Environmental Risk Factors for Acute Respiratory Distress Syndrome

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KEYWORDS

• Acute respiratory distress syndrome • Epidemiology • Modifiable risk factors • Alcohol abuse • Cigarette smoking • Mechanisms • Future interventions

KEY POINTS

- Multiple observational studies have demonstrated that chronic alcohol use is a risk factor for the development of acute respiratory distress syndrome (ARDS).
- Alcohol use may promote the development of ARDS via increased angiotensin II, producing increasing oxidative stress, which creates baseline alveolar epithelial dysfunction and primes the lung for developing noncardiogenic pulmonary edema.
- Although less studied than alcohol use, cigarette smoke exposure also seems likely to be a risk factor for ARDS.
- Cigarette smoke may prime the lung to develop ARDS by creating baseline epithelial and endothelial injury, likely through direct exposure to powerful oxidants contained in cigarettes.

The acute respiratory distress syndrome (ARDS) represents a significant health burden. Despite numerous efforts to identify effective treatments, few have been successful. As a result, considerable attention has now been given to the prevention of ARDS. Although many patients present with risk factors for ARDS, only a certain subset of these patients go on to develop it. Although some of this phenomenon is likely explained by genetic factors, recent research has revealed that modifiable risk factors for ARDS also exist. Alcohol use was the first major modifiable risk factor for ARDS to be identified. Significant details have since emerged over the past 2 decades about the mechanisms that underlie this relationship. These discoveries have spurred the search for additional risk factors. Further investigation has revealed smoking as an additional risk factor for ARDS. Although the data for this second association are newer and less developed, both of these relationships represent exciting discoveries in the quest to better understand, prevent, and treat ARDS.

ALCOHOL ABUSE

Alcohol is one of the most commonly used and abused drugs worldwide. In the United States, nearly 20 million adults annually meet the criteria for alcohol abuse or dependence.[1,2] Alcohol is known to have numerous systemic health effects, including on the liver and central nervous system.[3] From a respiratory standpoint, alcohol abuse has long been associated with an increased risk of pneumonia.[4,5] More recently, alcohol abuse has been strongly linked in epidemiologic studies to the development of ARDS in at-risk patients.

The first demonstration of an association between chronic alcohol abuse and ARDS was made by Moss and colleagues,[6] who retrospectively

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examined 351 patients at risk for ARDS. In this cohort, 43% of patients who chronically abused alcohol developed ARDS compared with only 22% of those who did not abuse alcohol, with the effect most pronounced in patients with sepsis. This study was limited by its retrospective design, particularly because this design required that the history of alcohol use be obtained by chart review and documented history; furthermore, this study did not adjust for concomitant cigarette smoking. Encouraged by these findings, Moss and colleagues conducted a multicenter prospective study of 220 patients with septic shock to further assess this relationship. Methodologically, this study improved on its predecessor by using the Short Michigan Alcohol Screening Test, which has previously been validated as a screening test for chronic alcohol abuse.[7] A multivariate analysis again found that those who chronically abused alcohol developed ARDS more frequently than those who did not, 70% versus 31%, respectively.[8] These two key studies, thus, served as the first major evidence that alcohol use was a risk factor for the development of ARDS.

Several studies have since reinforced the relationship between alcohol use and ARDS. Licker and colleagues[9] examined the incidence of ARDS in 879 patients with non–small cell lung cancer undergoing thoracic surgery. Multivariate logistic regression found that preoperative chronic alcohol consumption was associated with increased odds of developing acute lung injury. In addition, 2 studies examining the risk factors for transfusion-related acute lung injury (TRALI) found that chronic alcohol consumption was associated with the development of TRALI. Gajic and colleagues[10] found that patients who developed TRALI were more likely to be chronic alcohol users when compared with matched controls, 36.5% versus 17.6%, respectively. More recently, Toy and colleagues[11] found that in a multivariate model, chronic alcohol use in patients receiving blood product transfusions significantly increased the odds of developing TRALI. A later study by Gajic and colleagues[12] that evaluated 5584 patients at risk for ARDS to determine a lung injury prediction score found alcohol to be a positive risk factor for the development of ARDS. These studies, thus, supported the prior observations and solidified the association between chronic alcohol use and ARDS (**Table 1**).

Although the relationship between chronic alcohol abuse and ARDS has been demonstrated numerous times, the effect of alcohol on ARDS outcomes has been less clear. Early studies that examined this relationship showed conflicting results. In a retrospective study, Moss and colleagues[8] found that among patients who developed ARDS, those with a history of chronic alcohol abuse had a significantly higher in-hospital mortality rate compared with those that did not abuse alcohol, 65% versus 36%, respectively.[6] However, a follow-up prospective study that used a more validated measure of alcohol abuse did not demonstrate any difference in mortality in patients with ARDS when stratified by a history of alcohol abuse.

In order to better evaluate the effect of alcohol use on ARDS outcomes, Clark and colleagues[13] performed a secondary analysis of patients enrolled in 3 ARDS Network trials, albuterol to treat acute lung Injury (ALTA), early versus delayed enteral feeding (EDEN), and omega-3 fatty-acid/antioxidant supplementation (OMEGA), which examined the effects of aerosolized albuterol, omega-3 fatty acid supplementation, and early versus delayed parenteral nutrition, respectively, in patients with ARDS. Of note, all 3 studies were stopped early for futility. Participants enrolled in these trials (or their surrogates) completed the Alcohol Use Disorder Identification Test (AUDIT), a previously validated questionnaire[14] developed by the World Health Organization to stratify patients by level of alcohol consumption. In all, 1037 patients, representing 92% of all enrolled patients, had a completed AUDIT and were included

Table 1
Studies evaluating the relationship between ARDS and alcohol use

Author, Year	Study Size	Odds Ratio (History of Alcohol Abuse vs No Abuse)	*P* Value
Moss et al,[6] 1996	351	1.98[a]	<.001
Moss et al,[8] 2003	220	3.70	<.001
Licker et al,[9] 2003	879	1.87	.012
Gajic et al,[10] 2007	148	[b]	.006
Gajic et al,[12] 2011	5584	[c]	.028
Toy et al,[11] 2012	253	5.90	.028

[a] Relative risk.
[b] No odds ratio or relative risk reported. Twenty-seven of 74 patients with acute lung injury had a history of alcohol abuse versus 13 of 74 in matched controls.
[c] No odds ratio or relative risk reported. Forty-four of 377 patients with acute lung injury had a history of alcohol abuse versus 289 of 5207 in patients without acute lung injury.