alcohol is at present unknown, but cross-talk between these two pathways is possible. Finally, experimental evidence suggests that selective AT₂ receptor blockade in the acute setting could prevent cytokine- and/or oxidant-mediated alveolar epithelial cell death that is amplified in the alcoholic lung during sepsis. Although to date all of these strategies have been tested only in experimental models, these observations raise the exciting possibility that the alcoholic lung can respond to targeted therapies.

Summary. It is now recognized that alcohol abuse independently increases the incidence of ARDS two- to fourfold in at-risk patients. Within the past decade, studies in both experimental models and in human subjects implicate alcohol-mediated oxidant stress and alveolar epithelial dysfunction in rendering the lung susceptible to edematous injury in response to acute stresses such as sepsis and trauma. In parallel, impairments in upper airway barriers that normally prevent bacterial access to the lower airways, as well as dampening of both innate and adaptive immune functions within the alveolar space, render the alcoholic susceptible to serious infections including bacterial pneumonias and tuberculosis. These risks are inextricably linked, as bacterial pneumonia can itself lead to ARDS, and, in turn, patients with ARDS regardless of the initial cause are at increased risk for VAP. Although the mechanisms by which chronic alcohol abuse impairs both alveolar epithelial and macrophage function are complex, recent experimental findings are revealing some common mechanisms. Specifically, alcohol-induced oxidant stress, which is mediated via angiotensin II and ultimately leads to depletion of the critical antioxidant glutathione within the alveolar space, appears to be a key proximal step in the pathophysiology that leads to the phenotype of the alcoholic lung. Experimentally, glutathione supplementation prevents both alveolar epithelial

and macrophage dysfunction in alcohol-fed animals. Although chronic glutathione replacement and/or other dietary supplements, or chronic treatment with ACE inhibitors, could potentially limit development of the alcoholic lung phenotype in otherwise healthy alcoholics, they are unlikely to be effective treatments on their own for the acutely ill alcoholic with pneumonia and/or acute lung injury. In contrast, the more distal mechanisms by which alcohol abuse targets the alveolar epithelium and macrophage represent potential therapeutic targets even in the setting of acute illnesses. Most promising may be the acute administration of GM-CSF; experimental models have recently identified that alcohol dampens GM-CSF signaling in both the alveolar epithelium and macrophage and that treatment with recombinant GM-CSF rapidly restores epithelial and macrophage function. Clearly, the challenges are daunting, as the alcoholic lung is a complex and highly vulnerable phenotype. However, given the rapid pace at which laboratory and clinical studies are progressing in this field, one can hope that we are poised to translate recent and exciting experimental and clinical findings into new therapies that could significantly decrease the tragic consequences of pneumonia and/or acute lung injury in this susceptible patient population.

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