Pulmonary consequences of alcoholism: a critical review

Aj Mehta*

Abstract
Introduction
Alcohol use and abuse are prevailing practices in people throughout the world. Unfortunately, alcohol use disorders pose tremendous costs to both society and the individual. While alcoholism has many well-known medical consequences such as liver injury and pancreatitis, the effects of chronic alcohol exposure on the respiratory system are often overlooked. Specifically, studies have shown that alcohol abuse causes significant derangements in the lung and predisposes individuals to the development of pneumonia and acute lung injury. The aim of this paper was to discuss the pulmonary consequences of alcoholism.

Conclusion
Several important processes are responsible for this increased susceptibility to pulmonary pathology, including alterations in non-immunological defence systems, impairment of lung immunity and alveolar epithelial barrier dysfunction. These crucial defects comprise what has been referred to as the ‘alcohol lung phenotype’. Importantly, these abnormalities not only increase the risk of lung infections and injury but also they cause worse morbidity and mortality in alcoholics compared with non-alcoholics. While there are no current therapies to combat these alcohol-induced pulmonary abnormalities, current research has revealed several important mechanisms that may be exploited to develop new treatment options for this vulnerable population.

Introduction
Consumption of alcohol has been an important human custom since prehistoric times, and today it is the most widely used and abused drug in the world. While its moderate use is typically regarded as a social norm, many succumb to its pleasurable and addictive properties and develop an alcohol use disorder (AUD). For instance, approximately two-thirds of all adult Americans claim to drink alcohol, yet three-fourths of total alcohol consumption are by 10% of the population. While modest intake of alcohol has been associated with certain improved health outcomes such as decreased cardiovascular disease, unfortunately both acute and chronic intoxication can have devastating consequences. Specifically, alcohol abuse has been implicated in numerous homicides, suicides and motor vehicle accidents. By claiming more than 100,000 lives annually, it is the third leading cause of preventable death in the United States.

In addition to the adverse implications for society, alcoholism has significant psychological, health and social consequences for the individual. Pathological alcohol use has been linked to several mental health disorders such as depression, anxiety and post-traumatic stress disorder. In these cases, alcohol abuse can further exacerbate an already delicate mental state. Beyond these psychological consequences, alcohol can elicit changes in virtually every organ system in the body due its small size and solubility in both water and lipids. These properties facilitate its ability to saturate practically all bodily tissue types. Even though the most widely recognised target organ damage is alcohol-related liver dysfunction, overall there are roughly 60 types of diseases and injuries that have been linked to alcohol use. Other commonly recognised targets of alcoholism include the central nervous system, the heart and the pancreas, all of which contribute to significant morbidity and mortality for the individual.

Although not as well acknowledged, the organ that is perhaps most rapidly affected by chronic alcohol ingestion is the lung. While alcohol itself does not cause direct injury to the lung in a fashion similar to hepatic cirrhosis, chronic exposure to alcohol renders individuals susceptible to the development of pulmonary infections and lung injury. In fact, experimental studies have shown that these alcohol-induced pulmonary derangements occur in as little as 6 weeks of regular consumption. The notion that alcohol abusers have an increased tendency towards pneumonia and other lung infections has been recognised for centuries by prominent physicians such as Benjamin Rush and William Osler. Only within the last 20 years, however, it was described that alcoholics are at significantly increased risk for the development of acute lung injury and acute respiratory distress syndrome (ARDS). ARDS, which often occurs as a sequela of pneumonia, is a frequent yet devastating illness in intensive care units across the world with a mortality rate approaching 40% in most studies. Not only are alcoholics at greater risk of developing ARDS, they also portend a worse prognosis when they do.
Alcoholism and pneumonia: effects on non-immunological defences in the airway

Alcohol exposure has important consequences throughout the entire respiratory system, spanning from the oropharynx to the lung parenchyma, which are outlined in Figure 1. Clinical studies show that alcoholics have a much higher incidence of severe pneumonia caused by more virulent gram-negative organisms\(^\text{12,13}\), and many of these observations can be explained by changes that occur in the upper airway. Most clinical practitioners can attest to the fact that alcoholics have very poor oral hygiene. While this may be, in part, due to poor lifestyle choices and inadequate nutritional intake, alcoholism also plays a direct role in the process. For example, chronic alcohol ingestion has been shown to not only impair salivary gland secretion but also the ability of saliva to appropriately buffer acid. These defects accelerate gingival disease, promote tooth decay and encourage colonisation of the mouth with gram-negative bacteria such as *Klebsiella pneumonia*\(^\text{14}\). Still, under normal circumstances, the lungs would be protected from these potential pathogens by various protective reflexes that prevent aspiration. However, passage of these organisms into the trachea is facilitated by the effect of acute alcohol intoxication on diminishing host defences such as the gag and cough reflex. Taken together, these alcohol-related alterations in oral flora and the upper airway provide a simple path for virulent bacteria to reach the lower airways.

Once pathogens reach the lower airway, the host response involves both non-immunological and immunological defence mechanisms. The most important non-immunological method is a specialised clearance apparatus known as the mucociliary escalator. In healthy individuals, this process ensures that pathogens and debris are continuously cleared from the lower airways. Even when small aspiration events occur, this self-protective operation ensures that pulmonary infections do not occur. Specifically, the trachea and bronchi are lined with ciliated pseudostratified columnar epithelium, which consist of ciliated cells and goblet cells that secrete mucus. The mucus acts to trap foreign pathogens and debris, and the ciliated cells beat in concert to move material from the lower airways towards the laryngopharynx where it can be coughed out and/or swallowed. In addition to its inhibitory effect on the cough reflex, studies have shown that chronic alcohol exposure can decrease ciliary beat frequency and thereby interfere with the mucociliary escalator\(^\text{15}\). The combined effect of alcoholism on these non-immunological host defence systems leaves individuals much more vulnerable to the development of pulmonary infections.

Alcoholism and pneumonia: effects on lung immunity

Since the respiratory system is constantly exposed to the outside...
In normal healthy lungs, resident alveolar macrophages are the first immunological line of defence against infection and make up over 90% of all immune cells in the lower airways. These alveolar macrophages play a major role in lung homeostatic functions such as surfactant recycling, but their primary immune task involves phagocytosis of pathogens and foreign substances. However, alveolar macrophage phagocytic function is significantly compromised in a host that chronically ingests alcohol. Specifically, experimental studies have demonstrated that alcohol exposed alveolar macrophages have significantly decreased ability to not only phagocytose bacteria but also diminished respiratory burst required to kill ingested organisms. Further, human studies have illustrated similar impairment in alveolar macrophage immune function in alcoholics compared with non-alcoholics.

The mechanisms by which alcohol abuse impairs alveolar macrophage function have been evaluated in both experimental and human studies. While the exact mechanism responsible is not completely understood, it is likely that multiple processes contribute and act in concert. First, experimental models have consistently shown that alcohol is responsible for depletion of the antioxidant glutathione, which causes oxidative stress in the lung and impairs alveolar macrophage maturation and function. In these studies, treatment with glutathione precursors both reverses oxidative stress and restores alveolar macrophage immune function. Clinical studies have confirmed the presence of glutathione depletion in human alcoholic subjects. Second, alcohol abuse alters intracellular signalling of granulocyte macrophage colony-stimulating factor (GM-CSF), which is a peptide that is essential for alveolar macrophage terminal differentiation, maturation and function. Animal models of alcohol ingestion have demonstrated a decrease in GM-CSF receptor expression on the cell surface of alveolar macrophages. These alcohol-mediated defects prevent proper maturation and normal functioning of the alveolar macrophage, both of which can be reversed by treatment with exogenous GM-CSF. Interestingly, human studies have also confirmed that there is decreased cell surface expression of the GM-CSF receptor in alveolar macrophages from alcoholics compared with non-alcoholics. Finally, nutritional deficiencies have also been implicated in alcohol-induced alveolar macrophage dysfunction. Specifically, experimental models of alcoholism illustrate that there is both macrophage intracellular and extracellular zinc deficiency in the alveolar space even when animals are fed a zinc-sufficient diet. Zinc is an essential trace element that is required for numerous enzymatic activities and particularly plays an important role in the immune response. Dietary zinc supplementation in these animal studies re-establishes normal zinc levels in the lung even during continued alcohol ingestion and more importantly restores alveolar macrophage immune function. Interestingly, human alcoholics exhibit a similar alveolar macrophage zinc deficiency even when serum zinc levels fall in the normal range. Taken together, these studies demonstrate that multiple mechanisms can explain alcohol-induced alveolar macrophage immune dysfunction and more excitingly offer multiple potential targets for therapeutic intervention.

While the alveolar macrophage is an important first line of defence against microbial invasion, once bacterial infection actually occurs in the respiratory system, alveolar macrophages are responsible for production of pro-inflammatory cytokines that will recruit other immune cells to the lung to assist with pathogen clearance and cause lung consolidation in an effort to contain the infection. Specifically, tumour necrosis factor-α (TNF-α) is an important secretory product of alveolar macrophages and a mediator of neutrophil influx in the setting of pneumonia. While the effect of alcohol on TNF-α production and release remains controversial, studies have illustrated that alcohol exposure reduces pulmonary expression of important TNF-regulated neutrophil chemokines and modifies intrinsic functions of the neutrophil itself. Therefore, alcohol exposure results in an overall decrease in neutrophil recruitment during an infectious insult, and parallel to its effects on alveolar macrophage function, alcohol-mediated alterations in the neutrophil cause defects in their ability to adhere to the vascular wall as well as phagocytose and kill bacteria.

In addition to its effects on innate immunity, there are several important consequences of alcohol exposure on adaptive immunity as well. For example, it has been recognised for over a century that alcoholics are at increased risk for infection with Mycobacterium tuberculosis. Active tuberculosis is a unique pulmonary bacterial infection that involves cell-mediated immunity, which is one aspect of the adaptive immune response. While the mechanism by which alcoholics are predisposed to tuberculosis is not fully understood, there are significant alcohol-induced abnormalities in the number and function lymphocytes. Specifically, alcoholism has been shown to cause generalised lymphopaenia, especially in patients with chronic liver disease. Further, studies show that...
exposure to alcohol not only decreases lymphocyte count, but it also diminishes lymphocyte response to stimulation\textsuperscript{36}. Taken together, these findings highlight that chronic exposure to alcohol causes dysregulation of all aspects of lung immunity in the lower airway, including innate immune reactions as well as the adaptive immune response and cell-mediated immunity.

Alcoholism and ARDS: effects on alveolar epithelial barrier function

Given the multiple perturbations in the airway caused by alcoholism, individuals are vulnerable to aspiration and numerous pulmonary infections. Importantly, pneumonia and aspiration events are the most common direct causes of acute lung injury and ARDS\textsuperscript{27}. While this relationship may be one explanation for alcoholics’ increased risk for this syndrome, there is also experimental evidence that alcohol causes specific defects in the alveolar epithelium that leave the host susceptible to lung injury. ARDS is a life-threatening form of hypoxemic respiratory failure characterised by inflammation in the lung parenchyma leading to pulmonary oedema. Under normal conditions, alveolar epithelial cells form a tight barrier and prevent fluid from traversing the epithelium. In the case of ARDS, the inciting event (e.g. pneumonia) causes lung injury through release of pro-inflammatory cytokines, which result in toxic mediators that damage the pulmonary alveolar epithelium and capillary endothelium. This injury results in leakage of proteinaceous fluid into the normally dry alveolar spaces, causing a significant impairment in gas exchange. Clinically, patients exhibit bilateral pulmonary oedema and severe hypoxemia necessitating mechanical ventilation. While alcoholism does not directly cause ARDS, experimental evidence demonstrates that chronic alcohol exposure leaves the alveolar epithelium more leaky and primed for injury. Precisely, one animal study demonstrated that lung oedema is much more pronounced in response to endotoxin among alcohol-fed rats compared with control-fed rats\textsuperscript{28}. Further, when alveolar epithelial cells are isolated and cultured from animals that chronically ingest alcohol, they are much more much more permeable compared with epithelial cells cultured from non-alcoholic animals\textsuperscript{27}. Taken together, these studies illustrate that alcohol abuse gives rise to significant derangements in alveolar epithelial barrier function that cause increased permeability, and analogous to the pathogenesis of ARDS, oedematous injury will only occur in response to a stressor.

The mechanisms that underlie alcohol-induced alveolar epithelial barrier dysfunction are similar to those that are responsible for impairing alveolar macrophage immune function. Specifically, increased oxidative stress, impaired GM-CSF signalling and pulmonary zinc deficiency have all been implicated in causing similar defects within the alveolar epithelium\textsuperscript{7,21,29,30}. While the exact mechanism is not fully understood, these studies highlight that it is likely that multiple processes may be involved collectively. Importantly, and parallel to studies pertaining to the alveolar macrophage, treatment with glutathione precursors, exogenous GM-CSF and dietary zinc will reverse alcohol-related defects in the alveolar epithelium and restore normal barrier function. While these treatments have not been well studied in human subjects with alcoholism and lung injury, it is motivating that experimental studies have identified several potential treatment possibilities.

Conclusion

Alcohol use and abuse are burdensome for society and the individual. While the majority of literature emphasises liver disease, pancreatitis and central nervous system abnormalities as primary targets of alcohol consumption, there is a growing body of evidence that alcoholism causes significant derangements in the lung. Through a variety of mechanisms, chronic alcohol ingestion perturbs both immunological and non-immunological host defence mechanisms within the airway that result in alveolar macrophage immune dysregulation and alveolar epithelial barrier dysfunction. These important defects render alcoholic individuals susceptible to the development of pneumonia and ARDS. While there are no currently approved treatments for the alcohol lung phenotype, current research efforts are continuing to uncover several potential therapeutic strategies for this vulnerable population as they continue to try and work through their disabling addiction.

References


Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)