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Alcohol 90 (2021) 11–17

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Alcohol use disorder: A pre-existing condition for COVID-19?

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ARTICLE INFO

Article history:
Received 11 September 2020
Received in revised form
2 October 2020
Accepted 5 October 2020

Keywords:
alcohol
coronavirus
COVID-19
injury
lung
SARS-CoV-2

ABSTRACT

Alcohol misuse is long established as a contributor to the pathophysiology of the lung. The intersection of multi-organ responses to alcohol-mediated tissue injury likely contributes to the modulation of lung in response to injury. Indeed, the negative impact of alcohol on susceptibility to infection and on lung barrier function is now well documented. Thus, the alcohol lung represents a very likely comorbidity for the negative consequences of both COVID-19 susceptibility and severity. In this review, we present the known alcohol misuse ramifications on the lung in the context of the current coronavirus pandemic.

Introduction

The coronavirus disease 2019 (COVID-19) has become a pandemic with over 34 million people infected worldwide and more than 1 million deaths at the time of this writing (https://coronavirus.jhu.edu). COVID-19, caused by the betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is spread through respiratory droplets. The most common symptoms of COVID-19 are fever, dry cough, dyspnea, and fatigue, although asymptomatic infections are widely recognized as well (Ren et al., 2020). Other than those individuals with a pre-existing condition, morbidity and mortality appear to be greatest in men, older persons, and, in some reports, cigarette smokers (Grasselli et al., 2020; Wu & McGoogan, 2020). The pathogenesis of SARS-CoV-2 infection can be described in two phases: in the first phase, an initial innate defense occurs in an attempt to provide lung defense. This is followed by a subsequent second phase of inflammation-associated tissue injury. In susceptible people, SARS-CoV-2 infection can progress to severe viral pneumonia and can lead to acute respiratory distress syndrome (ARDS). ARDS is a severe, diffuse inflammatory lung injury that often requires mechanical ventilation. In response to such a "cytokine storm", uncontrolled hyperinflammation can result in multi-organ failure.

Very little is known about how heavy alcohol intake might influence COVID-19 infection. While less than 15% of consumed alcohol enters the lung, exhalation is nonetheless a significant process for alcohol excretion, as evidenced by the common use of the breathalyzer test to reliably estimate blood alcohol levels (Borkenstein & Smith, 1961). Heavy alcohol intake profoundly changes pulmonary innate and adaptive immunity, leading to higher rates of viral pneumonia (de Roux et al., 2006), influenza A infection (Greenbaum et al., 2014), respiratory syncytial virus (RSV) infection (Jerrells et al., 2007; Wyatt et al., 2019), and bacterial pneumonia (Cappa & Coleman, 1923; Fernández-Solá et al., 1995; Saitz, Ghali, & Moskowitz, 1997). In the 1918 influenza pandemic, heavy alcohol intake was recognized as a risk factor for poor outcomes (Oxford, 2000). Many recent publications describing COVID-19 patients failed to include alcohol use history (Bhatraju et al., 2020; Wu & McGoogan, 2020). Further complicating this omission is the need to make distinctions between those effects that are seen in the acute setting of intoxication versus those that would be expected from chronic, longstanding alcohol exposure.

Increased alcohol intake during the COVID-19 outbreak

Over half of the population surveyed in China reported increases in depression, anxiety, or stress in response to COVID-19 (Wang

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https://doi.org/10.1016/j.alcohol.2020.10.003

et al., 2020). During social isolation, alcohol use disorders (AUDs) increased in Hubei province compared to other provinces in China due to COVID-19 outbreak (Ahmed et al., 2020). Hubei experienced a 10-fold increase in hazardous drinking compared to other provinces with fewer restrictions (Ahmed et al., 2020). In the United States, late April 2020 alcohol sales exhibited a 477% increase in sales compared to the same week in April 2019 (Nielsen Retail Measurement Services, 2020). Social isolation and loneliness have long been recognized as a predisposing factor for problem drinking (Allen, Peterson, & Whipple, 1981). Depending upon local economic conditions during the COVID-19 pandemic, people may initially consume less alcohol due to financial constraints, but eventually increase alcohol use as a consequence of elevated stress over time (Rehm et al., 2020).

Alcohol intake has been implicated in at least one COVID-19 outbreak (Mungmungpuntipantip & Wiwanitkit, 2020). In Thailand, 15 people in their 20s gathered for a farewell party. Eleven of them drank alcohol out of a single glass and all developed COVID-19 within a week. Four other individuals at the party who did not drink did not develop the illness. Other large gatherings involving heavy alcohol intake such as the Mardi Gras in Louisiana also may have led to outbreaks and accelerated spread of the disease (Schuchat, 2020).

Another way alcohol can encourage infection is through myths that drinking alcohol can protect against COVID-19 infection. A myth was propagated in Iran that gargling or drinking alcoholic beverages would disinfect the mouth or inside of the body and prevent infection by killing the virus. Because alcohol production is not legal in Iran, it is typically obtained through the black market. At least 180 people in Iran died drinking black market alcohol that was contaminated with methanol, with over 2500 seeking medical care (Delirrad & Mohammadi, 2020). The myth that alcohol prevents COVID-19 infection prompted the World Health Organization (World Health Organization, 2020) and the National Institute on Alcohol and Alcoholism (National Institute on Alcohol Abuse and Alcoholism, 2020) to release statements that heavy alcohol intake does not prevent COVID-19.

AUDs and the lung

The ongoing pandemic is increasing hazardous drinking behaviors in a variety of ways. In spite of a recent report that heavy alcohol intake is not associated with COVID-19 hospitalization in the United Kingdom (Hamer, Kivimäki, Gale, & Batty, 2020), there are numerous ways in which alcohol misuse should be problematic in the context of COVID-19 infection (Testino, 2020). Alcohol has a negative impact on lung innate defense and response to injury (Yeligar & Wyatt, 2019). It has long been known that alcohol impairs the ability of the lung to fight infection (Yeligar, Chen, et al., 2016). The lung is exposed to more than 11 000 liters of air per day, based on average minute ventilation. This air contains viral particles, bacterial components such as lipopolysaccharide, dust, particulate matter, and pollutants. The healthy lung utilizes a complex system to protect itself from such environmental toxicants involving physical barriers such as cough and mucociliary clearance to help rid itself of these pathogens and pollutants. Once the mechanical barriers are breached, lung immune effector substances and cells exist to accomplish clearance. Heavy alcohol intake can have a detrimental effect on each of these protective mechanisms, making it likely that substantial and long-term alcohol intake contributes to poor outcomes with COVID-19. We will review each of these mechanisms in turn.

Lung function

A hallmark symptom of COVID-19 infection is dyspnea, or shortness of breath. Alcohol is already associated in some circumstances with dyspnea (Cardet et al., 2014), thus suggesting the risk for increased dyspnea in the AUD patient with COVID-19. Because exhalation of alcohol is the primary route of lung excretion, diminished removal of alcohol from the lungs of a COVID-19 infected individual could potentially result in increased exposure to direct alcohol impairment of lung innate defenses or elevated production of alcohol metabolites in lung injury.

Mechanical clearance

Although alcohol is long known to suppress coughing (Calesnick & Vernick, 1971), the first line of defense against inhaled infectious agents is typically ascribed to mucociliary clearance. The large airways are lined with ciliated and mucus-producing airway epithelial cells. Cilia beat in a coordinated manner to propel mucus containing trapped particles out of the lung to the oropharynx. Such clearance is not passive, as increases in cilia motion are regulated by the action of cyclic nucleotides localized to the ciliary axoneme (Wyatt, Forgèt, & Sisson, 2003). Heavy alcohol consumption uncouples this cyclic nucleotide pathway in cilia preventing any increase in cilia beat frequency (Wyatt & Sisson, 2001). If the heavy drinker also smokes cigarettes, which occurs frequently (DiFranza & Guerrera, 1990), the cilia may be actively slowed through the action of protein kinase C epsilon (Wyatt et al., 2012), an enzyme upregulated in the airway ciliated cells of older persons (Bailey, Kharbanda, Katafiasz, Sisson, & Wyatt, 2018). Indeed, both the duration and intensity of respiratory viral infection are increased in animal models of cigarette smoke and alcohol co-exposure (Wyatt et al., 2019). It is not known how heavy alcohol intake affects mucus quantity or quality in the lung. However, duodenal goblet cell hyperplasia has been reported in those with AUDs (Lev, Thomas, Parl, & Pitchumoni, 1980), making it possible that pulmonary goblet cells are also affected. Combined with the co-morbidity of cigarette smoking, AUDs would very likely result in compromised host mechanical clearance under conditions of SARS-CoV-2 exposure, particularly in older individuals.

Antimicrobial agents in the airway lining fluid

If a virus evades mucociliary clearance, the next layer of pulmonary defense is antimicrobial peptides. The human cathelicidin, LL-37, is produced by epithelial cells and neutrophils in a vitamin D-dependent manner. It has been shown to provide protection against influenza A (Tripathi et al., 2013). Recently, it has been speculated to play an important anti-microbial role against SARS-CoV-2, as vitamin D deficiency is a putative risk factor for COVID-19 (Crane-Godreau, Clem, Payne, & Fiering, 2020; Grant et al., 2020; Panfili et al., 2020). *In vitro*, human airway epithelial cells have been shown to produce lower levels of LL-37 after alcohol exposure in response to CYP2E1-generated reactive oxygen species (ROS) production, impacting vitamin D metabolism (Ogunsakin, Sriyotha, Burns, Hottor, & McCaskill, 2019). This lower airway level of LL-37 has the potential to impair the innate immune response to viruses such as COVID-19.

Once the viral particles have passed through the airways without being cleared, they enter the alveolus. The alveolus is the site where pneumonia and ARDS develop. When the viral particles enter the airways and alveolae, they are met by surfactants. The surfactant protein D (SP-D) is known to bind to the Spike protein of SARS-CoV-1 (Leth-Larsen, Zhong, Chow, Holmskov, & Lu, 2007), the virus that caused the SARS outbreak in 2002. When the Spike protein is bound by SP-D, it is unable to interact with ACE2 to infect cells. Heavy alcohol intake, especially in conjunction with smoking, can lead to protein adduction that alters its function (McCaskill et al., 2011). When it is adducted, it can also change the

inflammatory response of alveolar macrophages (Sapkota, Kharbanda, & Wyatt, 2016). Furthermore, decreased expression of lung surfactant has been shown in animal models of chronic alcohol (Lazic et al., 2007). This suggests that alcohol decreases lung surfactant mRNA, which may negatively impact host defense against viral infection.

Another important antimicrobial in mucosal surfaces such as the lung is secretory immunoglobulin A (sIgA). While little is currently known about the role of sIgA in COVID-19, some studies have identified the presence of serum IgA against SARS-CoV-2 in COVID-19 patients (Okba et al., 2020) and, in some cases, elevated IgA was demonstrated in bronchoalveolar lavage fluid (Du et al., 2008; Lu et al., 2010). Such reports point to examining the sIgA mucosal immunity response in COVID-19 patients (Moreno-Fierros, García-Silva, & Rosales-Mendoza, 2020). Again, alcohol could have a negative impact on any sIgA response to COVID-19, as individuals with AUD demonstrate decreased production of lung sIgA to some antigens (Sapkota et al., 2017).

Immune and inflammatory mediators

SARS-CoV-2 infection often leads to a "cytokine storm" involving the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1, IL-8, and MCP-1). To further complicate matters, the COVID-19-mediated cytokine storm is not self-limiting. In fact, the macrophage-derived "eicosanoid storm", which is characterized by the release of pro-inflammatory bioactive lipid mediators, such as prostaglandins and leukotrienes, often follows the initial cytokine storm. This rapid and severe inflammatory condition is thought to contribute to rapid systemic organ failure observed in critically ill COVID-19 patients. In addition, the effects of alcohol upon activation of danger-associated molecular pattern signaling cascades (DAMPS) may be important (Harris, Mcalister, Willoughby, & Sivaraman, 2019). Viral pulmonary infections such as influenza have been shown to activate the receptor for advanced glycation end products (RAGE) that are heavily expressed on the alveolar epithelium (Andersson, Ottestad, & Tracey, 2020). Alcohol-dependent activation of DAMPS in tissue may contribute to poor pulmonary prognosis in people experiencing COVID-19.

Similarly, the airways of individuals with AUDs have higher levels of inflammatory cytokines and chemokines at baseline, including CXCL8, IL-1β, IL-5, IL-6, IL-12, GM-CSF, IFNγ, and CCL2 (Camargo Moreno, Lewis, Kovacs, & Lowery, 2019). Likewise, alveolar macrophages from those with AUDs also express higher levels of inflammatory cytokines, including TNF-α, CXCL8, CXCL10, and CCL5 (O'Halloran et al., 2016). These data suggest that chronic smoldering inflammation caused by chronic alcohol use could exacerbate the acute inflammatory response to viral infection.

Alveolar macrophage function

Alveolar macrophages play an essential role in defending the lung from viral infection. Mice that lack alveolar macrophages have more severe hypoxia and respiratory failure in response to influenza viral infection (Schneider et al., 2014). The role of macrophages in host defense against SARS-CoV2 is ill defined. The current data suggest that macrophages contribute to systemic hyperinflammation, also known as macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistocytosis (sHLH), which is seen in COVID-19 subjects. Specifically, post-mortem analyses of hilar and subscapular lymph nodes, as well as spleens from patients who died from COVID-19, demonstrate increased numbers of ACE2-expressing CD68+CD169+ macrophages in both the lymph nodes and spleen. In addition, SARS-CoV-2 nucleoprotein antigen was detected in the macrophages and was associated with upregulation of IL-6 (Feng et al., 2020).

Heavy alcohol use significantly reduces lung macrophage cytokine production (Standiford & Danforth, 1997) and profoundly affects alveolar macrophage function (Mehta & Guidot, 2012; Rimland & Hand, 1980). Those with heavy alcohol use are unable to efficiently phagocytose infectious particles. This is because alcohol decreases glutathione availability in the lung (Brown, Harris, Ping, & Gauthier, 2004), which leads to increased oxidative stress (Liang, Harris, & Brown, 2014) and PPARγ activation (Yeligar, Mehta, Harris, Brown, & Hart, 2016). Alcohol further impairs macrophage function following engulfment, as antigen presentation, as well as lymphocyte numbers, are reduced by alcohol (Molina, Happel, Zhang, Kolls, & Nelson, 2010). In comparison, circulating monocytes from alcohol-abusing subjects express TNFα receptors and spontaneously produce TNFα (Gobejishvili et al., 2006). In addition, alcohol-associated monocytes stimulated by LPS release even higher levels of TNFα than monocytes from healthy subjects. Alcohol-using patients also exhibit elevated systemic levels of other cytokines (e.g., IL-6, IL-8, and IL-18) and chemokines produced by circulating monocytes and liver macrophages (Afford et al., 1998; Fisher, Neil, Williams, & Adams, 1999).

Collectively this suggests that alcohol use not only impairs the pulmonary macrophage response to SARS-CoV2 by inhibiting cytokine production, viral phagocytosis, and antigen presentation, but that it may also significantly contribute to MAS by increasing the inflammatory capacity of circulating and liver macrophages.

Neutrophil recruitment

Neutrophils are one of the first cells recruited to the lungs in response to infection, including viral infection (Galani & Andreakos, 2015). Specifically, SARS-CoV2, as well as other pandemic viruses, including influenza H1N1, SARS-CoV, and Middle East respiratory syndrome (MERS) coronavirus, are associated with neutrophilic infiltration at sites of infection and development of ARDS (Perlman & Dandekar, 2005). Alcohol has a direct toxicity on the bone marrow to impair the production of neutrophils (Perlino & Rimland, 1985). In fact, alcohol users with severe bacterial infection often present with granulocytopenia (Perlino & Rimland, 1985). Apart from diminished numbers of neutrophils, alcohol use also results in profound defects in neutrophil recruitment to sites of inflammation or infection, phagocytic activity, and activity of both superoxide and elastase (Stoltz et al., 1999). Thus, in chronic heavy alcohol use, neutrophils are slow to be recruited and neutrophilic inflammation is slow to resolve in bacterial lung infections (Molina et al., 2010).

Interestingly, it has been shown that sera from patients with COVID-19 have elevated levels of specific markers of neutrophil extracellular traps (NETs; i.e., cell-free DNA, myeloperoxidase-DNA, and citrullinated histone H3). This may be clinically important, as both cell-free DNA and myeloperoxidase-DNA levels were higher in hospitalized patients receiving mechanical ventilation as compared with hospitalized patients breathing room air (Zuo et al., 2020). Similar trends are seen in patients with influenza A infection, as high levels of NETs predict a poor prognosis (Zhu et al., 2018). Additionally, sera from individuals with COVID-19 triggered NET release from control neutrophils *in vitro*. Recently, alcohol has also been shown to impair the production of NET, as well as NET-mediated killing of both Gram-negative and Gram-positive bacterial pathogens (Jin, Batra, & Jeyaseelan, 2017), suggesting that alcohol may be protective, at least in regard to COVID-19-mediated NET release and NETosis. Similar results have been seen in influenza-infected mice, as inhibition of NETosis leads to protection from lethal infection. The benefits of blocking or reducing

neutrophils in alcohol-consuming individuals, however, may be limited as removal of neutrophils from influenza-infected mice led to higher viral titers and lethality (Meyerholz et al., 2008).

Alveolar barrier function

The alveolar barrier prevents edema in the alveoli by restricting the diffusion of large solutes and facilitating gas exchange (Burnham, Halkar, Burks, & Moss, 2009). Chronic alcohol ingestion increases the alveolar barrier permeability. Tight junctions are responsible for the barrier and regulate the diffusion of solutes between cells (Zhang, Li, Young, & Caplan, 2006). Alcohol deteriorates the proteins occludin and zonula occludins 1 (ZO-1), which are integral for tight junctions (Zhang et al., 2006). When occludin and ZO-1 deteriorate, this deterioration disrupts the tight junction's integrity and allows it to become leakier.

An increase in permeability in the alveoli barrier leads to higher chances of acute lung injury (ACI). A leakier tight junction from alcohol abuse increases water, sodium, and protein levels in the alveolar space (Zhang et al., 2006). Zinc deficiency in response to chronic alcohol consumption has been associated with loss of barrier function (Skalny, Skalnaya, Grabeklis, Skalnaya, & Tinkov, 2018). This causes a higher likelihood of an edematous injury. Patients with ACI or increased water in their lungs face higher chances of acquiring ARDS, which is more severe and can be fatal (Zhang et al., 2006).

Pulmonary capillary leak in response to COVID-19 infection has also been reported (Bahloul et al., 2020). Again, zinc status in the lung has been suggested to be important in the maintenance of capillary integrity, further underscoring the importance of understanding the impact of alcohol on zinc utilization in lung (Skalny et al., 2020).

AUDs and lung disease

ARDS

The most severe form of COVID-19 infection results in acute respiratory distress syndrome (ARDS). ARDS is characterized by severe hypoxemia and bilateral diffuse infiltrates on chest roentgenogram. Most patients with ARDS require high levels of oxygen or mechanical ventilation. A clear disconnect exists between an early report of severe COVID-19 and ARDS, which failed to find an alcohol use association (Liu et al., 2020), and the established risk factor of chronic, heavy alcohol use in developing ARDS (Inciardi et al., 2020). Heavy alcohol use also predisposes those with ARDS to develop multi-system organ failure (Wilke, Kaiser, Ferency, & Maisch, 1996).

Alcohol increases the mortality and severity of ARDS. Alcohol abuse alters the oxidative stress response and causes the lung to be more susceptible to edematous stress by increasing the alveolar barrier permeability (Esper, Burnham, & Moss, 2006). By decreasing glutathione (GSH), it impairs the immune response of the lungs. With higher oxidative stress, GSH levels are lower, and oxygen radical levels increase. Alveolar macrophage phagocytosis is hindered due to the increase in free oxygen radicals, and the cells cannot rid themselves of the toxic oxidants (Brown et al., 2004). Severity and mortality of ARDS increase when alcohol has increased alveolar barrier permeability and lowered GSH levels.

Chronic heavy alcohol use predisposes the lung to these changes by depleting GSH stores (Guidot & Roman, 2002). GSH is an antioxidant that detoxifies oxidant radicals and protects tissues from oxidant injury (Rahman & MacNee, 2000). Alcohol is metabolized through the cytochrome p450 system. Acetaldehyde is the major by-product, which induces oxygen radical generation and lipid peroxidation (Brown et al., 2004). Increased oxygen radicals and lipid peroxidation lead to a decrease in GSH concentration. Without high GSH levels, the lungs are more susceptible to oxidative stress because they cannot control the detoxification and excretion of toxic oxidants, increasing the likelihood of ARDS (Brown et al., 2004).

COPD

An early meta-analysis of individual reports reveals that severe COVID-19 is associated with COPD (Lippi & Henry, 2020). In fact, COPD is the single greatest predictor of comorbidity for severe COVID-19 leading to ICU admission (Jain & Yuan, 2020). Cigarette smoking is an established cause of COPD, and one putative mechanism for increased COVID-19 risk is the smoking-induced upregulation of ACE2 in lung (Brake et al., 2020). However, alcohol use is prevalent in smokers and alcohol itself has been shown to be an independent risk factor for COPD (Nihlen, Greiff, Nyberg, Persson, & Andersson, 2005; Siu, Udaltsova, Iribarren, & Klatsky, 2010; Tabak et al., 2001). Studies examining alcohol or its metabolites on ACE2 have yet to be reported.

PAH

Unusual vasculature endothelial pathologies are being observed with COVID-19 (Ackermann et al., 2020). It is not yet clear whether pulmonary arterial hypertension (PAH) is a risk factor for severe COVID-19 (Farha, 2020), although management of PAH in the context of coronavirus infection is a concern (Ryan et al., 2020). As with several chronic disease states, excessive alcohol consumption is associated with hypertension (Sterling et al., 2020). The intersection of alcohol, COVID-19, and pulmonary hypertension remains to be explored.

HIV

High-risk alcohol misuse is an established problem in the HIV population (Justice et al., 2006; Lewden et al., 2005). Such alcohol misuse is known to be associated with poor outcomes related to lung infections in HIV patients (Jolley, Alkhafaf, Hough, & Welsh, 2016). Recent studies implicate the effect of alcohol on altering gut microbiota as a mechanism for this HIV-associated susceptibility to lung infection (Samuelson et al., 2019). Not surprisingly, a recent meta-analysis showed that existing immunosuppression is associated with a 3.3-fold increased risk of severe COVID-19 disease (Gao, Chen, Liu, Shi, & Tian, 2020).

Conclusion

Alcohol affects nearly every cell in the lung. Most of these changes potentially put those that drink heavily at higher risk for COVID-19 infection, and more severe pneumonia or ARDS. More research is needed to help us understand how to better treat those with alcohol use disorders with COVID-19.

Author statement

Kristina Bailey: Conceptualization, Writing – Original draft preparation; Reviewing and Editing; **Derrick Samuelson:** Writing – Original draft preparation; Reviewing and Editing; **Todd Wyatt:** Conceptualization, Writing – Original draft preparation; Reviewing and Editing.

Funding

This work was supported by the Department of Veterans Affairs (I01BX003635 to TAW, and I01BX005413 to TAW and KLB) and the National Institutes of Health (R01AG053553 to KLB and R00AA026336 to DRS). TAW is the recipient of a Research Career Scientist Award (IK6BX003781) from the Department of Veterans Affairs.

Declaration of competing interest

None.

Acknowledgments

The authors wish to acknowledge Madyson Anglim for her contributions and thank Ms. Lisa Chudomelka for expert editorial assistance in the preparation of this manuscript.

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