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Reply to Eissenberg and Maziak: Are Electronic Cigarette Users at Risk for Lipid-mediated Lung Injury?

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Balmes, John R

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cluster is novel, pulmonary illness associated with e-cigarette use is not new: there are at least seven published case reports from 2012 to 2018 describing similar conditions in e-cigarette users, with no identifiable infectious etiology (i.e., acute lung injury, atypical pneumonitis, eosinophilic pneumonia, hypersensitivity pneumonia, or lipid pneumonia). Interestingly, of these seven reported cases, lung cell samples obtained via lavage or biopsy were available for five (3–7), and all five exhibited abnormally lipid-laden macrophages. Lipid-laden macrophages were also a prominent feature (>50%) in BAL of more recent case series from Utah (8). Such macrophages can trigger an inflammatory immune response (9) leading to lipid pneumonia and other pneumonitis-like reactions. One report suggested that residual lipids in vegetable glycerin derived from incompletely processed vegetable oil might be the exogenous source of lipid in an e-cigarette user diagnosed with lipid pneumonia (5). However, most of the publications related to this new entity focused on tetrahydrocannabinol, and a recent case series from the Mayo Clinic suggests chemical pneumonitis as a more probable etiopathology (10). The fact that not all e-cigarette-related lung injury cases were associated with tetrahydrocannabinol use, and that tetrahydrocannabinol vaping usually involves an oil vehicle (e.g., butane hash oils), does not rule out an important role for lipid-mediated lung injury in this clinical entity. This is particularly important to keep in mind given that most e-cigarette liquids contain vegetable glycerin as an essential component (helps make the e-cigarette aerosol visible). The implication is that many e-cigarette users who are currently asymptomatic (or experiencing milder symptoms for which they do not seek medical attention) may be undergoing lipid deposition in their airway, with concomitant inflammatory changes induced by lipid-laden macrophages and other immune cells. Therefore, we urge clinicians treating patients with acute and unexplained pulmonary complaints to identify whether the patient is an e-cigarette user and, if so, to obtain detailed history about their use and, when possible, to collect cell samples to determine whether evidence of lipid exposure is present. Similarly, we urge researchers to investigate lipid exposure and inhaled toxic substances in e-cigarette users systematically. Most important, we call for regulators to implement immediately strict regulation that prevents lipid and inhaled toxicants emissions from all e-cigarettes sold in the United States. ■

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Thomas Eissenberg, Ph.D.
Virginia Commonwealth University
Richmond, Virginia

Wasim Maziak, M.D., Ph.D.*
Florida International University
Miami, Florida

*Corresponding author (e-mail: wmaziak@fiu.edu).

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Reply to Eissenberg and Maziak



From the Author:

The letter from Eissenberg and Maziak is a welcome reminder that although most of the cases of e-cigarette or vaping product use-associated lung injury (EVALI) have been associated with tetrahydrocannabinol (THC)-containing liquids, cases have also been reported in which only nicotine-containing liquids were used. As of December 17, 2019, a total of 2,506 hospitalized EVALI cases have been reported to the CDC from all 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and the U.S. Virgin Islands), with 54 deaths in 27 states and the District of Columbia (1). Of 1,782 hospitalized patients for whom complete information was available on substances used in e-cigarette or vaping products in the 3 months before symptom onset, 13% reported exclusive use of nicotine-containing products (1). These data provide the basis for the CDC recommendation that “the best way for people to ensure that they are not at risk while the investigation continues is to consider refraining from the use of all e-cigarette, or vaping, products” (2). Since the publication of the Triantafyllou and colleagues case series and the accompanying editorial, more information has become available about the EVALI cases associated with vaping of a class of largely counterfeit THC-containing products of unknown origin, with “Dank Vapes” being

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the most common brand (3, 4). CDC laboratory test results of BAL fluid samples from 29 patients submitted to the CDC from 10 states found vitamin E acetate in all the samples (1). Vitamin E acetate is an oil used to thicken e-cigarette liquid. Although all the CDC BAL analyses were of THC-containing vape liquids, a recent report from South Korea showed vitamin E acetate present in nicotine-containing products, including JUUL pods (5). Eissenberg and Maziak suggest that lipid materials in e-cigarette liquids, particularly vegetable glycerin, are the likely cause of EVALI in patients who only used nicotine-containing products. Whether the lipid is vitamin E acetate or vegetable glycerin or another agent, inhaling lipid-containing aerosol generated by high heat can lead to the generation of lipid-laden macrophages, recently reported by Maddock and colleagues in cases of EVALI from Utah (6). Electronic nicotine delivery systems can play a beneficial role in tobacco smoking cessation, but only if the e-cigarette liquid is properly and safely prepared. I fully agree with Eissenberg and Maziak's call for strict regulation of e-cigarette liquid contents. ■

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John R. Balmes, M.D.*[†]
University of California, San Francisco
San Francisco, California
and

University of California, Berkeley
Berkeley, California

ORCID ID: 0000-0002-2246-7002 (J.R.B.).

*J.R.B. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

[†]Corresponding author (e-mail: john.balmes@ucsf.edu).

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Patient Registries in Idiopathic Pulmonary Fibrosis: Don't Forget Socioeconomic Status

To the Editor:

We appreciated the article by Culver and colleagues emphasizing the importance of large registries of patients with idiopathic pulmonary fibrosis (IPF) and the increased need for biobanking to identify relevant biomarkers to better understand this disease (1).

We fully agree with the comment of Nett and colleagues regarding the need to include in IPF registries data on occupational and environmental exposures, although it is currently difficult to obtain accurate information about a patient's lifetime exposure unless a specialized consultation is available (2). Another benefit of reporting occupational activities in IPF registries would be to provide information on the patient's socioeconomic status (SES), a critical health determinant of chronic lung diseases such as chronic obstructive pulmonary disease, asthma, and lung cancer (3). However, published data on the role of SES in IPF are exceedingly rare. A study conducted in the United States on lung transplant candidates suffering from IPF showed that black and Hispanic patients had increased mortality compared with white and Asian patients, likely owing to a lower SES (4). Based on a U.S. database of hospitalized patients, Gaffney and colleagues suggested that patients with IPF and lower incomes or poorer insurance coverage had reduced access to transplantation, rehabilitation, and lung biopsy, but no difference in hospital mortality (5). SES data can be useful for assessing patients' access to healthcare and health management, which is relevant in the varied contexts of national welfare systems. The evaluation of SES is complex because it is multidimensional and can change throughout the life cycle. Yet, it has been established that income is one of the most significant socioeconomic markers of the health social gradient. Unfortunately, income data are often missing in IPF registries, and it is difficult to specify this information retrospectively. Interestingly, if permission has been granted to obtain the patient's geocoded residential address, it is possible to impute to each patient an area-level income, as a proxy from national databases. In addition, collecting patient geocoded residential addresses enables the assignment of various environmental exposure data to each individual from air quality measurement stations, land cover (i.e., greenspaces), and distances from major polluted roads. Several studies observed a negative role of air pollution in IPF natural history (6), and large, collaborative registries involving several countries with different levels of air pollution would provide an opportunity to confirm these results. Indeed, disadvantaged individuals are more significantly exposed to air and occupational pollution than others. Environmental epidemiology traditionally has focused on the one-to-one relation between environmental exposures and health. However, in the last decade, an exposome approach has emerged for the study of factors associated with the occurrence of

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