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Environmental Factors

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KEYWORDS

- Acute respiratory distress syndrome (ARDS) • Acute lung injury (ALI)
- Environmental pollution • Wildfires • Tobacco smoke • e-cigarettes
- e-cigarette and vaping-associated lung injury (EVALI)

KEY POINTS

- Preventable environmental exposures are associated with an increased risk of developing the acute respiratory distress syndrome (ARDS).
- Environmental pollution and cigarette smoke likely predispose the lung to injury from other causes, whereas e-cigarettes are a direct cause of lung injury.
- Evidence-based strategies of lung protective ventilation, fluid conservative strategy, and early prone positioning for Pao_2/Fio_2 less than 150 mm Hg are the cornerstones of management regardless of environmental factors.
- Both patient- and policy-level interventions are needed to reduce harm from these exposures.

INTRODUCTION

The acute respiratory distress syndrome (ARDS) affects at least 10% of patients in the intensive care unit (ICU) and carries a high mortality rate of approximately 40%.[1] There have been effective advances in supportive care, but there are as yet no consistently proven effective pharmacologic treatments for ARDS.[2] One approach to addressing this problem is to target the heterogeneity of ARDS by understanding patient factors that impact response to treatment once ARDS has already developed. For example, secondary analyses of randomized clinical trials demonstrate that ARDS subphenotypes respond differentially to simvastatin therapy.[3] Another important facet is early intervention in hospitalized patients at risk of ARDS.[4] However, clinicians and researchers should also focus on identifying preventable patient exposures that increase the risk for ARDS, as demonstrated by a growing body of research. Understanding and

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addressing these exposures offers an opportunity for primary prevention (Fig. 1). This review summarizes the current literature on environmental exposures and ARDS development and outcomes, discusses underlying mechanisms, and outlines the implications for patient management and policy-guided solutions.

AIR POLLUTION

According to the World Health Organization, the pollutants with the greatest effect on human health are ozone, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and particulate matter (PM).[5] In 2014, PM less than 10 μm in diameter (PM 10) and less than 2.5 μm in diameter (PM 2.5) accounted for at least 3 million deaths and 85 disability-adjusted life years, primarily because of impacts on chronic cardiovascular and pulmonary conditions.[6] Recently, air pollution in the United States has begun increasing for the first time since 2016 (Fig. 2).[7] Ambient pollution is a risk factor not only for the development or worsening of chronic illnesses[8–10] but also for acute illness. For example, a case-control study of older adults in Canada found that long-term exposure to PM 2.5 and NO_2 was independently associated with an increased risk of hospitalization for community-acquired pneumonia.[11] Short-term exposure to increasing levels of PM 2.5 was also shown to increase the risk of hospital admission for cardiac and respiratory disease in the United States.[12]

Several recent studies have demonstrated that exposure to even low to moderate levels of ambient pollutants increases the risk of developing ARDS. In a prospectively enrolled cohort of patients with ARDS in the Southeastern United States, long-term ozone exposure was associated with the development of ARDS in a dose-dependent manner.[13] This association was most pronounced among patients with trauma as their primary risk factor. Although the association between ozone exposure and the development of ARDS remained significant when controlling for potential confounders including smoking status, there was a statistically significant interaction between ozone exposure and smoking. When patients were stratified by smoking status, ozone exposure

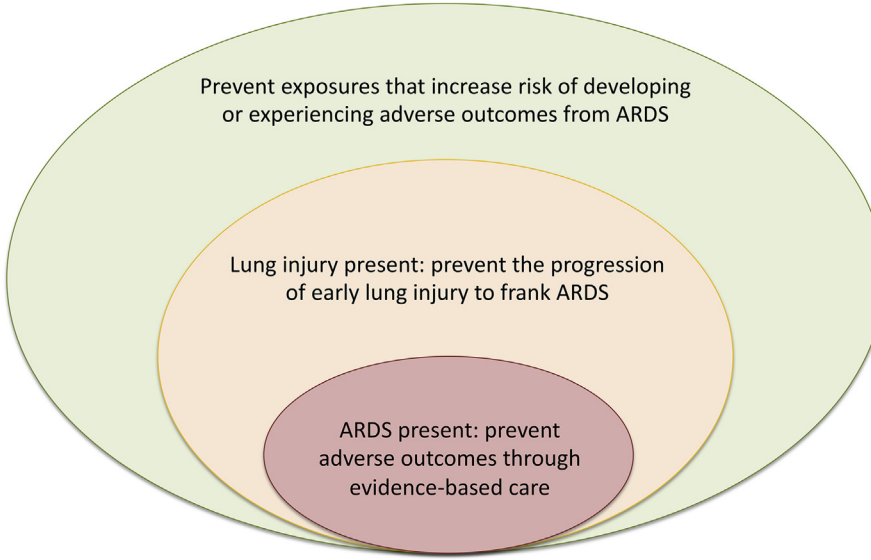

Fig. 1. Levels of intervention to prevent adverse outcomes from ARDS.

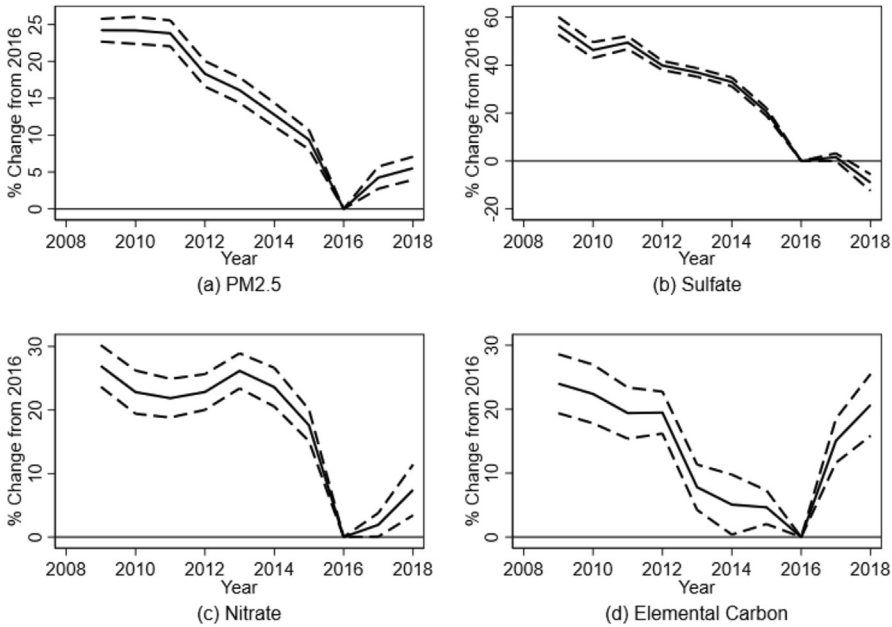

Fig. 2. Changes in ambient levels of major pollutants in the United States, 2008 to 2018. Dotted lines represent 95% confidence intervals. (*From* Clay K, Muller N. Recent increases in air pollution: Evidence and implications for mortality. 2019. https://doi.org/10.3386/w26381; with permission.)

remained significantly associated with ARDS only among smokers. The investigators concluded that cigarette smoking likely potentiates the risk from ozone exposure.[13]

A subsequent study of patients from a prospectively enrolled cohort in Philadelphia further investigated the relationship between exposure to pollutants and ARDS development among patients with trauma.[14] This study analyzed exposure to low to moderate levels of ozone, NO_2, SO_2, PM 2.5, and carbon monoxide (CO). Long-term exposure to each of the pollutants was independently associated with an increased odds of developing ARDS. Furthermore, even 6 weeks of exposure to NO_2, SO_2, and PM 2.5 increased the odds of developing ARDS.[14] Differences between the findings of the 2 studies might be accounted for by regional variation in levels of pollutants and air quality monitoring and by the shared risk factor of the population in the second study. Together these studies suggest that exposure to ambient pollution even at low to moderate levels for time periods as short as 6 weeks increases the risk of ARDS.

Large epidemiologic studies have also found associations between exposure to ambient pollution and an increased risk of developing ARDS. An observational study of more than 1 million hospitalizations between the years 2000 and 2012 among Medicare beneficiaries who developed ARDS used advanced modeling drawing on multiple data sources to predict average annual levels of ambient pollution across more than 30,000 zip codes.[15] The investigators found that the rate of ARDS hospitalizations increased with increasing levels of both PM 2.5 and ozone. These findings were consistent even in regions where pollutant levels were within national air quality standards. The effect of PM 2.5 was most pronounced among patients whose primary risk factor was sepsis. Ozone exposure had the greatest effect among patients with pneumonia or trauma as their primary risk factor. Although fully accounting for confounding

factors in observational studies can be difficult, results were similar in a propensity-matched analysis that included variables such as demographic variations and percent of ever-smokers.[15] The results of this large study demonstrate that the association between ambient pollution and ARDS is present outside of the trauma population in patients who are older with comorbid conditions. Another retrospective cohort study of more than 90,000 patients found that increases in average annual PM 2.5 and ozone concentrations independently increased the odds of death from ARDS, suggesting that ambient pollution impacts not only ARDS incidence but also its outcomes.[16] High levels of ambient pollution have also been associated with incidence and adverse outcomes in the coronavirus disease 2019 (COVID-19) pandemic,[17,18] although further studies in this area are needed.

The preponderance of the literature examining the connection between ARDS and ambient pollution has revealed an association between long-term rather than short-term exposure to pollutants and ARDS incidence and outcomes. For example, the investigators who found a link between long-term ozone exposure and ARDS did not find the same association for 3-day exposure to environmental pollutants.[13] However, one study from Guangzhou, China, demonstrated an association between short-term PM exposure and incident ARDS.[19] This association may be related to the exceptionally poor air quality of the region[20] in contrast to the other studies, which focused on settings with low to moderate levels of pollutants. There is some evidence, however, that short-term exposure to low levels of ambient pollution is associated with adverse pulmonary outcomes in critically ill patients. A study from Antwerp, Belgium—an area with historically low levels of ambient pollution—found that short-term pollution exposure was associated with longer mechanical ventilation.[21] This study included a broad range of critically ill patients, some of whom did not have ARDS, but does suggest that a deleterious effect from short-term pollution exposure is not limited to areas with exceptionally poor air quality.

Various underlying biological mechanisms may explain the basis for the relationship between environmental pollution and ARDS. A meta-analysis of exposure studies in healthy volunteers found that ozone increases the number of bronchoalveolar lavage (BAL) neutrophils,[22] which are implicated in ARDS pathogenesis.[23] Ozone exposure also increased total protein levels in this analysis,[22] reflecting loss of alveolar epithelial/endothelial barrier integrity.[24] Many components of air pollution exert deleterious effects on pulmonary surfactant.[25] Urban air particles directly stimulate an inflammatory response by pulmonary macrophages in vitro.[26] PM has also been shown to increase markers of apoptosis, oxidative stress, and inflammation[27] and to directly cause lung injury in mouse models.[28] In humans, increased PM 2.5 levels are associated with circulating markers of endothelial injury,[29] which is one of the key pathophysiological mechanisms in the development of ARDS.[30] Although environmental pollutants alone may not be sufficient to induce severe pulmonary injury in humans, they likely increase susceptibility to other causes of ARDS such as respiratory infection[31] and prime the alveolus for damage in these settings.

WILDFIRES

Wildfire smoke is an increasingly prevalent source of environmental pollution. Climate change has led to more frequent wildfires over a longer season.[32] In the United States, PM air quality has improved over the past 3 decades except in areas that are prone to wildfires.[33] Wildfires are associated with acute increases in ozone and PM as well as other pollutants such as volatile organic compounds.[34] As noted earlier, previous studies of the relationship between ambient pollution and ARDS[13–16] have generally

focused on the average exposure in various regions over time, rather than on events that might be expected to acutely increase ambient pollution. In addition, smoke from wildfires may have chemical properties that make its risk profile different from that of PM or smoke from other sources.[34,35] Although it is clear that wildfire-related pollution contributes to increased respiratory morbidity and health utilization overall,[36] the specific relationship between ARDS and exposure to pollutants generated by wildfire smoke has not been studied (in contrast to direct inhalational or thermal injury or burn-related ARDS in persons who are survivors of fire accidents,[37,38] which is outside of the scope of this review). In vitro evidence demonstrates that wood smoke exposure diminishes alveolar barrier function[39] and increases alveolar endothelial oxidative stress and apoptosis.[40] In mice, PM collected during wildfires induced a more proinflammatory response and greater oxidative stress than ambient PM collected in the absence of wildfires.[41] Woodfire smoke exposure has also been shown to induce a pulmonary and systemic inflammatory response in healthy volunteers.[42] It is mechanistically plausible that the increased inflammation, oxidative stress, and lung microvascular permeability in response to woodfire smoke demonstrated under experimental conditions would translate to an increased risk of ARDS. Future research should test whether ARDS incidence and outcomes change during or after wildfire events.

CIGARETTE SMOKE

The link between cigarette smoke and adverse health outcomes is well established, and reducing cigarette use has been a major focus of public health efforts over the past half century.[43] Although rates of tobacco smoking have generally declined globally, they remain unacceptably high, and cigarette smoking is a leading cause of avoidable death. For example, the 2015 Global Burden of Disease Study found that approximately 11% of women and 14% of men in the United States report daily smoking and that smoking accounted for 6.4 million deaths globally.[44] Alternative tobacco and nicotine delivery systems such as electronic cigarettes (e-cigarettes), or vapes, are increasingly popular, an especially concerning trend among children and adolescents.[45] Although their long-term health consequences are not well established, e-cigarettes cause a specific lung injury syndrome, e-cigarette- or vaping-associated lung injury (EVALI).[46] E-cigarettes will be discussed in detail in a separate section.

Although some retrospective studies have not found an association between cigarette smoking and ARDS,[47] many studies demonstrate that both active smoking and passive cigarette smoke exposure are associated with ARDS, especially among certain clinical populations. Importantly, this association is independent of alcohol use, which is frequently associated with smoking and is a known risk factor for ARDS.[48] A retrospective cohort study of patients in Northern California found that ARDS was more common among self-reported smokers in a dose-dependent manner. The investigators estimated that smoking carried an attributable risk in ARDS of 50%.[49] A 2014 study of 381 patients with ARDS previously enrolled in randomized clinical trials examined the relationship between tobacco exposure and ARDS.[50] Rather than relying on patient or surrogate reports, which lack sensitivity when compared with biomarkers for tobacco exposure,[51] urine levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) were used to determine smoking history. The rate of active smoking among patients with ARDS in this study was significantly higher than the population average (36% vs 20%, $P<.01$). Smokers were younger and had fewer comorbidities than nonsmokers despite similar ARDS severity. Although unadjusted mortality among smokers was significantly lower than in

nonsmokers, there was no significant difference after adjusting for comorbidities and severity of illness,[50] suggesting that smokers develop ARDS when their illness is less severe than that of otherwise similar patients.

Prospective studies have also demonstrated an increased risk of ARDS among smokers. Current cigarette smoking (determined through medical chart review) conferred increased odds (odds ratio, 3.4; 95% confidence interval, 1.22–9.7; $P = .020$) for the development of transfusion-related acute lung injury (ALI) in a two-center prospective case-control study.[52] Donor smoking history increased the odds of grade 3 primary graft dysfunction in a multicenter prospectively enrolled cohort of lung transplant recipients.[53] A prospective study of the association between tobacco exposure and the development of ALI[54] after blunt trauma used plasma levels of cotinine to differentiate between active and passive smoke exposure and to quantify exposure levels.[55] Active smokers and passively exposed patients in this cohort from a single level 1 trauma center had similarly increased odds of developing ARDS independent of confounding factors, including alcohol use and trauma severity. Higher levels of plasma cotinine were associated with higher odds of developing ARDS.[55] Another prospective study of patients with trauma enrolled between 2005 and 2015 confirmed that cigarette smoke exposure remains an important risk factor for ARDS and highlighted a particularly elevated risk among passive smokers in later years.[56] In patients with trauma, impaired platelet aggregation likely mediates at least part of the effect of cigarette smoke exposure on ARDS risk.[57] In addition, cigarette smoke alters the microbiota in patients with trauma such that their pulmonary microbiome is enriched for specific pathologic bacteria that are associated with ARDS development.[58]

In a prospectively enrolled cohort with diverse predisposing risk factors for ARDS, active cigarette smoking both by self-report and urine NNAL was associated with an increased odds of ARDS among patients with nonpulmonary sepsis as their primary predisposing risk factor.[59] Patients with trauma and transfusion as their primary risk factor were not included in this study because of the previously established link between smoking and ARDS in these populations. Again, the mortality rate of active smokers was lower in an unadjusted analysis, but mortality was similar after adjusting for baseline severity of illness.[59] This finding is consistent with the previous one that smokers are at increased risk of developing ARDS when their underlying illness is comparatively less severe.

Similarly to ambient pollution, cigarette smoke exposure likely predisposes the lung to injury in the setting of a second insult such as trauma, multiple transfusions, or sepsis (**Fig. 3**). This concept was elegantly demonstrated in an experimental model in healthy humans who were exposed to inhaled lipopolysaccharide (LPS).[60] BAL and plasma biomarkers for alveolar epithelial-capillary permeability, inflammation, and alveolar endothelial dysfunction were compared between self-reported smokers and nonsmokers. Absolute measurements were consistent with more alveolar permeability to protein and inflammation in smokers, and statistical tests of interaction demonstrated that smoking potentiated these responses to LPS.[60] In mice, cigarette smoke exposure itself does not cause frank lung injury, but mice exposed to cigarette smoke develop worse pulmonary edema, increased vascular permeability, worse histologic injury, and increased biomarker evidence of inflammation after exposure to LPS.[61] A similar pattern was demonstrated in a clinically relevant model of pneumococcal pneumonia after antibiotic treatment,[62] and other animal models have also shown that cigarette smoke increases alveolar epithelial-capillary permeability and susceptibility to lung injury.[63]

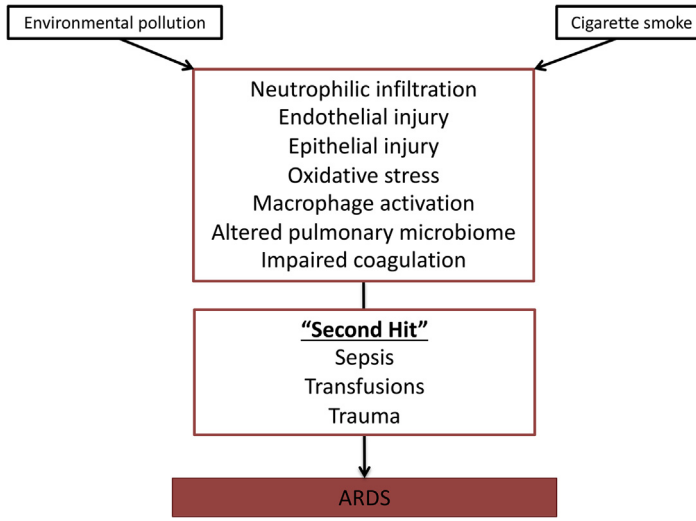

Fig. 3. Pollution and/or cigarette smoke exposure likely predisposes the lung to severe injury in the presence of risk factors for ARDS such as trauma, sepsis, or multiple transfusions.

The relationship between cigarette smoking and COVID-19, which in 2020 was the leading cause of ARDS in the United States,[64] is unclear. There is evidence that the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), angiotensin-converting enzyme 2 (ACE2), is more highly expressed in the lung epithelium of smokers than in nonsmokers.[65,66] It is not obvious from the available data, however, that this leads to an increased risk of SARS-CoV-2 infection or worse outcomes from COVID-19. In fact, smokers are disproportionately underrepresented among patients with COVID-19.[67] It has been proposed that nicotine as an isolated substance may have a protective effect in COVID-19.[68] The relationships among cigarette smoking, ACE2, nicotine, and inflammation are complex, and a full understanding of the implications of smoking on COVID-19 pathogenesis and outcomes requires further study.

E-Cigarettes

E-cigarette use has increased among young people in recent years.[69] Furthermore, using e-cigarettes increases the likelihood of future cigarette smoking among children and adolescents,[70] is associated with increased rates of smoking initiation in adults, and increases the risk of relapse among former cigarette smokers.[71] Therefore, promoting vaping as a harm reduction strategy from traditional cigarettes may be misguided. E-cigarette use likely has negative implications for long-term health based on the cellular and molecular mechanisms it affects,[72,73] although confirming this will require longitudinal studies. In addition, e-cigarettes pose an increased public health risk as a direct cause of ALI.

An outbreak of EVALI, mostly among patients younger than 35 years, emerged in the United States in the spring and summer of 2019. The Centers for Disease Control and Prevention has reported more 2800 cases and 68 deaths.[74] The diagnostic criteria are vaping within the prior 90 days and a new infiltrate on chest imaging in the absence of pulmonary infection.[75] EVALI most commonly presents as acute to subacute constitutional and respiratory symptoms with radiographic findings of bilateral ground glass

opacities (Fig. 4).[76] In one case series, 26% of patients required mechanical ventilation, and approximately 12% of patients met the Berlin criteria for ARDS by chart review.[77,78]

Vitamin E acetate (VEA) is likely the major causative agent among patients with EVALI. In one case series of patients from 16 different states, VEA was found in 94% of BAL fluid samples from patients with EVALI and in none of the samples from healthy comparators.[79] Most patients report using tetrahydrocannabinol (THC) products, in which VEA is frequently used as a diluent,[80] although some report exclusively using nicotine-based products.[76] The effect of VEA was recently studied in a murine model and in primary alveolar type II (ATII) cell culture.[81] In the mouse model, exposure to aerosolized VEA resulted in significantly increased BAL protein, excess lung water, and BAL biomarkers of alveolar epithelial damage and inflammation when compared with aerosolized tobacco or vegetable glycerin and propylene glycol. Histologic patterns closely mirrored those found in patients with EVALI.[82] VEA was also found to cause direct, dose-dependent ATII toxicity.[81] Because of the many ingredients found in e-cigarettes and the use of unregulated products,[83] however, identifying a single culprit in EVALI is difficult.

It is unknown whether chronic e-cigarette use also increases the risk of developing ARDS from other causes. Studies of cigarette smoke exposure and ARDS using biomarkers for nicotine may have included patients who were using both traditional cigarettes and e-cigarettes, and smoking histories in medical records do not always describe whether patients also vape. E-cigarette vapor both with and without nicotine increases rat endothelial cell permeability in vitro, although the effect is more pronounced with nicotine.[84] Mice chronically exposed to e-cigarette vapor with and without nicotine demonstrate altered lipid homeostasis in alveolar macrophages and changes to ATII lamellar body ultrastructure, which may indicate that e-cigarettes disrupt surfactant production.[85] Chronic e-cigarette exposure also delays the immune response and results in worse lung injury in mice exposed to influenza.[85] Similar changes in humans could plausibly prime the lung for injury as with cigarette use.[60] Further studies should examine whether e-cigarettes increase the risk of developing ARDS from infection, trauma, or other causes.

DIAGNOSIS AND MANAGEMENT IMPLICATIONS

Regardless of the environmental risk factors for ARDS, the cornerstones of diagnosis and management remain the same. None of the aforementioned exposures, including

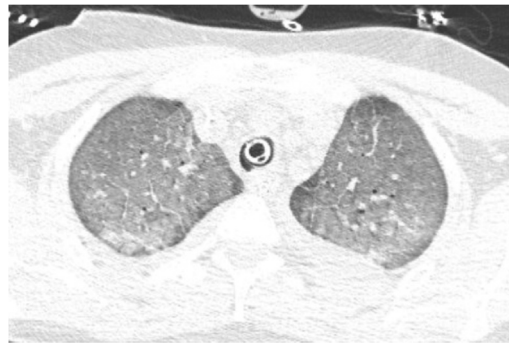

Fig. 4. Computed tomographic scan of a patient with EVALI, demonstrating diffuse bilateral ground glass opacities with characteristic subpleural sparing. (*Courtesy of* Dr. Carolyn Calfee, UCSF.)

e-cigarettes, results in a unique radiographic appearance,[76] and clinicians should use the Berlin criteria for ARDS for diagnosis.[78] Workup should include a thorough investigation of possible pulmonary and extrapulmonary infections, including viral pneumonia, and bronchoscopy may be warranted.[86] Understanding the environmental risk factors for ARDS underscores the importance of an accurate exposure history. For example, patients or surrogates should be asked about both personal use of cigarettes and passive (second-hand) cigarette smoke exposure. A thorough history should also include questions about e-cigarette use (vaping), regardless of whether patients also use combustible cigarettes. Providers should ask about product type; duration and frequency of use; use of nicotine-based products, cannabis products, or both; additives; and where the patient obtains their product.[87] Although corticosteroids are frequently used in EVALI,[76] this treatment has not been assessed in prospective randomized trials. Similarly, there is no pharmacotherapy specific to patients who smoke or who have been exposed to environmental pollutants. Management should therefore be based on the evidence-supported strategies of lung protective ventilation,[88] conservative fluid management,[89] and early prone positioning when Pa_{O_2}/ fraction of inspired oxygen is less than 150 mm Hg.[90]

The period during and after critical illness may be a unique opportunity for clinicians to encourage smoking and vaping cessation. Behavioral counseling for hospitalized patients, including critically ill patients, can lead to increased abstinence from smoking.[91] Providers caring for ICU survivors may also have an opportunity to encourage smoking cessation or continued abstinence.[92] Current American Thoracic Society (ATS) guidelines recommend pharmacologic therapy with varenicline and nicotine replacement for smoking cessation in adults.[93] Initiating varenicline therapy in critically ill patients has not been studied, and the role of nicotine replacement therapy in critically ill patients is not well established.[94] Research about pharmacologic therapy for teenagers who use cigarettes or electronic cigarettes is limited. The American Academy of Pediatrics recommends behavioral interventions, adding pharmacologic therapy depending on the severity of tobacco dependence.[95] The best approach for addressing tobacco dependence or e-cigarette use in patients with ARDS requires further investigation. Other exposures such as pollution and wildfire smoke are best addressed by public policy, which also plays a crucial role in smoking and vaping cessation.

PUBLIC HEALTH STRATEGIES AND KNOWLEDGE GAPS

The emerging data about chronic exposures and the risk of ARDS underscores how policy-level interventions impact the practice of critical care. Policy provides opportunities to fill current knowledge gaps through research funding and to limit risks of environmental exposures on a population level. Air quality measures and wildfire mitigation largely depend on public health and policy strategies. Upholding safe air quality standards is necessary to limit population-level exposure, but ambient pollution and the risk of wildfires will continue to increase as climate change progresses. The ATS has made climate change a priority for its public health and research agenda, citing the risk posed to cardiopulmonary health.[96]

Patient-level interventions are important for smoking and vaping cessation, but they should be part of a larger policy agenda (**Table 1**). Declining smoking rates are one of the great public health achievements of the twentieth and twenty-first centuries, and there are still many opportunities for progress such as expanded laws mandating smoke-free public environments, ongoing public awareness campaigns, and widespread adoption of evidence-based treatment of tobacco users.[43] The emergence

Table 1
Individual and policy-level interventions for reducing exposures that increase risk of ARDS

Exposure	Patient-Level Interventions	Policy-Level Interventions
Environmental pollution	Increased awareness of air quality metrics Staying indoors, avoiding strenuous activity when air quality is poor Compliance with evacuation orders during wildfires	Stringent air quality standards Focus on climate and environmental policies to limit impact of climate change
Cigarette smoke	Evidence-based approach to cessation	Expanded public health messaging, including about second-hand smoke Smoke-free public spaces Increased taxation of tobacco products
E-cigarettes	Avoid e-cigarettes as a harm reduction strategy Specific social history questions about e-cigarette use	Strict safety standards and regulation of market, including taxation Reduce availability of products that appeal to young people

of e-cigarettes and other alternative nicotine and cannabis delivery systems require new regulatory efforts. The Food and Drug Administration (FDA) has recently started enforcing regulations of flavored e-cigarette cartridges, for example, but many products still fall outside of this enforcement effort.[97] Illicit products necessarily are not subject to FDA regulations. Rates of EVALI may be higher in regions where cannabis is illegal,[98] and because it remains so on a federal level, there are no federal guidelines for the safe manufacturing or use of cannabis vaping products. There are also federal limitations on cannabis research, which restrict opportunities to study short- and long-term pulmonary effects of THC exposure.

Future research and policy priorities should focus on continuing to limit exposures that increase ARDS risk on both an individual and the population level. Researchers should investigate the optimum timing and method for encouraging smoking cessation after critical illness, including whether it may be appropriate to initiate pharmacologic therapy in the ICU. Priorities for e-cigarettes include strict safety standards, investigating whether e-cigarette exposure increases the risk of ARDS from other causes, and expanding research of potentially harmful electronic marijuana delivery systems. Public messaging about air quality standards should be expanded, and the medical community should continue to raise awareness about the impact of climate change on pollutants that threaten cardiopulmonary health. In summary, the scientific understanding of how environmental exposures increase the risk of ARDS is well established, but there is much to be learned. There are many opportunities to expand our knowledge and implement policy-level changes to continue combat this deadly syndrome.

CLINICS CARE POINTS

- Environmental factors such as cigarette smoking, environmental pollution, and the use of e-cigarettes (vapes) should be recognized as a contributing risk factor for ARDS.
- Evidence-based smoking cessation resources, including pharmacologic aids, should be offered to patients regardless of their stated readiness to quit as per ATS guidelines.

- When patients present with ARDS, clinicians should conduct a detailed exposure history including whether a patient uses combustible cigarettes or e-cigarettes. Vaping history should include frequency, type of product, duration, and source.
- Clinicians should rely on evidence-based cornerstones of ARDS management regardless of exposure history.

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