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The E-cigarette or Vaping Product Use–Associated Lung Injury Epidemic: Pathogenesis, Management, and Future Directions

An Official American Thoracic Society Workshop Report

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Abstract

E-cigarette or vaping product use–associated lung injury (EVALI) is a severe pulmonary illness associated with the use of e-cigarettes or vaping products that was officially identified and named in 2019. This American Thoracic Society workshop was convened in 2021 to identify and prioritize research and regulatory needs to adequately respond to the EVALI outbreak and to prevent similar instances of disease associated with e-cigarette or vaping product use. An interdisciplinary group of 26 experts in adult and pediatric clinical care, public health, regulatory oversight, and toxicology were convened for the workshop. Four major topics were examined: *1*) the public health and regulatory response to EVALI; *2*) EVALI clinical care; *3*) mechanisms contributing to EVALI; and *4*) needed actions to address the health effects of EVALI. Oral presentations and group discussion were the primary modes used to identify top priorities for addressing EVALI. Initiatives including a national EVALI case registry and biorepository, integrated electronic medical record coding system, U.S. Food and Drug Administration regulation and enforcement of nicotine e-cigarette standards, regulatory authority over nontobacco-derived e-cigarettes, training in evaluating exogenous exposures, prospective clinical studies, standardized clinical follow-up assessments, ability to more readily study effects of cannabinoid e-cigarettes, and research to identify biomarkers of exposure and disease were identified as critical needs. These initiatives will require substantial federal investment as well as changes to regulatory policy. Overall, the workshop identified the need to address the root causes of EVALI to prevent future outbreaks. An integrated approach from multiple perspectives is required, including public health; clinical, basic, and translational research; regulators; and users of e-cigarettes. Improving the public health response to reduce the risk of another substantial disease-inducing event depends on coordinated actions to better understand the inhalational toxicity of these products, informing the public of the risks, and developing and enforcing regulatory standards for all e-cigarettes.

Keywords: e-cigarette; vaping product; lung injury; EVALI; inhalation toxicity

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Contents

Overview

An American Thoracic Society (ATS) workshop was convened in 2021 to identify and prioritize research and regulatory needs to adequately respond to the e-cigarette or vaping product use–associated lung injury (EVALI) outbreak and to prevent similar instances of disease associated with e-cigarette or vaping product use. Herein, we summarize the content of the workshop sessions, including the presentations and discussion. The workshop identified an urgent need for the following:

- A national EVALI case registry and biorepository
- Physician education on screening for and documenting e-cigarette exposure
- Continued messaging on the risks of e-cigarette use
- Investment in research on EVALI and potentially harmful e-cigarette additives
- Regulation of e-cigarettes
- Development of manufacturing standards

Introduction

E-cigarette or vaping product use–associated lung injury (EVALI) is a severe pulmonary illness associated with the use of e-cigarettes or vaping products that was officially identified in 2019 during an EVALI epidemic. EVALI was primarily linked to the inclusion of vitamin E acetate (VEA) in e-liquids, mainly from tetrahydrocannabinol (THC)-containing e-cigarettes, largely but not exclusively from "informal sources like friends, family, or in-person or online dealers" (1, 2). Contributing to the widespread diagnosis of EVALI across the United States was the rapid and extensive adoption of e-cigarette use by more than 13 million individuals, including an alarming percentage of youth (25% in 2018), without federal regulation and manufacturing controls (3). Although e-cigarettes first appeared on the U.S. market in 2007, reported EVALI diagnoses peaked in 2019. However, cases of e-cigarette–related respiratory diseases have been documented since 2012 and continue to this day. A careful examination of contributing factors to the EVALI epidemic and identification of knowledge gaps is required to improve public health by preventing a similar or worse epidemic.

Methods

This workshop was convened in 2021 in response to the EVALI epidemic and was led by Drs. Rebuli, Rose, Noël, and Croft (co-chairs). The workshop subcommittee included clinicians who have cared for individuals with EVALI (adult and pediatric pulmonologists, pathologists, and radiologists), public health officials, epidemiologists, and toxicologists. The 26 workshop speakers and discussants participated in four sessions with expert presentations and included discussion that identified research and regulatory needs and priorities. Topics of discussion included *1*) the public health and regulatory response to EVALI; *2*) EVALI clinical care; *3*) mechanisms contributing to EVALI; and *4*) needed actions to address the health effects of EVALI.

Defining Key Terms

To ensure clarity throughout the workshop report, in Table 1 we define key terms.

Public Health and Regulatory Response to EVALI

An evaluation of EVALI would not be complete without a summary of the events leading up to disease diagnosis. A more comprehensive history of e-cigarettes can be found in the 2016 Surgeon General Report (4). Patents for the first e-cigarettes were granted to Joseph Robinson and Herbert A. Gilbert in 1930 and 1965, respectively. The first commercially available devices were created by Hon Lik in 2003. E-cigarettes were introduced to Europe and the United States in 2006 but did not gain popularity until the early 2010s. The Family Smoking Prevention and Tobacco Control Act was signed into law in 2009, granting the U.S. Food and Drug Administration (FDA) authority over regulation of cigarettes and other tobacco products. Tobacco-derived nicotine e-cigarettes were not included in FDA purview until 2016. FDA review of tobacco-derived nicotine e-cigarettes was delayed until 2020, when e-cigarette companies were required to submit their products for evaluation (5, 6). Most recently, in 2022, the FDA was granted regulatory authority over synthetic nicotine e-cigarettes (7), closing a loophole that had been exploited by e-cigarette companies to evade FDA regulatory authority (8). However, many e-cigarettes are still widely available and largely unregulated, including cannabinoid and other e-cigarette products outside FDA regulatory authority, potentially allowing for inclusion of compounds in e-liquids that are not tested for inhalational safety and may lead to other EVALI outbreaks.

E-cigarettes have steadily gained popularity since their introduction into the U.S. market. They have been rapidly adopted by youth and young adults, most of whom were prior never-smokers (9–11). Risks associated with youth use of nicotine

Table 1. Workshop key terms

E-cigarette: Electronically powered product delivering an inhalable liquid-based aerosol. This is an umbrella term for all devices that fit this definition (e.g., vaping product, ENDS, e-hookahs, e-pipes, vape pens, dab pens, personal vaporizers, etc.). E-cigarettes will be further subdivided by the primary active ingredients as below: • Nicotine e-cigarettes—contain tobacco-derived or synthetic nicotine, currently under FDA purview for regulation. • Cannabinoid e-cigarettes—contain cannabinoids, not currently under FDA regulatory authority. • Other e-cigarettes—contain other active ingredients (e.g., melatonin, vitamins, caffeine, essential oils, etc.), not currently under FDA regulatory authority.
EVALI: This term will be used to refer to all e-cigarette–related lung injury. This term will be used as an umbrella, as the EVALI epidemic has brought attention to e-cigarette–related health effects and is used broadly to document lung injury/disease attributable to e-cigarettes. It should be noted that the CDC does not limit EVALI diagnosis to those exposed to particular active ingredients, and use of all e-cigarettes were considered under the diagnostic criteria.

Definition of abbreviations: CDC = U.S. Centers for Disease Control and Prevention; ENDS = electronic nicotine delivery systems; EVALI = e-cigarette or vaping product use–associated lung injury; FDA = U.S. Food and Drug Administration.

e-cigarettes include nicotine addiction, the renormalization of cigarette smoking, and harm to developing organs, such as the lungs and brain (12–14). The popularity and rapid adoption of these products has been linked to early and intense marketing campaigns as well as the availability of youth-preferred flavors, such as fruit, mint/menthol, and candy (15–17). To address increases in youth use of e-cigarettes associated with the attractiveness of flavors, the FDA banned many youth-preferred flavors in the most popular pod-based devices (18–20). Flavors are currently still available in disposable nicotine e-cigarette products, which have since taken over as the most popular class of nicotine e-cigarettes (53.7%), and refillable e-liquids (21). Documented youth use declined in 2020; however, many hypothesize that this was due to coronavirus disease (COVID-19) pandemic restrictions, including closure of many schools to in-person learning, and reduced access to e-cigarettes (22).

EVALI was first officially identified in 2019, and this rapid-onset severe pulmonary illness was quickly linked to e-cigarette use. It was closely monitored by the U.S. Centers for Disease Control and Prevention (CDC) and the FDA as reported cases increased sharply from August 2019 to September 2019, peaking at 215 cases during the week of September 15 (23). Cases steadily declined after the reported peak, likely due in part to effective public health messaging on VEA, the EVALI-associated compound in cannabinoid e-cigarettes, by the CDC. The CDC stopped monitoring the disease incidence in February of 2020 because of considerable decline in EVALI cases and deaths, as well as the identification of the primary chemical of concern in the EVALI outbreak. Ceased monitoring also temporally coincided with the onset of the COVID-19 global pandemic (23). Throughout this period in the United States, 2,807 individuals were hospitalized with EVALI and 68 individuals died as a result.

The majority of individuals diagnosed with EVALI had used THC-containing e-cigarettes, a significant percentage of which contained VEA, which was identified as a probable contributor to the illness (23). Although not all the products provided by individuals with EVALI to the FDA contained VEA, identification of this additive as potentially harmful by the CDC was associated with the drop in case numbers seen across late 2019 and early 2020 (24). Although most affected individuals reported use of cannabinoid e-cigarettes, approximately 20% reported using only nicotine e-cigarettes (25). It is unknown whether these patients were unintentionally exposed to VEA through cross-contamination of e-liquids or sharing of e-cigarettes or whether additional ingredients, such as medium-chain triglycerides (MCT), can lead to EVALI (26). The direct effects of THC in the absence of VEA are also unclear, as there were case reports of acute respiratory syndromes brought on by aerosolized THC before the EVALI outbreak (27). Although VEA has a strong epidemiologic link to EVALI, there are certainly other substances and contaminants present in e-liquid that can induce lung injury. Thus, the assumption by both the general public and scientific circles that VEA was the causative agent, solely based on the association of VEA with significant percentage of EVALI patient products, may be contributing to continued incidence of e-cigarette–induced lung injury and delay necessary regulatory assessments of other potentially causative agents—a quandary of association not always equaling causation.

With a substantial drop in documented cases and the onset of the COVID-19 pandemic in early 2020, reporting of confirmed and probable cases of EVALI was shifted to individual state departments of health. Although attention has been substantially shifted away from EVALI because of the overwhelming nature of the COVID-19 pandemic, cases continue to be reported. Many workshop participants reported cases in their local hospital systems after the initial CDC reporting period. At least 92 additional cases have been reported by workshop participants from six medical centers in six states, in long-term case series, and in presentations at the American Thoracic Society 2021 International Conference since national reporting ceased in 2020. Although some speculate that EVALI has disappeared, based on the cases reported by attendees in this workshop, EVALI is still being documented, and experts remain concerned about its continued prevalence (28–30). Inconsistent reporting, cessation of reporting cases at a national level, and lack of attention to EVALI highlight a critical need for consistent and effective case reporting methods.

There are substantial concerns about youth adoption and use of e-cigarettes, as well as concerns about EVALI. Nicotine e-cigarette use may reduce prevalence rates of smoking combustible tobacco under some circumstances, although there is considerable controversy about the net population benefit (31). Cigarette smoking is a leading cause of preventable premature death and disability worldwide. In the United States, 14% of

adults smoke cigarettes, constituting 30–40 million people and causing nearly 500,000 premature deaths every year. More than 70% of smokers in the United States would like to stop smoking; more than 50% make an attempt each year. However, 80% of attempts result in relapse, with only 7% of smokers successfully quitting each year. These findings have been unchanged for 20 years. Nicotine e-cigarettes have been studied as a way to treat tobacco dependence (32). Some randomized clinical trials have shown higher quit rates using nicotine e-cigarettes than nicotine replacement medications, and nicotine e-cigarettes were found to be more acceptable to smokers (31, 33). Only four such studies were included in the 2021 Cochrane Review (34). Many of those who used nicotine e-cigarettes to stop smoking combustible tobacco continued to use nicotine e-cigarettes, and a meta-analysis of these randomized clinical trials has concluded that use of e-cigarettes as a therapeutic intervention may lead to permanent nicotine dependence (35–37). There is increasing evidence that dual use of combustible tobacco and e-cigarettes causes more adverse health effects than use of either alone (38–40). No studies have been done comparing nicotine e-cigarettes to varenicline, the most effective and recommended treatment for tobacco dependence. Considering both the risks and benefits of nicotine e-cigarettes, it may be possible but challenging to make nicotine e-cigarettes available to adult smokers while minimizing use by youth. Approaches include Tobacco 21 laws (enacted in the United States in 2019), youth educational efforts around risks of e-cigarette use, flavor restrictions, restricting access (e.g., limiting sales to adult-only tobacco shops or access only through prescription by a medical doctor), and FDA regulation of nicotine e-cigarette marketing—focusing on adult smokers and completely switching from cigarette smoking to e-cigarette use.

Public Health and Regulatory Needs to Address EVALI

In addition to the above initiatives to balance the potential risks and benefits of nicotine e-cigarette use, several public health and regulatory initiatives are needed to advance our understanding of EVALI and the contribution of VEA and prevent similar outbreaks (summarized in Table 2).

National case registry and biorepository. The key to the rapid detection of VEA as a potential causative agent of EVALI was the CDC's national case reporting and the FDA's e-liquid sample collection effort. However, the CDC national case registry and the FDA's sample collection only captured a period of less than 1 year, leaving case reporting and sample collection up to local institutions. This at least in part was because of the emergence of the COVID-19 global pandemic. This has severely limited our understanding of EVALI, particularly of the chemical and molecular initiating events, recovery timelines and outcomes, and long-term consequences of EVALI and continued e-cigarette use. It has also limited physician awareness that EVALI still occurs, that it can manifest with a spectrum of adverse outcomes, and that it is an ongoing concern for active e-cigarette users who present to the hospital or clinic with respiratory illness.

A potential solution that addresses multiple limitations is the creation and funding of a national case registry and biorepository, where the incidence of EVALI across the country can be monitored and biospecimens, as well as e-liquids, from a nationally representative pool of patients with EVALI can be collected for research. This comprehensive approach will help to better understand the onset, progression, recovery, and outlook for individuals with EVALI. These data will better prepare the scientific and medical community to surveil for and respond to similar future incidents, potentially prevent serious EVALI-like illness, and prepare for potential long-term care of individuals who have had EVALI. To ensure that a case registry and biorepository are comprehensive and nationally representative, substantial dedicated funding and oversight will be needed. It is suggested that a U.S. National Institutes of Health (NIH)-sponsored Request for Application (RFA), similar to the new RFA for the creation of a Cardiovascular Biorepository for Type 1 Diabetes (RFA-DK-21-010) or the Other Transaction Authority for the creation of a Post-Acute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Biorepository (OTA-21-015A), would be ideal for this initiative and would provide a sufficient platform for a focused research program to address the overall impact and long-term consequences of EVALI on public health.

Integrated electronic medical record coding system. A coding system to accurately capture e-cigarette use practices and associated disease is needed nationwide. In addition to a universal coding system, educational initiatives to ensure consistent case definitions are equally important for use by healthcare professionals and medical care facilities. Without such initiatives, we will continue to underreport individual and case clusters, making it virtually impossible to identify the number, nature, and scope of EVALI cases and the overall burden of EVALI events.

Table 2. Needed public health and regulatory action to address e-cigarette or vaping product use–associated lung injury

1. A national case registry and biorepository are needed to comprehensively evaluate the overall burden of EVALI-VEA and related disease as well as study the chemical constituents and biological alterations responsible for disease progression and recovery.
2. A dedicated EVALI EMR code, coding systems to collect information on vaping products and e-liquid components, and clinician education about vaping product use–related coding paradigms and assessments are needed to more accurately document EVALI and related disease.
3. FDA regulation of nicotine vaping products and development of product standards are needed to ensure that potentially harmful chemicals, such as VEA, are not unexpectedly added to products available to the public. In addition, state or federal regulatory frameworks are needed to address safety of cannabinoid and other vaping products. **A proactive approach of assessing inhaled products for respiratory safety before their availability on the market would additionally protect public health.**
4. Continued patient and public education on the risks of vaping product use are needed from researchers and public health officials, especially in regard to harmful vaping product constituents (like VEA) and for youth users.

Definition of abbreviations: EMR = electronic medical record; EVALI = e-cigarette or vaping product use–associated lung injury; FDA = U.S. Food and Drug Administration; VEA = vitamin E acetate.

Although thousands of cases of EVALI have already been reported across the United States to the CDC, most notably in 2019 and 2020, inconsistent data capture and a lack of clear International Classification of Diseases 10th Revision (ICD-10) codes and universally adopted case definitions for accurate and timely reporting have undoubtedly contributed to suboptimal event capture and limited public health awareness of the ongoing scale and scope of the problem. The current guidance offers ICD-10–Clinical Modification (ICD-10-CM) codes that may be appropriate for EVALI cases (Table 3), but it has significant limitations that remain unaddressed. First, an umbrella diagnosis of U07.0 Vaping-related disorder, should be used, which was first made available in September of 2019 (41). Additional codes should follow to fully characterize the event and comply with ICD-10 coding rules. Other codes that may be relevant in combination with those in Table 3 include: F12.- Cannabis related disorders and F17.29- Nicotine dependence, other tobacco product, with a clinical note describing the type of e-cigarette used.

Limitations with this current strategy include a lack of EVALI-specific codes, leaving EVALI events under a broad umbrella that may include a variety of e-cigarette–related clinical presentations. For example, acute nicotine or cannabinoid toxicity due to swallowing or inhaling e-liquid has been reported, in addition to absorption through the skin or mucosal surfaces. In addition to the U07.0 code, T65.291- Toxic effect of other tobacco and nicotine, accidental (unintentional) or T40.7X1- Poisoning by cannabis (derivatives), accidental (unintentional), may also be appropriate. Specifying EVALI diagnoses under this umbrella is limited to clinical notes, hampering ease of broad collection of information on this type of event. In addition, the announcement of this coding paradigm was overshadowed by an overwhelming viral pandemic, diminishing urgency around education for its use and reducing the potential for universal uptake. A concerted effort is needed to enhance awareness and increase education, especially about the spectrum of subcodes that can be used for specific condition diagnoses that may be related and relevant to EVALI, specifically codes related to the treatment of e-cigarette product use and dependence, including counseling.

Although timely and thorough use of the U07.0 coding paradigm will help identify new EVALI cases as they emerge, there is an additional need to collect detailed and comprehensive data on the e-cigarette that may be causal to EVALI and related illnesses. Specifically, ICD-10-CM codes are needed to capture patient use of e-cigarettes, to characterize constituents of e-liquids used (nicotine, cannabinoids, others, unknown, etc.), and to define use patterns/dosage. These data are also needed to help define the magnitude and scope of e-cigarette use across all users, independent of EVALI diagnosis, as well as characterize the total spectrum of e-cigarette–related injury/illness, justify cessation counseling, and improve public health and regulatory reporting. Given the widespread uptake and use of e-cigarettes, domestically and internationally, the lack of a unique code set for e-cigarettes poses a barrier to effectively use ICD-10-CM for health surveillance and research purposes.

E-cigarette regulation and established product standards. Critical to the prevention of a subsequent EVALI outbreak is the regulation of e-cigarettes and the establishment of product standards. The FDA has taken the initial steps to begin this process with nicotine e-cigarettes by reviewing premarket tobacco product applications and ruling on many submitted applications (5). Based on the current review trajectory, it appears that future availability of nicotine e-cigarettes will be substantially reduced, including limiting flavors. In limiting flavors, the FDA has considered the potential for these to be a primary attractant for prior never-users and has potentially reduced the number of new nicotine e-cigarette users. Regulating all of the e-cigarettes will require expanding FDA authority and/or giving another governmental regulatory body authority over nontobacco–derived e-cigarettes, including cannabinoid and other e-cigarettes. Ensuring that all products on the market are reviewed and regulated for safety before public sale, rather than allowing products to be

Table 3. Current e-cigarette or vaping product use–associated lung injury coding guidelines*

Current Coding Guidelines for EVALI Encounters
- U0.70 *Vaping-related disorder* (general category for a range of vaping product–related clinical presentations)

Additional specific condition diagnoses (examples):

- J68.0 *Bronchitis and pneumonitis due to chemicals, gases, fumes, and vapors*
  - Includes chemical pneumonitis
- J69.1 *Pneumonitis due to inhalation of oils and essences*
  - Includes lipoid pneumonia
- J80 *Acute respiratory distress syndrome*
- J82 *Pulmonary eosinophilia, not elsewhere classified*
- J84.114 *Acute interstitial pneumonitis*
- J84.89 *Other specified interstitial pulmonary disease*
- R04.89 *Diffuse pulmonary alveolar hemorrhage*

Acute lung injury with no additional conditions specified:

- J68.9 *Unspecified respiratory condition due to chemicals, gases, fumes, and vapors*

Note: Additional codes may be needed to fully characterize an event so that encounters fully comply with ICD-10 coding rules.

Definition of abbreviations: CDC = U.S. Centers for Disease Control and Prevention; EVALI = e-cigarette or vaping product use–associated lung injury; ICD-10 = International Classification of Diseases, 10th Revision.
*Materials developed by CDC.

mass-marketed and consumed before their inhalational safety is established, should be paramount. As the e-cigarette market is a creative and innovative sector, to uphold recent regulatory gains this sector should be carefully monitored for the development of new products, and regulatory authority, whether through the FDA or another agency, should be broadened to allow quick regulatory action on newly developed e-cigarette products that potentially skirt current FDA authority.

Development of product standards would make the study of e-cigarette–related health effects easier by reducing product variety and the fast-paced evolution of this product category. Currently, research studies on health effects or toxicity of e-cigarettes may be outdated by the time the study is published, as the e-cigarette market rapidly evolves and changes. If nicotine e-cigarette standards are enforced like other tobacco products, manufacturers will be required to submit ingredient lists for each product, which will further facilitate in-depth research into the toxicity and biological safety of these products. Enforced manufacturing standards on nicotine e-cigarettes by the FDA will also ensure that no unexpected chemical constituents, such as VEA, are included in nicotine e-cigarettes, reducing potential for unexpected mass-illness events like EVALI. Product standards would also allow for easy comparison of illicit products to those approved for marketing, to facilitate early surveillance and evaluate potentially harmful additives. However, it should be noted that nicotine-free, cannabinoid, and other e-cigarettes currently do not fall under FDA regulation and would require additional regulatory authority to be established (42).

Patient and public education on the risks of e-cigarette use. Timely, informed, and consistent public health messaging by the CDC was critical for notifying the public about the association between the EVALI outbreak and e-liquid constituents, like VEA (43). These messages potentially helped to decrease case numbers and curtail the outbreak, by making users aware of the potential danger of VEA-containing e-cigarettes (43). Similar messaging campaigns have been used in the past with success, for example to reduce youth cigarette smoking (44). With continued efforts by physicians, scientists, and public health officials to make the public aware of potentially harmful constituents as we identify them, we can prevent future outbreaks. In addition, education of youth, parents, and teachers can help to prevent youth use of potentially harmful and addicting inhaled substances, like e-cigarettes.

EVALI Clinical Care

EVALI Definition

EVALI is a syndrome, with no specific diagnostic test that defines the condition. Several definitions have been proposed that rely on a combination of clinical features and elements of the patient's history. The most widely used is based on CDC guidance, which was developed to aid in identification of probable and confirmed cases to allow for standardized reporting and tracking in the setting of an epidemic of cases (45) (Table 4). Briefly, confirmed cases are defined as the onset of pulmonary infiltrates on chest X-ray or computed tomography (CT) that occur within 90 days of e-cigarette use, with no alternative cause found after medical assessment. Notably, this definition does not include any elements related to the type of e-liquid used (e.g., nicotine- or THC-containing formulations, flavored or unflavored, or types of carrier liquids). It also does not specify how extensive the work-up for infection must be or what testing modalities should be used. Furthermore, the criteria for confirmed and probable cases are nearly identical, except that probable cases have incomplete testing for infection or a positive microbiology result that does not fully explain the illness. It should be noted that the CDC criteria solely pertain to acute respiratory illness due to e-cigarette use and do not address chronic respiratory disease or other illnesses that may be induced or exacerbated by e-cigarette use. This is a critical area that needs to be addressed.

Clinical Presentation

EVALI typically presents as an acute or subacute respiratory illness with nonspecific symptoms, including shortness of breath, cough, chest pain, and/or hemoptysis (46). Most patients also have gastrointestinal symptoms (nausea, vomiting, and/or diarrhea) and/or constitutional symptoms (fever, chills, fatigue, and/or weight loss). Symptoms develop over days to weeks. Laboratory findings are nonspecific and may include elevated white blood cell count and erythrocyte sedimentation rate.

In some cases, the presentation of EVALI-VEA in adolescents was distinct from the presentation in adults. One case series observed adolescents with EVALI who suffered significant weight loss from gastrointestinal symptoms requiring hospitalization (47). Another case series detailed the need for venovenous extracorporeal membrane oxygenation to treat EVALI in adolescents with preexisting asthma (48). Although the unique pathophysiology of EVALI in adolescents is not fully understood, it is reasonable to suspect a unique presentation in terms of severity, symptoms, or both. Overall, information on EVALI in adolescents is sparse and requires more investigation.

Imaging. Radiologic findings in EVALI are nonspecific in many cases. The most common pattern of lung injury seen with EVALI is the parenchymal organizing pneumonia (OP) pattern, seen in approximately 56% of cases, composed of bilateral lower lobe–predominant or diffuse ground-glass opacity (GGO) with varying degrees of consolidation (49–51). Areas of subpleural, peribronchovascular, and lobular parenchymal sparing are common. In a smaller subset of patients, approximately 9%, EVALI will appear as diffuse, often ill-defined, centrilobular nodules with little or no GGO, which can mimic excipient lung disease from intravenous drug use. However, in patients with excipient lung disease, centrilobular nodules are usually well-defined, and findings of right heart strain are common because of diffuse embolization of injected material into the pulmonary arterioles (51). In 20% of patients, a mixed OP pattern occurs consisting of upper lobe–predominant centrilobular nodules with diffuse or lower lobe–predominant GGO with areas of mosaic attenuation. Although this pattern closely mimics hypersensitivity pneumonitis, to date, no histopathologically confirmed case of hypersensitivity pneumonitis has been reported in EVALI. Instead, the centrilobular nodules in EVALI have been shown to represent airway-centered OP pathologically (52). The most severe pattern of lung injury in EVALI is a diffuse alveolar damage pattern, comprising approximately 4% of cases. Imaging patterns consist of diffuse GGO and consolidation with volume loss and airway dilation due to alveolar collapse. Similar to other causes of diffuse alveolar damage, mortality rates were seen in one-third of patients with this pattern of lung

Table 4. Definitions of confirmed and probable cases of e-cigarette or vaping product use–associated lung injury as defined by the U.S. Centers for Disease Control and Prevention*

Confirmed Case
E-cigarette use in 90 d before symptom onset
AND
Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT
AND
Absence of pulmonary infection on initial work-up. *Minimum criteria* are: 1. A negative respiratory viral panel† 2. A negative influenza PCR or rapid test, if local epidemiology supports influenza testing 3. All other clinically indicated respiratory infectious disease testing (e.g., urine antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough, BAL culture if done, blood culture, HIV-related opportunistic respiratory infections if appropriate) are negative
AND
No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)
Probable Case
E-cigarette use in 90 d before symptom onset
AND
Pulmonary infiltrate, such as opacities, on plain film chest radiograph or ground-glass opacities on chest CT
AND
Infection identified via culture or PCR, but clinical team‡ believes this infection is not the sole cause of the underlying lung injury *OR minimum criteria* to rule out pulmonary infection not met (testing not performed) and clinical team‡ believes infection is not the sole cause of the underlying lung injury
AND
No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)

Definition of abbreviations: BAL = bronchoalveolar lavage; CDC = U.S. Centers for Disease Control and Prevention; COVID-19 = coronavirus disease; CT = computed tomography; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
*Materials developed by CDC.
†This would include exclusion of COVID-19 infection since the emergence of the SARS-CoV-2 pandemic.
‡Clinical team caring for the patient.

injury (49). Distinction between EVALI and COVID-19–related lung injury can be difficult. However, the presence of findings, such as lymphadenopathy, centrilobular nodules, and peribronchovascular sparing, although common in EVALI, are relatively uncommon in COVID-19 lung injury, especially during the early stages of lung injury (51). Imaging findings in chronic users of e-cigarettes remain poorly defined.

Pathology. The histopathology of EVALI is also nonspecific. Most commonly, lung biopsies show a pattern of OP (52–54), which is not surprising because most biopsies are obtained in the subacute phase of illness. Less commonly, patterns of acute fibrinous pneumonitis or diffuse alveolar damage patterns can be encountered, typically in the more acute setting or from patients with more severe illness. To date, no specific histopathologic features of EVALI have been identified, but several clues can point to potential causes. Foamy macrophages are nearly always present, suggesting toxic injury, and changes are almost always distinctly bronchiolocentric (53, 54). Most cases show granular proteinaceous or pigmented debris in areas of injury. Notably, neutrophilic inflammation is often prominent, closely mimicking infection and acute interstitial pneumonia, which can create an important pitfall. For the pathologist, evaluation for infection is essential, and special stains for microorganisms and cultures should be performed (55).

It should be noted that early reports of EVALI describe lipid-laden macrophages in bronchioloalveolar lavage (BAL) fluid that can be identified by oil red O histochemical stains. Enthusiasm for performing oil red O stains on BAL fluid was understandable in the early stages of the EVALI outbreak as clinicians sought a useful diagnostic marker (56); however, this assay has low specificity for EVALI, and oil red O–positive macrophages can be seen in many other disorders, including COVID-19 and other infections, adverse drug reactions, and autoimmune disorders (57), all of which result in the accumulation of lipid-containing macrophages from the breakdown of cell membranes. Because of its nonspecificity, technical performance challenges, and lack of data on its sensitivity for EVALI, oil red O staining should be avoided or interpreted with extreme caution (58, 59).

Was EVALI an isolated incident solely attributable to VEA?. Although most cases identified during the 2019 outbreak shared features consistent with the CDC case definition, sporadic cases of pulmonary disease attributable to e-cigarette use, which would not necessarily meet the current CDC

case definition, have been reported for the past decade, both before EVALI and after national case tracking ceased. Histologically, most cases of EVALI are associated with diffuse alveolar damage, fibrinous pneumonia, and OP (60). A review of case reports of adverse pulmonary reactions to e-cigarette use before the outbreak in 2019 shows a variety of diagnoses. Most diagnoses in that time period were based solely on clinical and imaging findings; only a few were histologically confirmed. Clinical presentations were also varied, with acute, subacute, and hyperacute presentations described, primarily presenting with cough and shortness of breath. In these older reports, patients were presumptively diagnosed with respiratory bronchiolitis interstitial lung disease (61), lipoid pneumonia (62–66), eosinophilic pneumonia (67, 68), OP (69), diffuse alveolar hemorrhage (70), hypersensitivity pneumonitis (71), or acute respiratory distress syndrome (72, 73), although only a subset had biopsies. Most of these reported cases were associated with nicotine e-cigarettes, although some were associated with cannabinoid e-cigarettes. Because EVALI gained international attention during the epidemic, it is the most commonly known term to designate individuals with e-cigarette–related lung disease and is now a diagnosis used by clinicians nationally and internationally.

Unfortunately, there are no confirmatory tests for EVALI. Despite the wealth of published clinical, radiologic, and pathologic data that have accumulated in the last two years, this remains a diagnosis of exclusion that requires a detailed exposure history, careful correlation of clinical, radiologic, and laboratory findings, and a high index of suspicion.

Clinical Management

No randomized clinical trials have been performed to date to test any therapy for EVALI. Most patients survived to hospitalization, with 68 deaths reported among 2,807 hospitalized patients with EVALI (2.4%) reported to the CDC (74). Data on long-term outcomes of patients who survived EVALI remain insufficient to determine the best management approach. Although emerging prospective long-term studies indicate that a significant proportion of those diagnosed with EVALI experience long-term adverse effects including respiratory limitations, as well as cognitive and mood impairment, these patients continue to use e-cigarettes (28, 75).

Reported therapy was mainly supportive oxygenation, through supplemental oxygen, noninvasive ventilation, mechanical ventilation, and, rarely, extracorporeal membrane oxygenation (76–80). The majority of patients in reported case series, 78–100%, also received some antibiotic therapy (77–80). This was common early in the course of treatment of admitted patients, as EVALI-induced respiratory failure can present very similarly to bacterial or viral pneumonia. In addition, there have been reported cases of concomitant EVALI and viral infections, like COVID-19. It should be noted that e-cigarette use has been reported to be associated with up to seven times the likelihood of nonusers to be diagnosed with COVID-19 (81) and increased risk of COVID-related symptoms (82). Another common treatment was corticosteroids. In some case series, 67–90% of patients received corticosteroid therapy, although the initial dosing and duration of therapy were widely variant (46, 77–80). However, many patients were managed with supportive care without steroids, with rapid clinical improvement.

Critical to clinical management of EVALI is e-cigarette use cessation. Cases have been reported of patients who continued to use e-cigarettes and had recurrent EVALI and/or respiratory failure (28, 80). However, because of their addictive nature, especially of nicotine e-cigarettes, cessation can be difficult. The CDC recommends offering or connecting patients to services to stop using e-cigarettes in both the inpatient and outpatient setting (76). As most patients were found to have used cannabinoid e-cigarettes, consideration must be given to chemical dependence on THC as well as nicotine (83–85). There are limited data on nicotine or cannabis cessation approaches in adolescents and younger adults (86, 87). More research is needed.

Overall, despite the lack of controlled clinical trials and long-term outcomes evidence for the management of patients with EVALI, the CDC offered a management algorithm in late 2019 (88). As medical centers across the country gained experience in managing EVALI, some regional treatment algorithms were developed, which were largely consistent with the CDC algorithm (79). As the case presentations declined and with the emergence of the SARS-CoV-2 pandemic, no interventional trials have been performed or appear to be planned.

Clinical Follow-Up

Follow-up on patients with EVALI continues to be challenging. Because of a high proportion (roughly 25%) of patients with EVALI being rehospitalized within 48 hours during the epidemic, the CDC recommended clinical follow-up within 48 hours after initial presentation to the emergency department or outpatient clinic (24). Close follow-up was specifically encouraged for patients with comorbid chronic health conditions. The risk of readmission appeared to be most tightly linked to resumption of vaping activities or the use of other inhaled toxins (combustible cigarette or cannabis use) (24). Anecdotally, successfully reaching patients for follow-up after hospitalization proved difficult either because of aversion to further medical contact or general lack of regular medical follow-up in young age.

Despite the CDC guidance, in practice there does not appear to be a clear consensus among clinicians on the appropriate follow-up interval. There are sparse data on follow-up outcomes; however, intervals range from 1 month in studies evaluating pulmonary function test (PFT) outcomes to 1 year in a retrospective study evaluating imaging outcomes and 1-year mortality and one prospective study (28, 75, 89). In PFT studies, initial findings in patients with EVALI included obstructive, restrictive, normal, or bronchodilator responsiveness with spirometry or decreased diffusing capacity for carbon monoxide (89). At 1-month follow-up, multiple patients from one study were found to have continued obstructive patterns (89); however, another study found continued improvement of abnormalities with cessation (90). Longer-term PFT-based follow-up studies have similarly mixed findings (28). With imaging studies, at EVALI diagnosis, CT findings of pulmonary bilateral GGO with subpleural sparing were common. After recovery and with cessation, most follow-up studies found the majority of patients had resolution of imaging abnormalities (28, 90). However, there are rare instances of persistent parenchymal changes and scarring (28, 91).

Overall, symptomatic, radiologic, and PFT improvement appeared to occur in parallel. This is reassuring, in that follow-up can be effective in detecting patient improvement even if not all diagnostic modalities (i.e., PFTs, imaging) are accessible by the patient or clinic.

Clinical Initiatives Needed to Address EVALI

Based on in-depth discussions in and around the workshop, several clinical initiatives were identified that are needed to advance our understanding of EVALI and prevent a similar outbreak in the future (summarized in Table 5).

Clinical training in evaluating exposures. Clinicians are not commonly trained in conducting exposure assessments, resulting in delayed diagnoses or failed courses of treatment before landing on the accurate diagnosis. In the case of EVALI, diagnoses might have happened more quickly with careful assessment of potential environmental or self-induced exposures. Although the availability of electronic medical record coding systems for EVALI, types of e-cigarettes used, included additives, and duration of use would be useful (as outlined above), their utility is limited to the knowledge that e-cigarettes are being used by the patient. In addition, comprehensive drug screenings are warranted in patients who report any e-cigarette use or if inhaled product use is suspected. Standardized exposure queries and assessments should be developed and implemented by physicians for early identification of e-cigarette use or other kinds of common environmental or occupational exposures.

Clinical studies to prospectively study emerging cases over their treatment course. The ongoing cases of EVALI, although less frequent than the epidemic levels seen in 2019–2020, should be formally studied. Having prospective clinical studies to enroll, study, and follow these patients will be important to standardize assessments and diagnoses, evaluate the effectiveness of treatments, and assess long-term outcomes. Governmental agencies, such as the CDC and NIH, should devote grant funds and organize research programs to study these patients. In addition, a prospective clinical study would allow for the rapid evaluation of future outbreaks of EVALI from future ingredients, additives, or adulterants in e-cigarettes. Furthermore, assessment of distinguishing features between VEA- and nicotine-induced effects are areas of needed research, although this likely will require translational research using animal models to evaluate because of the known clinical risks of VEA exposure.

Standardized follow-up assessments. Given the heterogeneity of findings in published follow-up studies, likely due to differences in clinical assessments and follow-up timing, a working group should be established to evaluate an ideal follow-up time frame to assess recovery from EVALI and any long-term effects in susceptible populations. Because of increased risk of readmission from continued inhaled product use, patients who are initially evaluated in the emergency department and discharged would benefit from early follow up (24–72 h), as well as careful exposure evaluations, as described above. In midterm follow-up assessments after hospitalization, as studies are continuing to find PFT and imaging abnormalities at 1 month after diagnosis, waiting a few more months (2–3 mo) may provide insight on a more definitive resolution time frame for imaging and pulmonary function abnormalities. Additional follow-up data on long-term outcomes are sparse and also much needed to evaluate development of long-term disease or mortality (e.g., $\geq$1 yr) (28).

Consensus on therapeutic management algorithms. Although the CDC and others provided clinical management algorithms toward the end of the peak of the epidemic, there has been no prospective evaluation of the efficacy of a variety of treatments used, such as the use of corticosteroids and antibiotic therapy. Therefore, future work should include prospective evaluation of therapeutic management options. In addition, monitoring the recovery of patients with EVALI was discussed as a critical need to ensure lower rates of readmission, management of potential longer-term effects, and adherence to cessation of product use. However, no consensus has been reached about the timing of long-term follow-up and which evaluation metrics to include. Therefore, this area of inquiry remains a critical need.

Diagnostic criteria consensus. The workshop group recommended evaluating updates to the diagnostic criteria for EVALI. Updates are especially urgent because the established criteria predate the COVID-19 pandemic and because of the striking similarity in presentation of EVALI and COVID-19. Guidelines for ruling out COVID-19 should be considered, such as multiple tests to rule out SARS-CoV-2 infection. Furthermore, testing suspected cases for biomarkers of e-cigarette use, such as urinary cotinine or THC, should be considered in diagnostic criteria updates. Other considerations that were discussed and should be evaluated included reducing the window of likely e-cigarette use before EVALI presentation to 30 days.

Potential Mechanisms Contributing to EVALI

Toxic Chemicals and Constituents of E-cigarettes Associated with EVALI

Individuals with EVALI reported using both nicotine e-cigarettes and cannabinoid e-cigarettes. Major ingredients in nicotine e-cigarettes include vegetable glycerin (VG) and propylene glycol (PG), and they may contain 1–4% flavoring chemicals and 0–10% nicotine (e.g., in reusable tank systems and reusable or disposable

Table 5. Clinical initiatives to address e-cigarette or vaping product use–associated lung injury

1. Clinical training in evaluating patient exposures is needed to ensure that comprehensive assessments of vaping product exposures are thoroughly conducted.
2. Prospective clinical studies are needed to enroll, study, and follow patients with EVALI to create better standardized diagnosis and treatment protocols as well as learn more about long-term outcomes.
3. Standardized follow-up assessments and timing are needed to ensure comparability across follow-up studies to better characterize the risks of long-term EVALI-related disease.
4. Consensus on therapeutic management algorithms is needed.
5. Consensus is needed on diagnostic criteria to define EVALI, particularly an update to CDC guidelines that requires exclusion of COVID-19.

Definition of abbreviations: CDC = U.S. Centers for Disease Control and Prevention; COVID-19 = coronavirus disease; EVALI = e-cigarette or vaping product use–associated lung injury.

pod-based devices) (92–94). User topography varies greatly, and, depending on flow rate and puff duration, between 5 and 40 mg per puff of e-liquid may be inhaled (95). In cannabinoid e-cigarettes the most common active ingredient, Δ^9-THC, can also be the most abundant ingredient, although other solvents, notably MCT oil, VEA, terpenes, triethyl citrate, etc., and other cannabinoids (cannabidiol [CBD], Δ^8-THC, etc.) are known to be present at varying concentrations (96–98). Cannabinoid e-cigarettes can deliver up to 5 mg Δ^9-THC per puff depending on composition and applied power (99). In addition to primary constituents of e-cigarettes, it is well understood that the heat applied in aerosolization combined with instability of some chemical constituents can result in degradation products that potentially contribute to underlying pathogenesis, including metals, carbonyls, and other organic compounds (100–102). As described below, many factors associated with the e-liquid composition can impact the physicochemical profile of the aerosols produced by e-cigarettes and thus ultimately contribute to e-cigarette–associated health effects.

VEA in cannabinoid e-cigarettes. VEA (also known as α-tocopherol acetate) is a highly lipophilic, synthetic form of vitamin E that was first developed to increase compound stability compared with its natural form (103). Although safely and commonly used in the food and cosmetic industry, VEA has been suspected as a primary chemical responsible for EVALI outbreaks (53, 104, 105). VEA was initially identified in 23 of 38 (60.5%) cannabinoid e-cigarettes collected from patients with EVALI in New York during the summer of 2019 (96), as well as in 24 of 46 (52.2%) e-cigarettes used by patients with EVALI in Minnesota during the summer and fall of 2019 (106). In addition, VEA was found in BAL fluid from 48 of 51 (94.1%) hospitalized patients with diagnosed EVALI across 16 states during summer and fall of 2019 (107). Finally, in an animal model, aerosolized VEA was found to increase the number of leukocytes, neutrophils, and inflammatory cytokines in BAL, as well as increase the number of lipid-laden macrophages in BAL (108, 109). The animal model findings are generally consistent with clinical observations in patients with EVALI.

Compared with other common solvents used in e-cigarettes, such as PG and VG, VEA has a similar density. However, VEA has a much higher viscosity than PG and VG (107). Studies with other liquids of similar physical properties suggest that aspiration of such highly viscous liquids could result in significant pulmonary inflammation and in not maintaining oxygenation at clinically acceptable levels (107, 109–115). Another important concern is low stability of VEA when heated. Laboratory studies have shown that thermal degradation of solvents typically used in e-cigarettes, such as PG and VG, can occur at temperatures above 133°C, resulting in the generation of many respiratory toxicants, including acrolein, acetaldehyde, and formaldehyde (116). VEA has been shown under vaping pyrolysis conditions to degrade to ketene gas, a respiratory poison that exhibits delayed toxicity to alveolar structures (mainly capillaries) and can cause pulmonary damage even in low concentrations (as low as 30 ppm) (117, 118). In the presence of a nucleophile, ketene will acetylate proteins in aqueous solution, such as the lung. At sufficient concentrations, protein damage secondary to acetylation can contribute to cytotoxicity (119). It should be noted that ketene is highly reactive and may be difficult to identify directly. Other respiratory irritants and known airway toxicants have also been identified with degradation of VEA, such as carbonyls, quinones, and other volatile products (120–123). In addition, VEA's mode of action has been hypothesized to be a modification of pulmonary surfactant surface tension contributing to lung atelectasis, functioning as a linactant or line-activating molecule that binds to the boundary between lipid membranes, displacing endogenous surfactant. Supporting this hypothesis, increasing concentrations of VEA in mixture with surfactant mimetics increased membrane fluidity and area compressibility, resulting in higher surface tension (110, 111). Furthermore, heated VEA via an e-cigarette may enhance the pulmonary deposition of VEA as fine and ultrafine droplets are generated, resulting in substantially increased bioavailability in the lungs. Thus, the role of VEA in EVALI is likely and merits further investigation. Although VEA was attributed to the rapid increase in EVALI (1, 80, 107), the possibility of other compounds acting by different pathophysiologic mechanisms, and the possibility of synergistic effects of compounds in the complex mixture of cannabis oils with VEA, are currently being studied.

PG and VG. Concentrations of PG and VG in e-liquid formulations are present in various ratios, ranging from 0:100 to 100:0, respectively (124). PG and VG are heated through e-cigarettes to produce an aerosol that can be inhaled. PG and VG are FDA Generally Recognized as Safe food additives for oral ingestion, yet their safety for inhalation into the lungs after aerosolization has not been established (125). VG-based e-liquids produce aerosol mixtures with large particles, smaller aerosol mass per puff, and VG-derived products (e.g., acrolein, dihydroxyacetone, etc.) in their composition (100–102). In contrast, PG aerosolization yields higher carbonyl concentrations, known to be mouth and throat irritants, thus yielding a user-described "throat hit" sensation (101, 102). PG and VG have been shown to alter the molecular alignment of pulmonary surfactant (126) and impact its surface tension (127). In culture, PG/VG aerosols reduced the metabolic activity and increased release of cytokines including interleukin 10 (IL-10) and C-X-C Motif Chemokine Ligand 1 in human bronchial epithelial cells exposed at the air–liquid interface (128). In mice, PG/VG aerosol inhalation exposures over a period of weeks dysregulated expression of several genes related to lung inflammation and biotransformation, impaired pulmonary lipid homeostasis, and decreased immune function (129, 130). This may indicate that inhaled PG and VG through an e-cigarette are respiratory hazards. Because PG and VG are the most widely used e-liquid humectants, additional studies on the long-term pulmonary effects of these humectants are critically needed.

Nicotine and flavorings. Nicotine in e-cigarettes comes in a range of strengths from 3 to ⩾50 mg/ml (reviewed in References 131–134). The health effects of nicotine on the respiratory system are complex, multifaceted, and well documented (135). Pulmonary responses to nicotine in humans include increased airway flow resistance, suggesting obstruction of the conducting airways (136). In addition, *in vitro* and *in vivo* models show that nicotine can lead to pulmonary inflammation and oxidative stress (135, 137). Although nicotine has been shown to contribute to adverse pulmonary outcomes, its role in EVALI is unclear and requires further research.

Currently, there are more than 200 unique flavoring chemicals, which are used to produce more than 16,000 distinct flavored e-liquids that are available on the

U.S. market (reviewed in References 138 and 139). Yet, little is known about the pulmonary toxicity of these flavoring chemicals upon heating and aerosolization in e-cigarettes. Flavored e-liquids can negatively impact the phagocytic ability of pulmonary macrophages, more so than PG/VG alone, and with significant differences between flavors (140). Flavored e-liquids can generate more toxic carbonyls (141) and free radicals (142) in mainstream aerosol than PG/VG alone, and certain ingredients have been shown to catalyze solvent degradation reactions (143, 144). In addition to aerosolization-associated degradation products, direct treatment of e-cigarette flavoring chemicals on monocytic cells causes cytotoxicity and IL-8 secretion dose-dependently, potentially by causing the formation of reactive oxygen species that activate inflammatory transcription factors (145). The health effects of flavoring chemicals contained in e-liquids are currently being documented. However, the large variety of e-cigarette flavoring chemicals can cause dose-dependent and cell-specific toxicity. Hence, it is difficult to generalize the toxicity of e-cigarette flavoring chemicals. Thus far, cytotoxicity has been reported for flavoring chemicals including diacetyl, cinnamaldehyde, vanillin, menthol, and ethyl maltol (138). Although flavoring chemicals have been shown to contribute to altered cellular function in airway models, their role in EVALI is still unclear and requires more research.

Other carrier oils for THC/CBD in e-cigarettes. THC and CBD are commonly used in e-cigarettes. These cannabinoids can be used in e-cigarettes in highly concentrated liquid forms, requiring other solvents in addition to PG/VG to aerosolize THC or CBD (98, 146). This is due to the nonpolarity of extracted cannabis oil and insolubility in water (146). In addition, MCT, long-chain triglycerides, polyethylene glycol 400, coconut oil, or olive oil have become increasingly common in cannabinoid e-cigarettes (147). Although most of these lipophilic solvents are typically marketed for use in ingestible tinctures, they have been found in e-cigarettes. Of particular concern is use of MCT in cannabinoid e-cigarettes, because this oily solvent was found in 20 of 46 (42.5%) products from potential EVALI cases in Minnesota during the summer and fall of 2019 (106). It has been documented that VEA and MCT were used as cutting agents in illegal cannabinoid e-cigarettes that were associated with EVALI (2, 106). The exact mechanisms by which THC- and CBD-associated solvents contribute to EVALI are still unknown and require further research.

Needs to Understand Mechanisms of EVALI

In addition to the initiatives mentioned above to assess the mechanistic role of the myriad of compounds in e-cigarettes associated with EVALI, several basic and translational initiatives were identified that are needed to advance our understanding of EVALI and prevent a similar outbreak in the future (summarized in Table 6).

The ongoing studies in the field of regulatory science, including on the chemistry of e-cigarettes, as well as on the cellular and molecular mechanisms associated with EVALI pathogenesis, are essential to further our understanding of both the short- and long-term effects of nicotine or cannabinoid e-cigarettes. In light of the unexpected and severe nature of EVALI, a complete understanding of these products and their mechanisms of toxicity is particularly important. Because the number of e-cigarette users exceeds 10 million in the United States (10, 21), additional research on the health effects of e-cigarette use will have significant public health and economic impacts. Knowledge gaps identified below provide directions for future research.

Comparative toxicity data and compound libraries for e-cigarette constituents. Potential respiratory side effects associated with e-cigarette use are likely to depend on the specific chemicals used. The various combinations of humectant ratios (PG and VG) and nicotine, added to more than 16,000 unique e-liquid flavors, makes it difficult to test all the possible distinct e-liquid formulations (138). In fact, many chemicals used in e-cigarettes have not been tested adequately for safety when heated and inhaled in aerosolized form. Thus, it is critical to develop high- and mid-throughput assessments that can be used to systematically evaluate the toxicity of e-cigarette aerosol constituents and their mixtures to prevent EVALI outbreaks in the future. This is likely to involve both *in vitro* and animal model–based systems evaluating delivery, dosimetry, and toxicity. In addition, this type of toxicity assessment may inform current outstanding questions about the mechanisms of EVALI, such as the role of VEA in systemic inflammation that was observed in EVALI but has been difficult to replicate in research studies (26, 53, 108, 109).

To standardize research across studies, it would be valuable to create a standardized library of compounds included in e-cigarettes that can be easily accessed by researchers across the world, including humectants, flavorings, nicotine, solvents, cannabinoids, and natural terpenes present in cannabis and hemp products. The library should be established by systematically testing products available to consumers or those collected in the proposed national biorepository by researchers and informed by manufacturer-submitted product standards. This way, the library could evolve as new commercial products are released and relevant information about ratios of compounds used in e-cigarettes can be collected. When thinking about compounds to include, some foresight should be used, especially around products used to

Table 6. Outstanding basic and translational initiatives to address e-cigarette or vaping product use–associated lung injury

1. Comparative toxicity data and accessible compound libraries are needed for all e-cigarette constituents and their mixtures to use for regulatory assessment.
2. Increased research around identifying and evaluating biomarkers of exposure to nicotine and cannabinoid e-cigarettes and related disease is needed to understand pathogenesis and differential effects between the vast variety of products available and the sensitivity and predictiveness of current biomarkers of interest and to prevent future EVALI outbreaks.
3. Governmental restrictions around the study of THC-containing products need to be relaxed to facilitate research to develop a comprehensive plan for regulation of THC-containing products.

Definition of abbreviations: EVALI = e-cigarette or vaping product use–associated lung injury; THC = tetrahydrocannabinol.

functionally aerosolize cannabis-based compounds, given the link between THC-containing compounds and EVALI. As an example, it was hypothesized in the workshop by multiple researchers that VEA may be substituted by other compounds or chemicals that function similarly. Thus, predictive functional modeling could be used to identify likely substitutes for known toxicants (like VEA) to evaluate inhalational safety before these additives are included in e-cigarettes, reducing the risk of other EVALI outbreaks.

Overall, the development of comparative toxicity data (e.g., based on oxidative stress, DNA damage, and inflammation resulting from inhalation exposure to aerosols generated from e-cigarettes, as well as compound libraries) are urgently needed. Taken together, it is imperative to have guidelines based on inhalation toxicity data for each e-cigarette constituent. This is to ensure that regulatory endpoints acknowledge and protect for differences between route of exposure (e.g., ingestion and inhalation).

Biomarkers of exposure. Identification of biomarkers related to EVALI is a necessary task not only to help diagnose patients but also to effectively study the epidemiology and pathogenesis of this diversely presenting syndrome. Biomarkers that may aid in distinguishing the type of e-cigarettes used may be identified by focusing on the active ingredients of each product. Positive urine ELISA screening for Δ^9-THC helped trace the EVALI outbreak to cannabinoid e-cigarettes (107), and likewise negative results for Δ^9-THC in patients with EVALI has prompted investigation into potential mechanisms of nicotine e-cigarette–related acute lung injury (3). However, the increase of inhaled products containing alternative cannabinoids (i.e., CBD, Δ^8-THC, etc.) that may not show up on routine toxicological panels should be kept in mind, and more comprehensive drug screenings are warranted in patients who report any e-cigarette use.

In addition to active ingredients, chemical degradation products that form during heating and aerosolization may be important sources of exposure biomarkers (148). Major aerosol products in nicotine e-cigarettes may include formaldehyde, acrolein, acetaldehyde, and glycolaldehyde-releasing agents (149); for cannabinoid e-cigarettes, isoprene, methacrolein, methyl vinyl ketone, isoprene epoxide, butadiene, etc. are present (123, 149, 150). However, given the potential for cooccurrence of cigarette smoking among patients, care in selecting degradation product metabolites unique to the delivery mode is extremely important. For example, a urinary biomarker for acrylonitrile (N-acetyl-S-[2-carboxyethyl]-l-cysteine) was reported to be significantly higher in nicotine e-cigarette users than in nonusers but lower than in cigarette smokers (151). Indeed, acrylonitrile is an abundant cigarette and cannabis smoke toxicant (150, 152), as the formation of nitrogenous volatile organic compounds is accessible because of N-containing compounds in tobacco and cannabis plant matter; conversely, across-the-board abundance of acrylonitrile in nicotine and cannabinoid e-cigarettes is not expected because of a lack of N-containing additives. Other abundant volatile organic compounds in e-cigarettes include acetaldehyde and acrolein (95); however, these are also present in cigarette smoke (152).

One group of compounds that are unique to nicotine e-cigarettes are PG and VG formaldehyde hemiacetals (153, 154). These putative formaldehyde-releasing agents are present at concentrations of up to 350 μg per puff, and four to eight times as much formaldehyde is in the aerosol in this form as is in the gaseous state (155). Formaldehyde, a lightweight gas that partitions to the aerosol gas phase, is absorbed rapidly in the upper respiratory tract because of its high water solubility. However, formaldehyde hemiacetals likely have lower vapor pressures and partition heavily into the aerosol particle phase, potentially leading to alveolar deposition and absorption into the blood stream (153, 154). Taken together, this shows that further work is required to determine exclusive biomarkers of exposures for the variety of existing e-cigarettes, which could aid in the study of the pathogenesis of EVALI.

Biomarkers of disease. Disease-related biomarkers are another important aspect to understanding pathogenesis of not only acute conditions such as EVALI but also chronic conditions in e-cigarette users. Nicotine e-cigarette aerosols contain reactive oxygen species, which cause oxidative stress and can damage cells and organs leading to cardiovascular disease, chronic obstructive pulmonary disease, and cancer, making them promising biomarkers of nicotine e-cigarette–induced toxicity (156, 157). Commonly measured biomarkers of oxidative stress include 8-isoprostane (8-iso) and 4-hydroxy-2-nonenal (157). Markers of DNA damage and inflammation include 8-hydroxy-2′-deoxyguanosine (8-OHdG) (158, 159) and CC16 (club cell protein 16) (112, 160), respectively. Utility of these biomarkers specifically in nicotine e-cigarette users has been demonstrated. Specifically, elevated concentrations of urinary 8-iso and 8-OHdG and spot urine 8-iso were found in nicotine e-cigarette users versus nonsmokers (157, 161). In fact, a significant elevation of oxidant stress biomarkers 8-OHdG and 8-iso, and a reduction in proresolving lipid mediators Resolvin D1 and CC10/16 (markers of acute lung injury), have been shown in patients with EVALI compared with nonusers (162). Similarly, reduced concentrations of plasmalogen are shown in patients with EVALI (163). Other biomarkers of oxidative stress, lipid peroxidation and malondialdehyde, could be used to distinguish effects between e-cigarette users, cigarette smokers, and dual users, as decreases were shown in these markers when smokers switched to nicotine e-cigarettes or dual use (164). These studies highlight potential biomarker candidates for e-cigarette use and related disease, but more research is needed to determine the sensitivity and predictiveness of these biomarkers, as well as the evaluation of other biomarkers potentially specific to EVALI.

Facilitate the study of cannabis-derived compounds. As VEA was the primary compound linked to EVALI and was found in cannabinoid e-cigarettes, it is essential that researchers are easily able to study cannabis-based compounds for respiratory toxicity. Currently, because of governmental regulatory restrictions around marijuana and THC in the United States, it is difficult to evaluate these compounds for inhalational safety in a research setting (165). Declassification of marijuana as a Schedule I substance under the Controlled Substances Act (165) and/or a waiver of requirements around the use of Schedule I substances for research purposes would facilitate further study of THC and other cannabis-based compounds. More limited ways than the above suggestion to facilitate this research would be to issue more Drug Enforcement Administration licenses to researchers for the study of marijuana and more manufacturer licenses to sell products for research. This is especially important because of the increase of consumer use of products that include THC after legalization of marijuana in a

variety of states. However, because of federal restrictions, the potential toxicity and inhalational safety of cannabis-derived products are understudied. Of particular interest are the effects of interaction of cannabinoids (THC, CBD, etc.) with carrier oils that contributed to EVALI, like VEA, as well as both acute and long-term effects of active compounds within cannabis products, which could most effectively be studied in animal models. These efforts would also allow for more comprehensive and systematic regulation of cannabis-based products throughout the United States, ensuring consistent manufacturing standards and lowering the risk of unintended adulterants being present in consumer products (166). The ability to carefully study and compare both cannabinoid and nicotine e-cigarettes would also allow for differentiation between these products. Overall, although cannabis-based products are readily available and used in many parts of the United States, and illicit THC-containing e-cigarettes were commonly linked to EVALI, we know little about their toxicity and safety. Thus, reductions or alterations in governmental regulations addressing research on cannabis products, or enhanced federal licensures, are needed to ensure thorough research and overall improve public health.

Conclusions

Addressing the root causes of EVALI and preventing a similar epidemic in the future will require an integrated multidisciplinary approach including public health, clinical, and basic/translational researchers; policy makers; and users of e-cigarettes. These initiatives will require substantial federal investment as well as changes to regulatory policy. Public health improvement and reduced risk of another substantial disease-inducing event depends on coordinated action to better understand the inhalational toxicity of these products, informing the public of risks of use, and the development and enforcement of regulatory standards for inhaled nicotine- and cannabis-based products. ■

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