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E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI): A Significant Health Crisis in the Digital World

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Abstract

E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI) is a severe respiratory illness with acute or subacute presentation, often posing a diagnostic challenge due to its clinical overlap with other pulmonary conditions. First identified in the United States in mid-2019, it emerged as a significant public health concern, particularly among adolescents and young adults. Substances such as Vitamin E acetate and Tetrahydrocannabinol (THC) are strongly implicated in its pathogenesis. The continuously evolving landscape of vaping products, coupled with limited information regarding the long-term prognosis and outcomes of the condition, complicates efforts to mitigate associated health risks. This review provides an overview of the current understanding of EVALI, focusing on its epidemiology, clinical presentation, diagnostic challenges, and management strategies.

Keywords: E-cigarette or vaping product use-associated lung injury, e-cigarettes, vaping

Introduction

E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI) is a novel severe respiratory illness characterized by acute or subacute clinical presentation, simulating various pulmonary diseases, thereby complicating its diagnosis. EVALI can also be referred to as Vaping-Associated Pulmonary Injury (VAPI) or Vaping-Associated Lung Injury (VALI). Those who use electronic cigarettes (e-cigarettes) within the last 90 days are susceptible to developing EVALI. (1–3)

E-cigarettes are battery-operated devices that yield aerosol from a liquid solution. Generally, it comprises nicotine, flavoring chemicals, and other additives. Whenever an e-cigarette is utilized for inhalation, it is known as vaping. E-cigarettes are also known as e-cigs, e-cigars, electronic nicotine delivery systems (ENDS), electronic hookah (e-hookah), and so on. It was introduced as a substitute for traditional smoking, with the belief that it holds fewer detrimental effects. (4–7) Although the concept of e-cigarettes dates back to the mid-20th century, the modern form was invented by a Chinese pharmacist, Hon Lik, in the early 2000s. Similarly, as their popularity has surged, e-cigarettes have been evolving, and their various forms are shown in **Figure 1**. Despite heterogeneity, the device's working principle remains consistent, with its fundamental elements: a liquid reservoir, a power source, a heating element, and a mouthpiece. (5–10)

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Epidemiology

With recent advancements in e-cigarettes, the history and epidemiological background of EVALI remains unclear. The first case was reported to the US Centers for Disease Control and Prevention (CDC) in August 2019. A subsequent EVALI outbreak peaked in September 2019. It was challenging for the clinicians to accurately diagnose EVALI during the COVID-19 era. Almost 215 possible cases were reported to the CDC in August 2019 from 25 different states. (1,12) Approximately 2800 hospitalized EVALI cases, along with 68 deaths, were reported to the CDC from fifty different states and three US territories by the end of February 2020. A higher prevalence was found among young non-Hispanic white males (11–13 years old). Subsequently, an increase in public awareness regarding the risk of EVALI with vaping products, removal of suspected constituents, i.e., Vitamin E acetate, from e-cigarettes, and strict law enforcement against illegal access to vaping products aided in minimizing the cases of EVALI. (12) Consequently, with the decline in EVALI cases, proactive data collection is missing, leading to a misinterpretation of existing threats. Besides having a potential threat of EVALI, appropriate documentation regarding e-cigarette use and the prevalence of EVALI in most countries remains shrouded. Only about half of the countries in the world monitor the use of e-cigarettes, with their prevalence ranging from 3.5% to 23%. Thus, estimating the prevalence of use of vaping products and their consequences is challenging globally. (14)

Etiology

The etiology of EVALI remains unclear. However, the chemical constituents such as nicotine, flavoring agents, and additives, as shown in **Table 1**, present in vaping products are considered to correlate with the condition. Nearly 94% of cases were found to have vitamin E acetate (VEA) in samples collected from bronchoalveolar lavage fluids. Tetrahydrocannabinol (THC) vaping was considered the leading suspect of EVALI due to its association with most of the reported cases. Besides, nicotine and cannabidiol (CBD) products are also responsible for developing EVALI, as shown in **Table 1**. The prevalence of use of e-cigars was higher among young non-Hispanic white males, often receiving the products from an unofficial source. Likewise, the risk escalates with the use of higher doses and frequency of vaping products. (1,15–21)

Pathophysiology

Being a novel disease, the exact pathogenesis of EVALI remains unfamiliar. However, single or multiple chemical constituents within the e-cigarettes are believed to cause EVALI. The ultrafine particles in e-cigarettes can reach the bloodstream via the lung tissue. EVALI, being a component of acute lung injury, results in damage to alveolar epithelial cells and pulmonary vascular endothelial cells. The definitive mechanism of lung injury in EVALI has yet to be established. Nonetheless, two hypotheses have been proposed to define the underlying mechanism: a) Direct cytotoxicity and b) Two-hit hypothesis.

Any chemical components inhaled during vaping can have direct cytotoxic effects on lung cells, contributing to neutrophilic inflammation and cellular necrosis. Likewise, the two-hit hypothesis can be explained as a two-stage process. Based on this theory, lung injury results from a combination of factors rather than a single event. The first hit, i.e., initial exposure to vaping products, can contribute to lung irritation and a mild immune response. The patient remains asymptomatic, but it can sensitize the lungs. The second hit then follows with re-exposure to vaping products with the same or other irritants and triggers an exaggerated immune response. This amplified inflammatory response can lead to severe lung damage and symptoms characteristic of EVALI. The two-hit hypothesis thus suggests that lung injury could result from the cumulative effects of repeated exposure and individual susceptibility. Moreover, various physiological functions, such as mucociliary clearance, phagocytosis, and surfactant function, are also altered. (17,24–28) The schematic representation of pathophysiology is shown in **Figure 2**.

Vitamin E acetate has been identified as a primary culprit for EVALI so far. It is used as an additive or thickening agent in conjunction with e-liquids. It leads to impairment in pulmonary function by interacting with phospholipids and the surfactants. Furthermore, it tends to yield noxious ketene gas, which may further worsen the respiratory function. (17,29–31)

Clinical Features

The varying clinical features of EVALI may include respiratory symptoms (cough, dyspnea, chest pain) and gastrointestinal symptoms (nausea, vomiting,

abdominal pain, diarrhea), as well as constitutional symptoms (fever, fatigue, weight loss). Patients often get symptomatic within 90 days (mostly ≤ 7 days) of exposure to the vaping products. The majority of cases present with dyspnea, followed by cough. Likewise, fever and nausea are more frequent constitutional and gastrointestinal features. Auscultatory findings can be normal or may include diffuse bibasilar crackles, end-inspiratory squeaks, or wheezes. However, diagnosis may be challenging due to its non-specific clinical features, which can mimic other pulmonary conditions, such as pneumonia, pleural effusion, pneumothorax, and others. (16,28,32–36)

Diagnosis

Since EVALI resembles other respiratory disorders clinically, it often creates a diagnostic dilemma. Furthermore, the lack of specific diagnostic tools complicates the physician's ability to make a definitive diagnosis. However, a diagnostic criterion developed by the Centers for Disease Control and Prevention (CDC) has proven to be supportive. This is shown in **Table 2**. (1,37,38) Generally, diagnostic evaluation of EVALI encompasses laboratory testing and imaging. Additionally, consideration could be given to chemical profiling and histopathological evaluation following bronchoscopy. (34,38,39)

Laboratory Investigations

The detailed history and clinical examination will guide the initial essential workup, which includes a complete blood count, metabolic panel, respiratory infectious panel, urine analysis, and blood cultures. Furthermore, sputum gram staining & culture, urine toxicology, and urine for Legionella and Pneumococcus antigen can be examined. However, the findings are nonspecific; most show leukocytosis with a predominance of neutrophils. Additionally, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and procalcitonin), as well as liver enzymes, can also be elevated. Electrolyte derangement, along with impairment in renal function, may be noted. (16,28,34,40)

Radiological Imaging

Radiological imaging (chest X-ray, computed tomography scan) is crucial for the diagnosis of EVALI. Generally, chest radiography shows nonspecific bilateral opacities with consolidation sparing the subpleural area. Likewise, features suggestive of pleural effusion, pneumothorax, and pneumomediastinum may be noted. However, a chest CT scan can be performed in severe cases when there are no significant X-ray findings. The CT chest could demonstrate ground-glass opacities despite a nonspecific X-ray finding. It is superior to a chest X-ray because it is more sensitive at ruling out other pulmonary diseases, including complications of EVALI such as infection, malignancy, pneumothorax, and pneumomediastinum. Additionally, a CT scan can be used to select the optimal sampling site during bronchoscopy. (16,28,34,40–44)

Bronchoscopy

Bronchoscopy is a minimally invasive diagnostic procedure used to obtain bronchoalveolar lavage (BAL) and transbronchial biopsy specimens. Cytological studies demonstrate lipid-laden or foamy macrophages with oil red O positivity. Histochemical stains can be negative for infections. Likewise, biopsy specimens show organizing pneumonia, diffuse alveolar damage, and other patterns suggestive of acute lung injury. Thus, due to nonspecific findings, bronchoscopy is not routinely recommended. However, it can be beneficial in a critically ill patient or to rule out an alternative diagnosis. (21,38,40,45–50)

Additionally, pulmonary function tests and lung biopsy can be performed. Both restrictive and obstructive patterns can be identified in spirometry, accompanied by a reduction in the diffusing capacity of the lung for carbon monoxide (DLCO). Lung biopsy is usually not performed but can be considered if unusual patterns are seen on imaging or if the diagnosis via bronchoscopy remains uncertain. (50,51)

Management

EVALI, being an emerging issue in the medical field, continues to spark questions. The definitive treatment is yet to be explored. However, its treatment revolves around symptomatic management and empirical therapy, with corticosteroids being the cornerstone. A simplified flow chart for its management is shown in **Figure 3**.

Firstly, patients should be encouraged to discontinue vaping or dabbing. The further management contrasts somewhat, based on whether the patient is hospitalized or treated on an outpatient basis. Generally, patients with EVALI are admitted if they present with respiratory distress, hypoxemia (oxygen saturation <95%), severe lung injury, and comorbid conditions (as shown in **Table 3**). A suspected patient with a stable condition and less intense lung

injury who can ensure scheduled follow-up is considered for outpatient management. Outpatient management of EVALI encompasses symptomatic treatment and the empiric use of antimicrobials or antivirals, if deemed desirable. Additionally, follow-up should be considered, as most patients undergo rapid deterioration within 48 hours. (37,40,53)

Hospitalized EVALI cases are often admitted to the intensive care unit, requiring oxygen supplementation, non-invasive ventilation, mechanical ventilation, or even extracorporeal membrane oxygenation (ECMO). In the presence of insufficient ventilation, the use of neuromuscular blockade and prone positioning may be encouraged. Furthermore, admitted patients are treated aggressively with empirical therapy, which comprises antimicrobials, antivirals, and corticosteroids. Antimicrobials, preferably cephalosporins and macrolides, are considered. (28,33,37,54–56) As most cases have shown improvement following the use of corticosteroids due to their anti-inflammatory property, it remains critical in managing severe cases. However, their dose and duration may vary depending on individuals. During admission, IV methylprednisolone 0.5-2 mg/kg/day is administered for 1 week, followed by oral prednisolone at a tapering dose for a variable duration. Furthermore, the addition of pirfenidone therapy was beneficial due to its antifibrotic and anti-inflammatory effects, and it has been associated with improved symptoms and pulmonary function. Corticosteroids are considered a two-edged sword as they have the potential to increase the risk of infections, and they need to be withheld in case of suspected fungal pneumonia. Similarly, ipratropium, salbutamol, or albuterol inhalations can be helpful in patients with severe bronchospasm. Besides, the routine use of influenza and pneumococcal vaccines needs to be emphasized. (28,37,40,44,51,53,56–58)

EVALI treatment would be incomplete without proper follow-up. According to the CDC, follow-up is recommended 1-2 weeks after discharge, with consideration of pulse oximetry and a chest X-ray. Subsequent follow-up is advised after 1-2 months, during which the patient is evaluated based on spirometry, chest X-ray, and diffusion capacity testing. (37)

Prognosis

Despite having fatalities, the prognosis seems to be good even in severe cases. However, the long-term effects of EVALI have yet to be determined. Thus, long-term follow-up studies should be performed. (37,53,59)

Conclusion

EVALI is a potentially fatal respiratory condition that has emerged in recent years, with a higher impact among young males. Its growing significance as a public health concern demands a comprehensive epidemiological surveillance system. As vaping products continue to evolve and diversify, a coordinated multidisciplinary approach, involving clinicians, public health officials, and policymakers, is warranted to mitigate the risks and promote safer practices. The long-term health outcomes and overall prognosis of EVALI remain uncertain, highlighting the necessity for continued research and vigilance.

Table 1. Toxic constituents of vaping products (22,23)

Solvents: Vitamin E acetate (VEA), propylene glycol, glycerin
Heavy metals: Nickel, lead, zinc
Flavoring agents: Vanilla, cinnamon, menthol
Others: Volatile organic compounds (VOC), formaldehyde, acrolein, vegetable oils

Table 2. Case definition given by the CDC for severe pulmonary disease associated with the use of e-cigarettes (1,37)

Criteria	**Confirmed case**	**Probable case**
Use of e-cigarettes (vaping) or dabbing	Within 90 days before the onset of symptoms	
Imaging	Pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest computed tomography	
Infectious workup	Absence of pulmonary infection on initial work-up with minimum criteria: a) A negative respiratory viral panel b) A negative influenza PCR or rapid test c) All other clinically indicated respiratory infectious disease testing (e.g., urine antigen for Streptococcus pneumoniae and Legionella, sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, HIV related opportunistic respiratory infections if appropriate)	Infection identified via culture or polymerase chain reaction (PCR), but the 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)
Alternative diagnosis	No evidence of alternative diagnosis (e.g., cardiac, rheumatologic, or neoplastic process)	

Table 3. Factors exacerbating the severity of EVALI (37,54)

Age (>50 years)
Pregnancy
Diabetes
Cardiac disease
Pulmonary disease

Figure 1. Schematic representation showing (A) different generations of e-cigarettes along with (B) their fundamental elements (5,8,11)

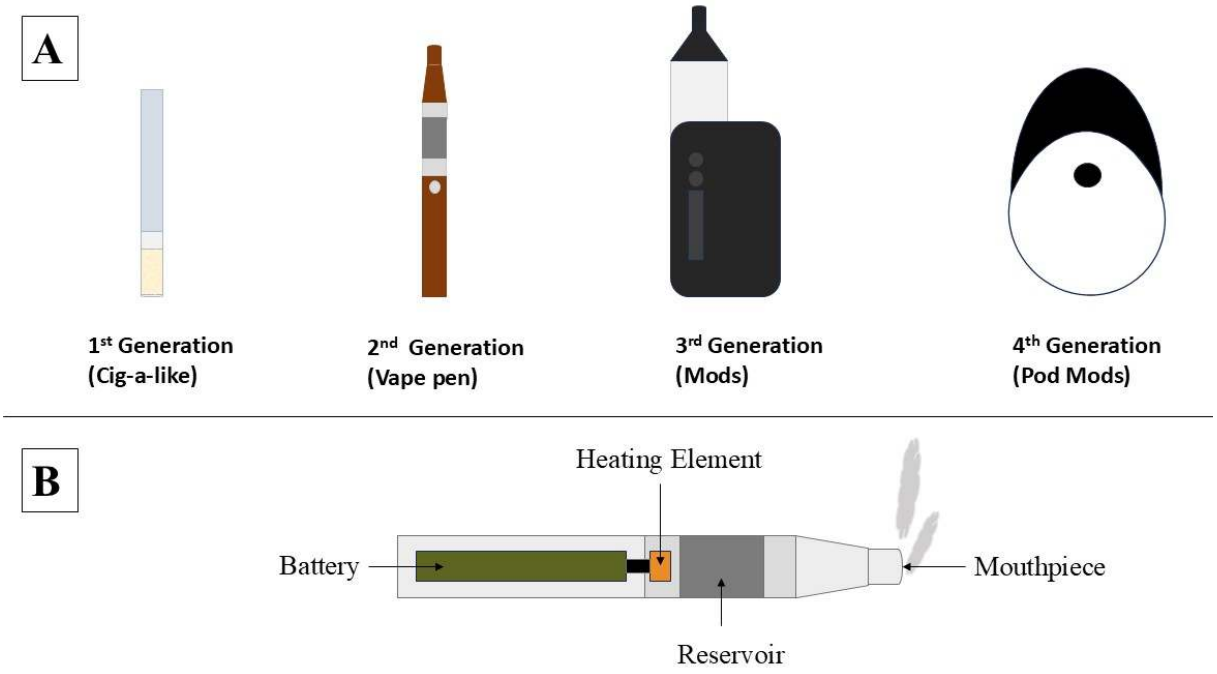
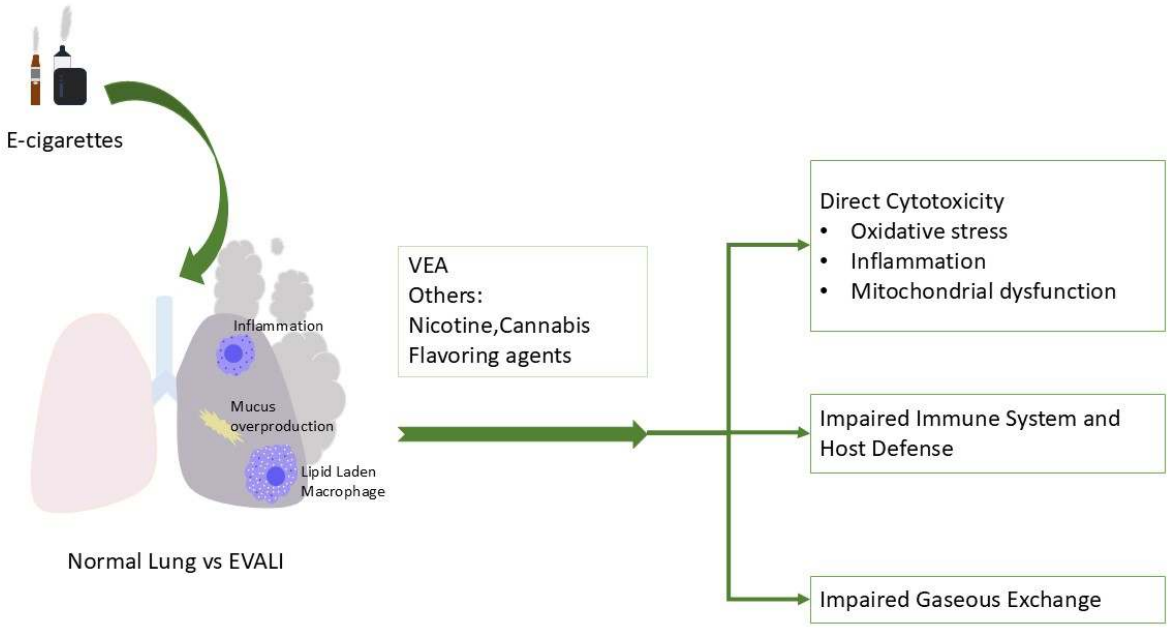
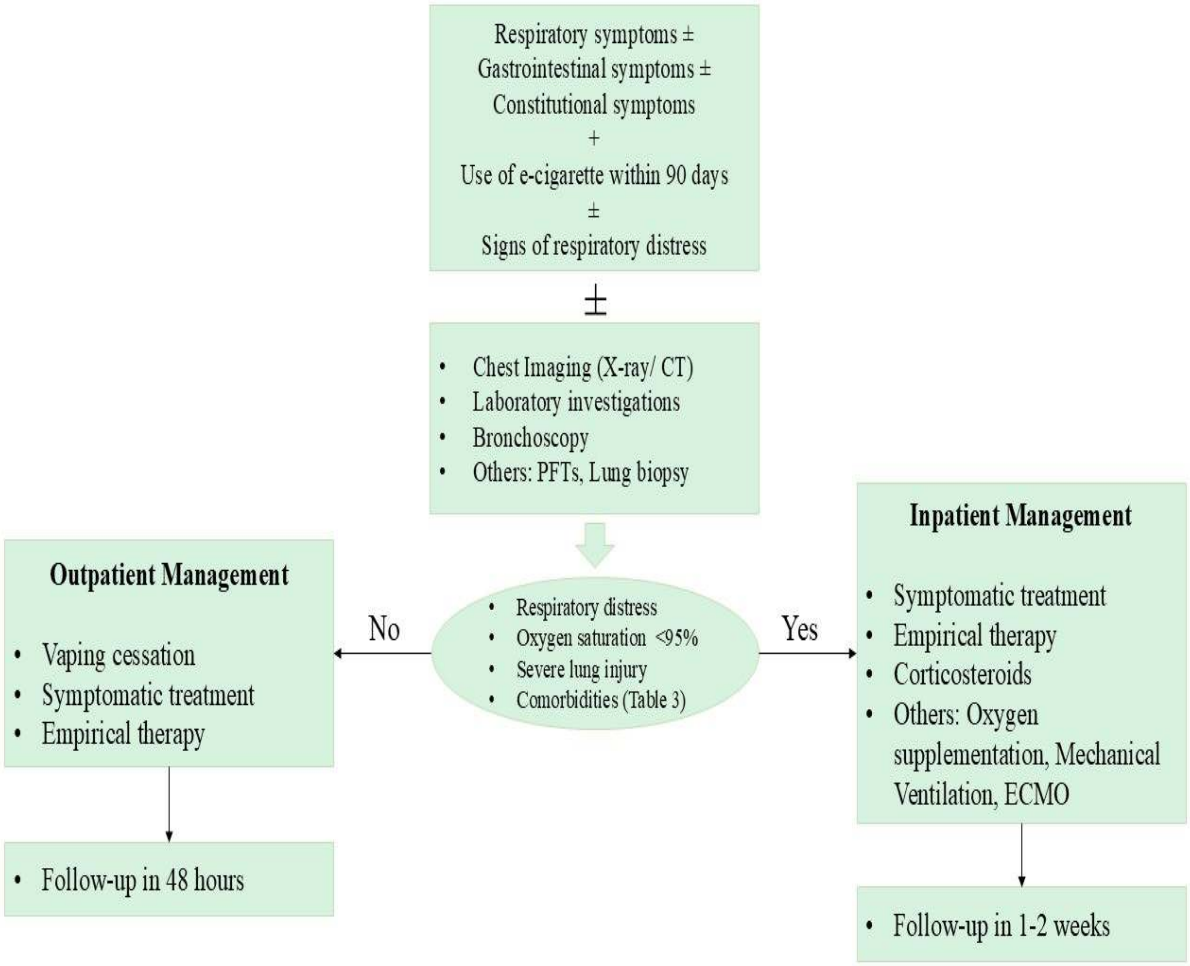


Figure 2. Schematic representation showing the pathophysiology of EVALI (24,25,29)



Legend: E-cigarettes=electronic cigarettes; EVALI=E-cigarette or Vaping Product Use-Associated Lung Injury; VEA=vitamin E acetate.

Figure 3. Flowchart showing approach to EVALI, including therapeutic guidance (37,39,52)



Legend: CT=computed tomography; ECMO=extracorporeal membrane oxygenation; PFT=pulmonary function test.

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