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Guidance on the Clinical Management of Electronic Cigarette or Vaping-Associated Lung Injury



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ABSTRACT

In the summer of 2019, there was a rise in clusters of adolescents and young adults in the United States reporting to emergency departments with acute respiratory distress related to use of e-cigarette (electronic cigarette) or vaping. The number of patients with e-cigarette or vaping-associated lung injury continued to rise through the summer before peaking in September 2019. Through the efforts of state and federal public health agencies, officials were able to define the condition, identify the relationship of the respiratory injury to tetrahydrocannabinol-containing products, and stem the rise in new cases. In this report, we present a comprehensive review of the clinical characteristics and features of patients with e-cigarette or vaping-associated lung injury and guidelines for patient care and management to inform and navigate clinicians who may encounter these patients in their clinical practice.

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Introduction

Beginning in early 2012, a disturbing trend was building in the background of the public health arena, and it would develop into one of the largest public health mysteries of the decade. Sporadic cases of lung injury associated with vaping began in 2012,¹ and in July of 2019, clusters of young people (ages 10–19 y) began entering hospital emergency departments (EDs) with complaints of shortness of breath and chest pains associated with vaping.² Although the early cases are not necessarily reflective of the cause of the 2019 e-cigarette

(electronic cigarette) and vaping-associated lung injury (EVALI) series, they suggest that unregulated development of inhaled devices has the potential for considerable health consequences in some proportion to individual risk coupled with the breadth of distribution. The cases in the summer of 2019 were particularly worrisome because the increase in ED visits was primarily among young males from up to 10 states with no known cause for respiratory distress or illness.³ EVALI usually presents with symptoms of dyspnea, fever, nausea, and cough.⁴ A common theme in these patients is that they reported the use of e-cigarette or vaping products within 90 days of their ED visit. Through February 18, 2020, 2807 cases and 68 deaths from a mysterious lung injury have been reported in the United States and involved all 50 states.⁵ The outbreak of EVALI was primarily limited to the United States. These cases developed before the current coronavirus disease 2019 (COVID-19) pandemic though many of the symptoms and radiographic findings are overlapping. Although it is possible to diagnose viral infections with polymerase

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chain reaction testing, the current state of testing in the United States is susceptible to false-negatives and false-positives for both polymerase chain reaction–based and antibody-based methods. Therefore, careful consideration must be applied when EVALI and COVID-19 are the possible diagnoses. Identifying the causative agent of EVALI and characterizing the lung injury from vaping became a top public health priority.

Vaping or e-cigarettes involve high-temperature heating of a liquid to generate an aerosol vapor that can deliver substances, such as nicotine or tetrahydrocannabinol (THC), to the lungs. Generally, these liquids contain flavoring agents, diluents, nicotine, THC, nicotine and THC, or less typically, neither nicotine nor THC; the ingredients can vary greatly in chemical composition, especially between manufacturers or homemade mixtures. It became apparent early in the outbreak that most patients (86%–92%) admitted to using THC vaping liquids within 3 months of developing the disease.^{3,4} This proved to be an important observation, as laboratory analyses of these vaping liquids sought to identify candidate agents resulting in EVALI. Vitamin E acetate, medium-chain triglyceride oil, and other lipids rose to the top of the list of causative agents.⁴ By mid-December 2019, a causative agent for EVALI was finally identified. Using bronchoalveolar lavage (BAL) fluid from patients with EVALI and healthy donors who have not used THC-containing products, researchers used isotope dilution mass spectrometry and identified vitamin E acetate in over 90% of the EVALI cases versus none in the healthy controls. According to the Centers for Disease Control and Prevention (CDC), new cases of EVALI in the United States have continued to decline through February 2020, since its peak in mid-September 2019.

Guidelines on the clinical management of EVALI are important for these acutely ill patients. A timely diagnosis and treatment course can improve patient experiences and outcomes. Here, we present a comprehensive review of EVALI to aid physicians in the management of these patients. A PubMed search was performed on March 21 using the keywords “vaping” and “lung injury” to collect references that included EVALI and those that may report respiratory injuries before the naming of the condition EVALI, which led to retrieval of 116 articles. Review articles and commentaries were excluded from the data set of articles. We reviewed the remaining literature with focus on the patient characteristics, clinical features, and guidance for patient care and management.

Clinical Definition and Characterization of EVALI

Patient Demographics

In 2019, clusters of patients with severe acute respiratory symptoms began to appear in the United States among midwest states (Minnesota, Illinois, Indiana, and Wisconsin) and western states (Utah and California). The respective states and national health agencies created the Lung Injury Response Clinical Working Group to track and monitor these patients resulting in the emergence of numerous case studies and reports. These clusters indicated that a larger issue existed. We identified 27 case reports or case series related to the description of patients with EVALI in our data set of EVALI literature from 2017 to 2020 as revealed in [Supplementary Table 1](#).^{6–26} Although these studies provide insight into the characteristics of patients with EVALI, the limited number of patients in these studies does not allow for definitive conclusive recommendations about the disease and its management. Therefore, we focused our attention on the larger observational studies. The CDC established case definitions for the surveillance of EVALI to identify and track patients ([Table 1](#)). Cases are classified as confirmed or probable based on the presence or absence of signs of other etiologies for respiratory symptoms, that is, other infectious agents. Probable cases are those in which infectious agents may present in a patient airway but the clinical team deems that the agent is likely not the cause of the respiratory symptoms.

EVALI cases began to rise in the United States throughout the summer of 2019 before peaking in September, and they continued to decline through February of 2020 ([Fig. 1A](#)). As of February 18, 2020, a total of 2807 patients with EVALI have been reported to the CDC and 68 confirmed deaths have been attributed to the disease ([Fig. 1B](#)). EVALI cases have been identified in all 50 states, and deaths have occurred in 29 states and the District of Columbia ([Fig. 1B](#)). The CDC published monthly reports on the characteristics of EVALI cases for the United States, and summaries for limited state clusters have also been reported, which are summarized in [Table 2](#).^{27–33} Patients across all the data sets tended to be male (62%–79%), less than 30 years old (median age 23–27 y), and have used THC-containing products within the last 90 days (76.9%–91%). Affected cases were primarily White non-Hispanic (46%–79%) and Hispanic (12%–47%), with California having a lower number of

Table 1. CDC Case Definitions for EVALI Surveillance

Confirmed Case	Probable Case
<ul style="list-style-type: none"> E-cigarette/vaping use within 90 d of symptom onset Radiograph opacities, pulmonary infiltrates in the chest or ground-glass opacities on chest CT No evidence of other pulmonary infections 	<ul style="list-style-type: none"> E-cigarette/vaping use within 90 d of symptom onset Radiograph opacities, pulmonary infiltrates in the chest or ground-glass opacities on chest CT Evidence of infection, but the clinical team deems the infection is not likely the cause of the respiratory symptoms, or if testing for infectious agents were not performed
<ul style="list-style-type: none"> Patient medical history does not indicate an alternative diagnosis 	<ul style="list-style-type: none"> Patient medical history does not indicate an alternative diagnosis

CDC, Centers for Disease Control and Prevention; CT, computed tomography; EVALI, e-cigarette and vaping-associated lung injury.

White non-Hispanic (46%) and a higher proportion of Hispanic (47%) cases, which may be because of the small sample size (n = 160) and demographics of the state.²⁷

Vaping or E-Cigarette Use Among Patients With EVALI

As e-cigarette and vaping became associated with lung injury in youths, it is important to understand how

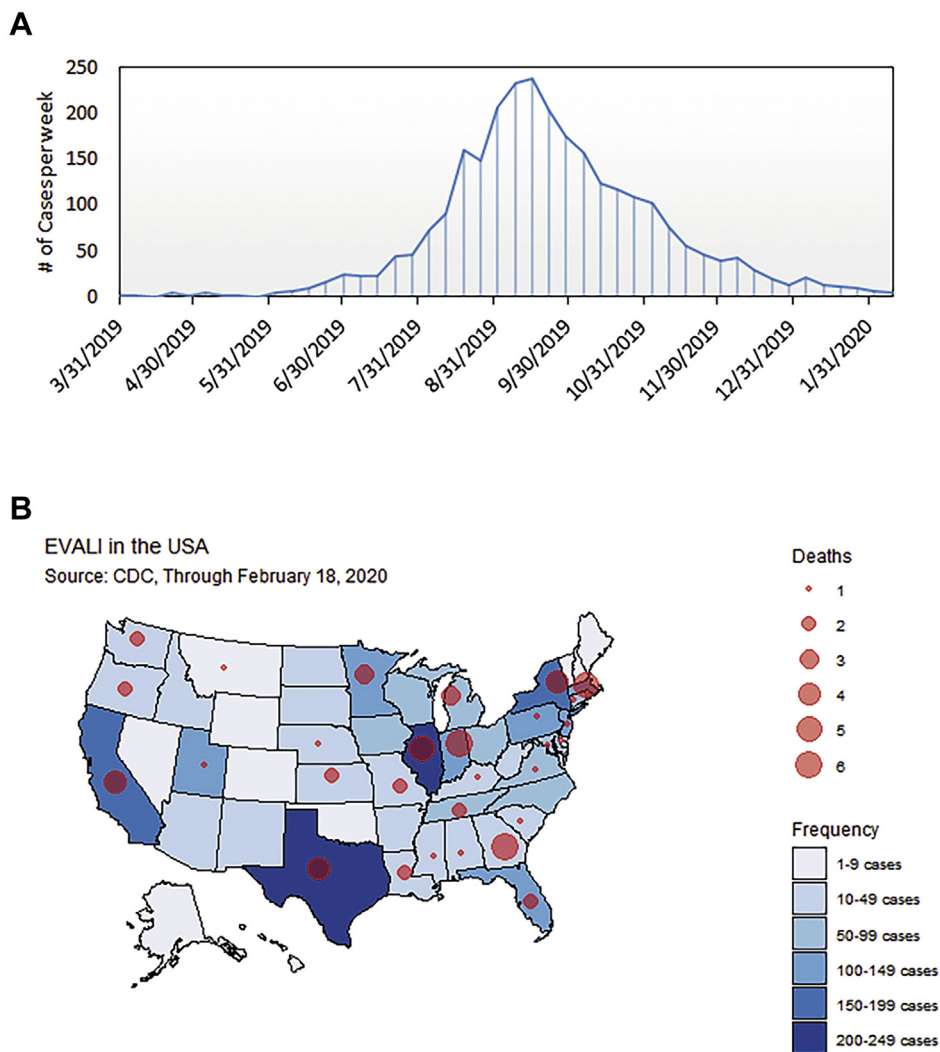


Figure 1. Summary of patients with EVALI in the United States reported to the CDC (March 3, 2019-February 2, 2020). Data of patients with EVALI were downloaded from the CDC website. (A) Weekly new EVALI cases reported to the CDC from March 31, 2019 to February 18, 2020. (B) Distribution of EVALI cases by states (blue) and EVALI-related deaths (red circles). CDC, Centers for Disease Control and Prevention; EVALI, e-cigarette and vaping-associated lung injury.

Table 2. Clinical Characteristics at Presentation of Patients With EVALI From Nationwide US Cases and State Clusters

Characteristics	Chatham-Stephens et al. (2019) ²⁸	Taylor et al. (2019) ²⁹	Gaub et al. (2019) ³⁰	Ghinai et al. (2020) ³¹	Layden et al. (2020) ³²	Blagev et al. (2019) ³³	Heinzerling et al. (2020) ²⁷
Demographics Region	US	Minnesota	Indiana	Illinois	Illinois and Wisconsin	Utah	California
Data cutoff date	11/5/19	10/1/19	10/28/19	12/1/19	9/6/19	6/27/19-10/4/19	8/7/19-11/8/19
Total no. of cases	2016	96	127	195	98	60	160
No. of deaths	42		3		2	2	4
No. of states	49	1	1	1	2	1	1
% Hospitalized	95	—	76	—	95	90	46
Duration of symptoms, d (range)	NR	—	—	—	6 (0-155)	5 (3-8)	5 (0-30)
% Male	68	—	70	73	79	80	62
Median age, y (range)	24 (13-78)	—	26 (16-68)	—	21 (15-53)	27 (22-36)	27 (14-70)
% White non-Hispanics	79	—	—	60	78	72	46
% Hispanic	12	—	—	15	13	22	47
% Other	NR	—	—	8	<5	—	<5
Substance use							
% any THC use	83	91	—	86	89	78	83
% Any nicotine use	61	71	—	73	73	67	47
% THC only	35	22	24	—	27	30	31
% Nicotine only	13	5	24	—	11	17	8
% THC and nicotine	48	64	45	—	60	48	—
% Neither THC nor nicotine	4	—	7	—	—	—	—
Presentation							
% Respiratory symptoms	85	—	—	95	97	98	94
% GI symptoms	57	—	—	84	77	54	79
% Constitutional symptoms	76	—	—	90	100	53	89
% Corticosteroid treatment	81	—	65	50	82	95	80
% Oxygen saturation < 95% on room air	30	—	—	63	58	83	69
% Tachycardia (>100 beats/min)	40	—	—	39	63	83	89
% Tachypnea (>20 breaths/min)	0	—	—	26	43	72	65
Imaging							
% Abnormal chest radiograph	82	—	—	—	83	97	—
% Bilateral radiograph findings	76	—	—	—	—	—	—
% Abnormal chest CT	100	—	—	—	100	100	—
% Bilateral CT findings	96	—	—	—	—	—	—

Note: These were early and partial studies that apparently were published quickly to get the word out to the general population. The sharp and sustained decline in new EVALI cases is a testament to the effectiveness of this approach in putting a halt to the outbreak.

CT, computed tomography; EVALI, e-cigarette and vaping-associated lung injury; GI, gastrointestinal; NR, not recorded; THC, tetrahydrocannabinol; US, United States.

this group of patients was using these devices. Patients with EVALI report using various types of vaping liquids containing products of THC, nicotine, and cannabidiol.³⁴ For patients with EVALI in the United States, most use THC or nicotine-containing products daily, 74% and 85%, respectively.³⁴ The use of THC-containing products more than five times a day is associated with a higher

risk for developing EVALI (adjusted OR 3.1, 95% confidence interval: 1.6–6.0).³¹ The source of products differed between THC and nicotine-containing liquids. Most patients report getting THC products from only informal sources (78%), that is, family or friends, although most nicotine products were acquired from commercial sources (69%).³⁴ Youths, less than 18 years,

primarily acquire either THC or nicotine products through informal channels. This is problematic because informal sources can be dangerous and difficult to track. A comparative analysis of symptomatic patients with EVALI versus e-cigarette or vaping users without EVALI symptoms determined that acquiring THC-containing products from informal sources and using dank vapes (a class of counterfeit THC-containing products distributed under informal sources) were associated with increased odds of developing EVALI, 9.2 (95% confidence interval: 2.2–39.4) and 8.5 (3.8–19.0), respectively.³⁵ It is worth noting that although most cases of EVALI report use of THC-containing products, a minority of the cases (8%–24%) report use of only nicotine products or neither nicotine nor THC products (2%–7%) (Table 2). Some of this discrepancy may be attributable to patient recall error, secondhand inhalation, or some other unknown explanation, but it could suggest that there may be two or more agents able to affect the EVALI symptoms. The CDC recommends that people abstain from e-cigarette and vaping products, but if one must use such a product, they should be acquired through formal commercial channels.

Clinical Presentation

Examination of medical records and patient interviews through the surveillance initiative of the CDC provided insights into the presentation and clinical characteristics of EVALI, summarized in Table 2. Although the CDC reports provide an overview of the characteristics across the entire United States, three state-level studies provide more in-depth clinical and outcome data. Therefore, we will focus our discussion on the clinical presentation of patients with EVALI in Illinois and Wisconsin,³² Utah,³³ and California²⁷ data sets (Table 2). The patients often presented with respiratory (85%–98%), gastrointestinal (57%–90%), and constitutional (76%–100%) symptoms (Table 2). The respiratory symptoms included cough (78%–85%), shortness of breath (82%–85%), chest pain (43%–52%), and hemoptysis (8%–12%).^{27,32,33} The gastrointestinal symptoms included nausea (61%–75%), vomiting (56%–72%), abdominal pain (31%–47%), and diarrhea (34%–44%).^{27,32,33} The constitutional symptoms included subjective fever (76%–84%), fatigue (41%–48%), weight loss (12%–26%), and headache (18%–34%).^{27,32,33} At the time of the presentation, the patients often had an elevated temperature greater than equal to 38°C (33%–57%),^{27,32,33} elevated heart rate (30%–83%), elevated respiratory rate (40%–89%), and oxygen saturation on room air less than 95% (0%–83%) (Table 2). Abnormal chest radiographic or computed tomography (CT) results were observed in most patients

(Table 2), including bilateral infiltrates or opacities in 94% to 100% of the cases.^{27,32} EVALI is a diagnosis of exclusion; therefore, in the current COVID-19 pandemic in which many features of the clinical presentation may overlap with those of COVID-19 infection, it is important at present to rule out COVID-19 by viral testing. Patients should continue to be monitored closely as the fidelity of viral testing is limited. Although data on vaping, e-cigarettes, and smoking are limited because they are derived primarily from a small number of observational studies, early guidance suggests that those who smoke (traditional or e-cigarettes) may tend to have more severe COVID-19 disease.^{36,37} In addition, smoking and nicotine alone can up-regulate the angiotensin-converting enzyme-2 receptor in lung cells.^{38,39} Because angiotensin-converting enzyme-2 is a possible receptor used by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter human cells, those who smoke or use nicotine products may be more susceptible to developing a SARS-CoV-2 infection and subsequent COVID-19.

Clinical Care of Patients With EVALI

Most patients (90%–95%) who present with symptoms of EVALI are admitted to the hospital for a median of 4 to 6 days, and 3% to 10% of discharged patients will require readmission for EVALI symptoms.^{28,32,33,40} Deaths occurred in 0.6% to 3% of patients admitted to the hospital.^{27,32,33,40} Confirmed and probable EVALI cases (Table 1) represent 52% and 48% of patients, respectively.²⁸ Patients that required hospitalization were more likely to be confirmed cases (Table 1) versus those who did not require hospitalization, 55% and 12% ($p = 0.001$), respectively.²⁸ Mikosz et al.⁴⁰ studied patients who were discharged after a hospitalization related to EVALI. The median age of the patients who died was higher (54 y, $n = 7$) than those who were readmitted to the hospital (27 y, $n = 31$) or were neither readmitted nor died (23 y, $n = 768$).⁴⁰ The patients who died or were readmitted to the hospital had a history of one or more chronic conditions ($p = 0.006$ and $p < 0.001$, respectively).⁴⁰ These conditions included cardiac disease ($p < 0.001$), obstructive sleep apnea ($p = 0.002$), and chronic obstructive pulmonary disease ($p = 0.01$) for patients who died. Obstructive sleep apnea ($p = 0.002$) and diabetes mellitus ($p = 0.009$)⁴⁰ were also noted. The care that the patients with EVALI required during hospitalization included supplemental oxygen (76%–88%), a high-flow nasal cannula (29%–47%), noninvasive positive pressure ventilation (22%–28%), intubation and mechanical ventilation (17%–29%), intensive care unit care (46%–55%), initiation of antibiotics (90%–98%), and steroids (80%–95%).^{27,32,33} All

these procedures are aerosol generating creating a high degree of risk if there is a presence of secondary viral or bacterial infection. Of the patients admitted to the hospital who received steroids, 51% to 68% had an improvement.

Radiologic and Histologic Features

Patients with EVALI usually have abnormal chest radiograph (83%–97%) or chest CT scans (100%), with changes frequently involving both lungs (Table 2). Unfortunately, these abnormalities associated with EVALI represent heterogeneous pathologic findings and include various imaging patterns associated with use of e-cigarette and vaping products.^{41,42} Therefore, a single pathologic finding or imaging pattern is insufficient to diagnose EVALI. One study that included 17 patients with high-resolution CT reported that all patients with EVALI displayed ground-glass opacities and consolidation, but there was no preference for lobe distribution. On the basis of lung biopsy samples, these patients had a variety of histopathologic patterns associated with acute fibrinous pneumonia with organization (53%), acute and organizing diffuse alveolar damage (24%), organizing pneumonia (18%), and acute fibrinous pneumonitis in a patient with a recent pneumothorax (6%).⁴¹ Histologic features that were most often observed in these patients (>75%) were foamy or vacuolated macrophages and pneumocytes, intra-alveolar fibrin, organizing pneumonia, and bronchiolitis. A second, smaller, study reported similar finds as reported previously.⁴³

The above-mentioned histologic and imaging features represent observations from adult patients, but because EVALI also affects many adolescent patients, it is important to consider this group of patients separately. Adolescents tend to display similar features as adult patients with EVALI, but additional common imaging findings are noted in these patients, including pleural effusions (50%), mild thickening of the bronchial wall (50%), and enlarged lymph nodes (75%).⁴⁴ In addition, unlike adult patients, adolescents have a tendency to display a lower lobe predominance on CT images.⁴⁵ Radiologic changes are similar in COVID-19 infections, so viral testing is critical at present. These characteristics in adolescent patients have limitations as they are based on a few studies with small sample sizes.

The quest for a definitive diagnostic marker for EVALI has led some to suggest that lipid-laden or foamy macrophages (LLMs) in BAL fluid may be such a biomarker.⁴⁶ LLM is observed in most patients with EVALI; however, their applicability as a biomarker for EVALI has been contested.^{32,41,47,48} Although LLM is common to patients with EVALI, they are not specific for these patients, as these can also be found in other forms

of acute lung injury related to infection, aspiration, adverse drug response, and autoimmune diseases.^{47,49-51}

It is likely that relying on LLM to diagnose EVALI could lead to misdiagnoses and inferior patient care.⁵² Presence of clinical signs and symptoms as described previously with LLM lends support to the diagnosis of EVALI, but LLM alone is not a definitive diagnostic marker.

Vitamin E Acetate as a Potential Cause of EVALI

Once the clinical characteristics of EVALI were determined, the investigation focused on determining an agent or agents responsible for the condition. The most likely source of the offending agent was in THC-containing products because 77% to 91% of the patients with EVALI reported to using these products 90 days before the onset of the EVALI symptoms (Table 1). Analysis of THC-containing liquids identified vitamin E acetate, medium-chain triglyceride oil, and other lipids as hypothetically detrimental constituents.³ In a preliminary study, Blount et al.³ (2019) measured these compounds by isotope dilution mass spectrometry in BAL samples from 29 patients with EVALI. Vitamin E acetate was the only analyte found in all the patient samples, and other analytes were rarely detected. In addition, THC and nicotine metabolites were measured in 23 and 16 patients, respectively. These data suggest that vitamin E acetate is a likely candidate for causing EVALI; however, additional data are required to confirm this observation. A subsequent study was performed which included BAL samples from 51 patients with EVALI and 99 healthy patients with diverse smoking histories without EVALI (nonsmokers, cigarette smokers, and e-cigarette/vaping product smokers). Several compounds suspected to be the cause EVALI were selected to be measured in BAL samples using isotope dilution mass spectrometry.⁵³ Vitamin E acetate was detected in 94% (48 of 51 patients with EVALI) and none of the healthy controls. In addition, only coconut oil and limonene were detected in one patient with EVALI among the other 10 analytes measured. Another study used nontargeted mass spectrometry to analyze vaping liquids collected from 38 patients with an EVALI diagnosis. This study found that vitamin E acetate is present in 64% of the samples whereas the pesticide piperonyl butoxide and the fungicide myclobutanil were detected in 47% and 58% of the samples, respectively.⁵⁴ On the basis of these limited studies, vitamin E acetate is present in most samples, but it is much less common than that found in BAL fluid samples. This disparity may be because of the fact that samples of e-liquid are an indirect measure of the presence of the agent, as a previous vaping liquid or liquid shared from a friend may be responsible for

delivering the vitamin E acetate. Collectively, these data reveal that vaporizers can deliver vitamin E acetate to the lung, and it is present in most THC vaping products and patient samples with EVALI. These findings support the assertion that vitamin E acetate is a likely cause of EVALI, but they do not rule out other possible agents, as some patients with EVALI did not have detectable vitamin E acetate in BAL samples and 8% to 24% patients with EVALI reported smoking nicotine only (Table 2). Vitamin E acetate is used as a diluent for vaping products that contain THC because it has the advantageous characteristics of being inexpensive and tasteless.⁵⁴

Although vitamin E acetate seems to be a strong candidate for causing EVALI, our understanding of the mechanism behind the lung damage is limited. Vitamin E acetate can form a noncovalent complex with THC in aerosols produced during vaping, which would allow the complex to be delivered to the lungs.⁵⁵ However, the effect of this complex on the lung is not known and warrants further investigation to establish a possible mechanism of lung toxicity. Vaping involves aerosolizing a liquid containing many constituents (nicotine, THC, flavorings, etc.) by applying high temperatures for inhalation into the lungs. Heating of vitamin E acetate can induce pyrolysis resulting in the toxic agent ketene gas and the carcinogens alkenes and benzene.⁵⁶ Therefore, vitamin E acetate may be acting in a direct or indirect manner to trigger lung injury. A mouse model of vitamin E acetate lung injury has recently been established.⁵⁷ Mice were exposed to 77.3 to 167.5 μg vitamin E acetate, propylene glycol and vegetable glycol, or air. After a 2-week exposure period, BAL fluid and lung tissue were harvested from the mice. Mice exposed to vitamin E acetate display similar phenotype to human patients with EVALI, including a rise in albumin levels and elevated leukocytes and lipid-laden macrophages in BAL fluid, relative to the propylene glycol and vegetable glycol and air groups. Mice exposed to vitamin E acetate displayed profuse oil red O-stained alveolar macrophages within the pneumocytes of the alveoli. This model could be used to prove that vitamin E acetate does in fact cause EVALI, establish a mechanism of action, and identify other agents that cause lung injury.

Guidelines for Clinical Management of EVALI

The CDC and the Lung Injury Response Clinical Working group have established an algorithm for the management of patients with EVALI to improve outcomes, reduce hospital readmission, and prevent death (https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/Algorithm-EVALI-Dec-2019-p.pdf). The

guidance includes diagnosis, inpatient and outpatient management, postdischarge follow-up and support, and considerations for seasonal influenza.⁵⁸ Patients who present with respiratory, gastrointestinal, and constitutive symptoms should be evaluated for EVALI using definitions in Table 1. The CDC offers suggestions on questions to ask during the initial clinical assessment to obtain information essential for an EVALI diagnosis (https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/pdfs/dont-forget-to-ask-assessing-the-risk-of-lung-injury-508.pdf). Once EVALI is suspected, patients should be assigned for inpatient or outpatient management. Outpatient care is appropriate if the following conditions are met: oxygen saturation is greater than or equal to 95% on room air, no respiratory distress, no comorbidities, and availability of social support. Inpatient treatment is warranted if the above-mentioned conditions are not met. Inpatient care should include chest imaging studies (chest radiograph or CT scan), infectious disease testing (including COVID-19 testing), consultation with other disciplinary teams (i.e., pulmonology), BAL or lung biopsy, and psychiatric evaluation, as clinically indicated. During hospitalization, patients should abstain from e-cigarette and vaping products and antimicrobial agents and corticosteroids should be initiated as the condition warrants.

The previous steps are important for managing the acute effects of EVALI, but generating a thorough plan for discharging the patient may be important for reducing readmission and death.^{40,58} The CDC has established an "EVALI Discharge Readiness Checklist" to aid clinicians in the discharge planning process (https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/evali-discharge-readiness-checklist-508.pdf). The treatment team should screen patients for substance abuse disorders and provide the patient with contact information for the appropriate support that the patients will need to complete their recovery. Patients should also be offered an influenza vaccination, if applicable. These include pharmacists to ensure medications are being taken as prescribed (i.e., corticosteroids) and outpatient follow-up appointments within 48 hours of discharge with a primary care physician and at 2 to 4 weeks with a pulmonologist. Patients should be urged not to use e-cigarettes or vaping products, as these could cause a recurrence of respiratory symptoms, with substance abuse support and clinically proven methods of smoking cessation. Considerations for outpatient care include chest radiograph, influenza virus testing, stopping e-cigarette and/or vaping use, corticosteroids, smoking cessation support, influenza vaccination, and 24 to 48 hours follow-up with a primary care physician. Following these guidelines can be an effective

way to improve outcomes for patients with EVALI; however, they have not been established from prospective studies.

The EVALI outbreak highlights the importance of regulation of these products by agencies, including the United States Food and Drug Administration, and the importance of these regulations and efforts to reduce use of these products through taxation, education, and other efforts.

Conclusions

Lung injury and severe acute respiratory distress associated with vaping emerged abruptly in 2019. EVALI was effectively contained through the mobilization of state and federal health agencies in the United States, who were able to rapidly begin surveillance and disease monitoring. As a result, EVALI cases continued to fall from a maximum in mid-September 2019 through February of 2020. These efforts also lead to the identification of THC-containing products as a major source of the injury and later to the identification of vitamin E acetate as a likely causative agent for lung damage. Although vitamin E acetate is one likely cause of EVALI, other agents may also be involved because patients who do not have a history of THC use or detectable levels of vitamin E acetate in BAL fluid do exist. This story would have likely looked much different if COVID-19 have come up in December 2018 instead of 2019. COVID-19 would have overwhelmed the public health system. The similarity of the clinical presentation between EVALI and COVID-19 would have made the two diseases difficult to distinguish especially when viral testing for SARS-CoV-2 was limited. In such an environment, the EVALI outbreak would have likely expanded to include far more cases and deaths before it could be identified, if at all. In a post-COVID-19 era, it will likely be more difficult to recognize agents, such as vitamin E acetate that can cause acute respiratory distress when inhaled. Therefore, it is essential to have and maintain the appropriate networks in place to identify and track clusters of these respiratory illnesses that emerge, such as those that effectively managed the EVALI outbreak.

E-cigarettes and vaping products are often thought to be a less harmful alternative to combustible cigarettes, but the EVALI story highlights the fact that hidden dangers to these products can emerge. Vitamin E acetate is a canary which may warn of future respiratory illnesses, such as EVALI, that are associated with vaping and e-cigarette products, commercial or illicit. Illicit THC-containing products seemed to be the major source of the EVALI outbreak.⁵³ Acute respiratory illnesses, such as EVALI, will likely continue if illicit markets for these products continue to flourish

without restriction. Governmental regulation, transparent product labeling, active surveillance, and consumer education are warranted to prevent or mitigate future respiratory injuries associated with vaping and e-cigarette. As new chemical additives to these products become available, similar to vitamin E acetate, lung injuries may follow. Recently, the sale of flavored e-cigarettes has been banned in several states, including Massachusetts, New Jersey, New York, and Rhode Island, but such bans may have limited influence on curbing future EVALI-like outbreaks that seem to arise from the illicit market. Although e-cigarette bans may have public health benefits and could help curb e-cigarette use among youths, a better way to prevent other EVALI-like outbreaks is through improved regulation and monitoring of the illicit substance markets, especially those for THC and cannabis. Two effective policies to curb vaping use would be to put a worldwide ban on sales of e-cigarettes to persons under the age of 21 years and increasing taxes on these products. The International Association for the Study of Lung Cancer, in November of 2019, has issued a policy statement on e-cigarettes and vaping (<https://www.iaslc.org/About-IASLC/News-Detail/iaslc-policy-statement—electronic-cigarettes>). In summary, they suggest that all persons, including patients with cancer, should quit smoking by using a clinically proven cessation strategy, that is, pharmacotherapy or counseling, constituents of e-cigarette liquids may contribute to adverse health effects associated with vaping, and e-cigarettes should not be used by adolescents or adults who do not currently smoke. EVALI seems closely linked to THC products purchased on the illicit market and vitamin E acetate, but some patients with EVALI report only nicotine-containing product use and use of neither nicotine nor THC-containing products. A variety of health effects associated with e-cigarettes and vaping have been reported; however, these illnesses are often in the form of case reports or small case series reports of infrequent events.⁵⁹ There is a need for more clinical studies to appropriately address the safety and potential complications associated with e-cigarettes and vaping to prevent EVALI-like conditions from arising in the future. There is also a need for regulation of these products and worldwide efforts to reduce consumption through education, taxation, and other efforts.

Supplementary Data

Note: To access the [supplementary material](#) accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <https://doi.org/10.1016/j.jtho.2020.08.012>.

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