

Clinical Progress Note: E-cigarette, or Vaping, Product Use-Associated Lung Injury

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E-cigarettes are handheld devices that are used to aerosolize a liquid that commonly contains nicotine, flavorings, and polyethylene glycol and/or vegetable glycerin. These products vary widely in design and style (Figure 1); from the disposable “cigalikes” to vape pens, mods, tanks, and pod systems such as JUUL, there has been a dramatic increase in the recognition, use, sale, and variety of products.¹ In addition to the known risks of e-cigarette use, with youth nicotine addiction and progression to cigarette smoking, there is evidence of a wide range of health concerns, including pulmonary and cardiovascular effects, immune dysfunction, and carcinogenesis.¹ The emergence of patients with severe lung injury in the summer of 2019 highlighted the harmful health effects specific to these tobacco products.² Ultimately named EVALI (e-cigarette, or vaping, product use-associated lung injury), there have been 2,807 hospitalized patients with 68 deaths reported to the Centers for Disease Control and Prevention (CDC).^{2,3} This clinical progress note reviews the epidemiology and clinical course of EVALI and strategies to distinguish the disease from other illnesses. This is particularly timely with the emergence of and surges in COVID-19 cases.⁴

SEARCH STRATEGY

As the first reports of patients with e-cigarette–associated lung injury were made in the summer of 2019, and the CDC defined EVALI in the fall of 2019, a PubMed search was performed for studies published from June 2019 to June 2020, using the search terms “EVALI” or “e-cigarette–associated lung injury.” In addition, the authors reviewed the CDC and US Food and Drug Administration (FDA) website and presentations on EVALI available in the public domain. Articles discussing COVID-19 and EVALI that the authors became aware of were also included. This update is intended for hospitalists as well as researchers and public health advocates.

DEFINING EVALI

Standard diagnostic criteria do not yet exist, and EVALI remains a diagnosis of exclusion. For epidemiologic (and not diagnostic) purposes, however, the CDC developed the fol-

lowing definitions.³ A confirmed EVALI case must include all of the following criteria:

- Vaping or dabbing within 90 days prior to symptoms. *Vaping* refers to using e-cigarettes, while *dabbing* denotes inhaling concentrated tetrahydrocannabinol (THC) products, also known as wax, shatter, or oil
- Pulmonary infiltrates on chest X-ray (CXR) or ground-glass opacities on computed tomography (CT) scan
- Absence of pulmonary infection (including negative respiratory viral panel and influenza testing)
- Negative respiratory infectious disease testing, as clinically indicated
- No evidence in the medical record to suggest an alternative diagnosis

The criteria for a probable EVALI case are similar, except that an infection may be identified but thought not to be the sole cause of lung injury, or the minimum criteria to rule out infection may not be met.

EPIDEMIOLOGY AND DEMOGRAPHICS

Although cases have been reported in all 50 states, the District of Columbia, and two US territories, geographic heterogeneity has been observed.³ Hospital admissions for EVALI reported to the CDC peaked in mid-September 2019 and declined through February 2020.^{3,8} Although the CDC is no longer reporting weekly numbers, cases continue to be reported in the literature, and current numbers are unclear.^{4,9,10} The decrease in cases since the peak is thought to be due to increased public awareness of the dangers associated with vaping (particularly with THC-containing products), law enforcement actions, and removal of vitamin E acetate from products.^{3,8}

Risk factors associated with EVALI include younger age, male sex, and use of THC products.^{5,6} The median age of hospitalized patients diagnosed with EVALI is 24 years, with patients ranging from 13 to 85 years old.³ Overall, 66% of all EVALI patients were male, 82% reported use of a THC-containing product, and 57% reported use of a nicotine-containing product. Approximately 14% of patients reported exclusive nicotine use.³

Nearly half (44%) of hospitalized EVALI patients reported to the CDC required intensive care.⁷ Of the 68 fatal cases reported to the CDC, the patients were older, with a median age of 51 years (range, 15-75 years), and had increased rates of preexisting conditions, including obesity, asthma, cardiac disease, chronic obstructive pulmonary disease, and mental health disorders.⁷

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FIG 1. E-cigarette Devices and E-cigarette Solutions. (A) Tank system, (B) vape pen (Njoy), (C) pod system (JUUL), (D) pod system (Suorin), (E) e-cigarette solution “Candy King,” (F) disposable mango-flavored e-cigarette (Mojo).

tory viruses and influenza, as well as SARS-CoV-2 testing.^{11,12}

IMAGING AND ADVANCED DIAGNOSTICS

CXR may show bilateral consolidative opacities.¹¹ If the CXR is normal but EVALI is suspected, a CT scan can be considered for diagnostic purposes. Ground-glass opacities are often present on CT imaging (Figure 2), occasionally with subpleural sparing, although this finding is also nonspecific. Less frequently, pneumomediastinum, pleural effusion, or pneumothorax may occur.^{6,11}

Finally, bronchoscopy may be used to exclude other diagnoses if less invasive measures are not conclusive; pulmonary lipid-laden macrophages are associated with EVALI but are nonspecific.⁵ Cytology and/or biopsy can be used to eliminate other diagnoses but cannot confirm a diagnosis of EVALI.⁵

HISTORICAL FEATURES

Patients with EVALI may initially present with a variety of respiratory, gastrointestinal, and constitutional symptoms (including fever, muscle aches, and fatigue).¹¹ For this reason, clinicians should universally ask about vaping or dabbing as part of an exposure history, taking care to ensure confidentiality, especially in the adolescent or youth population.¹² If the patient reports use, details, including the types of devices, how they were obtained and used, the ingredients in the e-cigarette solution (e-liquid), and the presence of additives or flavorings, should all be noted.^{3,5,9,12} This history may not be volunteered by the patient, which could result in a delay in diagnosing EVALI.^{9,12} Although the CDC uses vaping within 90 days in the criteria for diagnosis,³ the likelihood of EVALI decreases with increased time from last use; longer than 1 month is unlikely to be related.¹¹

PHYSICAL EXAM AND LABORATORY STUDIES

Physical assessment of a patient with EVALI may be notable for fever, tachypnea, hypoxemia, or tachycardia; rales may be present, but the exam is often otherwise unrevealing.^{5,11,12} Lab studies may show a mild leukocytosis with neutrophilic predominance and elevated inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein. Procalcitonin may be normal or mildly increased, and, rarely, impaired renal function, hyponatremia, and mild transaminitis may also be present.^{5,7} As EVALI remains a diagnosis of exclusion, an infectious workup must be completed, which should include evaluation of respira-

DIFFERENTIAL DIAGNOSIS

Hospitalists care for many patients with respiratory symptoms, particularly in the midst of the COVID-19 pandemic and influenza season. Common infectious etiologies that may present similarly include COVID-19, community-acquired pneumonia, influenza, and other viral respiratory illnesses. Hospitalists may rely on microbiologic testing to rule out these causes. If there is a history of vaping and dabbing and this testing is negative, EVALI must be considered more strongly. Recent case studies report that patients with EVALI have been presumed to have COVID-19, despite negative SARS-CoV-2 testing, resulting in delayed diagnosis.^{4,9} Two small case series suggest that leukocytosis, subpleural sparing on CT scan, vitamin E acetate or macrophages in bronchoalveolar lavage (BAL) fluid, and quick improvement with steroids may suggest a diagnosis of EVALI, as opposed to COVID-19.^{4,10}

Consultation with pulmonary, infectious disease, and toxicology specialists may be of benefit when the diagnosis remains unclear, and specific patient characteristics should guide additional evaluation. Less common diagnoses may need to be considered depending on specific patient factors. For example, patients in certain geographical areas may need testing for endemic fungi, adolescents with recurrent respiratory illnesses may benefit from evaluation for structural lung disease or immunodeficiencies, and patients with impaired immune function need evaluation for *Pneumocystis jirovecii* infection.⁵ Diagnostic and treatment algorithms have been developed by the CDC; Kalininskiy et al¹¹ have also proposed a clinical algorithm.^{12,13}

TREATMENT AND CLINICAL COURSE

Empiric treatment for typical infectious pathogens is often provided until evaluation is complete.^{11,12} Although no randomized clinical trials exist, the CDC and other treatment algorithms recommend supportive care and abstinence from vaping.¹¹⁻¹³ Although there are limited data regarding dose and duration, case reports have noted clinical improvement with corticosteroids.^{6,11-13} Use of steroids can be considered in consultation with a pulmonologist based on the clinical picture, including severity of illness, coexisting infections, and comorbidities.^{6,11-13} Overall, the clinical course for hospitalized patients with EVALI is variable, but the majority improve with supportive therapy.^{11,12}

Substance use and mental health screening should be performed during hospitalization, as appropriate social support and tobacco use treatment are essential components of care.¹³ The FDA and CDC recommend universal abstinence from all THC-containing products, particularly from informal sources. These agencies also recommend that all nonsmoking adults, including youth and women who are pregnant, abstain from the use of any e-cigarette products.³ Resources for patients who are tobacco users include the nationally available quit line, 1-800-QUIT-NOW, and Smokefree.gov. Similarly, follow-up with a primary care provider within 48 hours of discharge, as well as a visit with a pulmonologist within 4 weeks, is recommended by the CDC per the discharge readiness checklist, with the goal of improving management through earlier follow-up.¹³ Hospitalists should report confirmed or presumed cases to their local or state health department. Correct medical coding should also be used with diagnosis to better track and care for patients with EVALI; as of April 1, 2020, the World Health Organization established a new *International Classification of Diseases, 10th Revision* (ICD-10) code, U07.0, for vaping-related injury.¹⁴

FUTURE RESEARCH

As EVALI has only recently been described, further research on prevention, etiology, pathophysiology, treatment, and outcomes is needed. Although the precise pathophysiology of EVALI remains unknown, vitamin E acetate, a diluent used in some THC-containing e-cigarette solutions, was detected in the BAL of 48 of 51 patients with EVALI (94%) in one study.¹⁵ However, available evidence is not sufficient to rule out other toxins found in e-cigarette solution.³ Longitudinal studies should be done to follow patients with EVALI with an emphasis on sustained tobacco use treatment, as the long-term effects of e-cigarette use remain unknown. Furthermore, although corticosteroids are often used, there have been no clinical trials on their efficacy, dose, or duration. Finally, since the CDC is no longer reporting cases, continued epidemiologic studies are necessary.

CONCLUSIONS AND IMPLICATIONS FOR CLINICAL CARE

EVALI, first reported in August 2019, is associated with vaping and e-cigarette use and may present with respiratory, gastro-

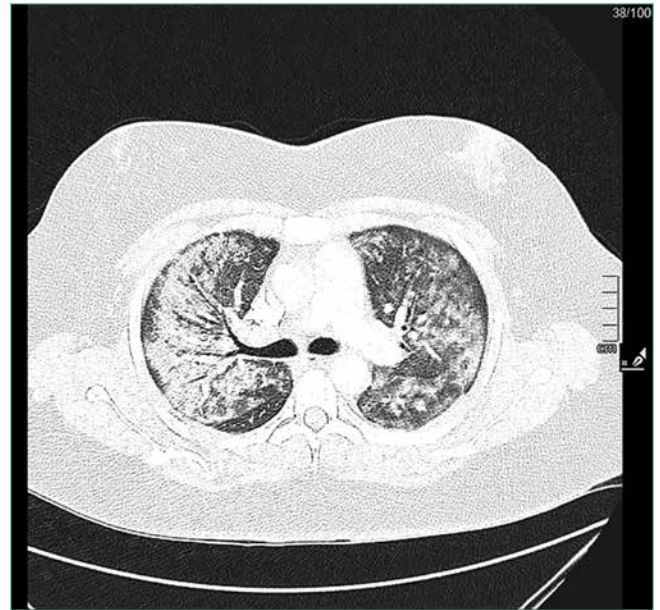


FIG 2. Computed Tomography Angiography With Contrast. These coronal images with lung windows show bilateral ground-glass opacities in a 17-year-old diagnosed with E-cigarette, or vaping, product use-associated lung injury.

intestinal, and constitutional symptoms similar to COVID-19. Healthcare teams should universally screen patients for tobacco, vaping, and e-cigarette use. The majority of patients with EVALI improve with supportive care and abstinence from vaping and e-cigarettes. Tobacco cessation treatment, which includes access to pharmacotherapy and counseling, is critical for patients with EVALI. Additional treatment may include steroids in consultation with subspecialists. The pathophysiology and long-term effects of EVALI remain unclear. Hospitalists should continue to report cases to their local or state health department and use the ICD-10 code for EVALI.

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