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E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI) and Other Known Consequences of E-Cigarette Use – A Literature Review

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ABSTRACT

Introduction and Purpose: E-cigarettes, introduced to the market at the beginning of the 21st century, have become a popular alternative to traditional cigarettes, though their long-term health effects remain unknown. In 2019, the United States recorded a sudden surge in cases of e-cigarette or vaping product use-associated lung injury (EVALI) - a severe lung disease linked to the use of these products. The aim of the study is to review the current knowledge on E-cigarette or vaping product use-associated lung injury (EVALI), with particular emphasis on pathogenesis, clinical presentation, and diagnostic and therapeutic challenges.

State of knowledge: EVALI is primarily associated with the inhalation of vitamin E acetate (VEA), used as a thickener in illegal THC liquids. Pathogenetic mechanisms include toxicity from thermal degradation products of VEA leading to destabilization of pulmonary surfactant. The disease manifests with a broad spectrum of symptoms: dyspnea (85–100%), cough (60–85%), fever (57–84%), and gastrointestinal complaints (nausea, vomiting). Diagnosis requires the exclusion of infections (including COVID-19) and is based on CDC criteria, encompassing changes in lung imaging studies and a history indicating e-cigarette use.

Conclusions: EVALI remains a public health challenge, particularly among young adults. Despite progress in identifying VEA as a key risk factor, many questions remain unanswered – including the role of other liquid components (e.g., flavoring substances) and the long-term effects of the disease. Further research is needed on the standardization of treatment (including the use of glucocorticosteroids) and regulation of the e-cigarette market. EVALI prevention should focus on educating about the risks of using products from illegal sources and promoting complete cessation of vaping.

Keywords: EVALI; e-cigarette or vaping-associated lung injury; vaping; e-cigarette; vitamin E acetate; VEA

INTRODUCTION

E-cigarettes typically resemble traditional cigarettes in appearance and are the most popular devices for delivering nicotine electronically, but vape pens do not externally resemble traditional cigarettes [1]. They were invented in the early 2000s by a Chinese pharmacist and have since gained increasing popularity, as evidenced by statistics [2][3]. They are a relatively new "invention" considering the history of smoking, and their youth-targeted marketing, combined with claims of being a "better substitute" for traditional cigarettes and an aid for smoking cessation, has proven highly effective [4]. New forms of smoking or nicotine use come with new health risks. Many of these risks are not yet well understood or documented, partly due to the time required after exposure to harmful factors to observe effects. E-cigarettes contain a liquid that, in addition to nicotine, includes a solvent (propylene glycol or vegetable glycerin) and flavoring agents [1].

One of the better-understood, though still incompletely systematized, consequences of e-cigarette use is EVALI - e-cigarette or vaping-associated lung injury. This broad term describes lung diseases linked to the electronic delivery of nicotine, which can result in hospitalization or even death. In 2019, the U.S. saw a significant rise in cases of this condition [5]. Since then, numerous case reports and studies have emerged to investigate its exact cause, pathogenesis, clinical presentation, disease course, prognosis, diagnostic and treatment approaches, and risk factors [6].

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Epidemiology

The disease was registered mainly in the USA. [5] The registry maintained by the Centers for Disease Control and Prevention (CDC) in the USA by February 2020 reported over 2800 cases from all 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and U.S. Virgin Islands). Additionally, 68 deaths were recorded. The majority of cases concern young people (average age 19–35 years). After the peak of cases in September 2019, the number of cases by 2020 continued to decline. Since then, data on nonhospitalized cases is collected by state, tribal, local, and territorial (STLT) health departments. For example, according to the California Department of Public Health (CDPH), 250 cases were registered by January 1, 2024, of which 5 deaths were recorded. The CDC justifies the decision to stop collecting data on the number of nonhospitalized EVALI patients with a significant decline in the number of cases after the peak in 2020. This may be linked to identifying the cause of EVALI and more precise control of the composition of liquids [7].

Etiology and Pathogenesis

Vitamin E Acetate

The etiology of EVALI remains unconfirmed to this day. Vitamin E acetate (VEA) present in non-compliant liquids plays a significant role. As demonstrated by the study of Blount et al. (2020), this compound was detected in 94% of cases in patients with EVALI who underwent bronchoalveolar lavage fluid (BALF) analysis (48 out of 51 tested), while it was absent in healthy individuals [8]. However, its role remains inconclusive [8][9]. The presence of VEA is likely linked to the misuse of e-cigarettes - specifically, the use of liquids from illegal sources, primarily those containing (tetrahydrocannabinol) THC, where VEA served as a thickening agent [10]. Approximately 80% of patients confirm THC use [11]. Furthermore, the significant decline in EVALI cases after informing users about the prohibition of THC administration via vaping products appears to support VEA's role [7].

Vitamin E, encompassing a group of fat-soluble antioxidant compounds, primarily exists as tocopherols and tocotrienols. Among these, only α-tocopherol is biologically active in humans due to a specific transport protein (α-TTP) [12][13].

Theories on VEA's Role in EVALI Pathogenesis

VEA was used as a solvent in THC preparations from illegal sources. When heated in e-cigarettes, VEA undergoes thermal degradation, and its strong lipophilic properties destabilize pulmonary surfactant, leading to the accumulation of macrophages incapable of metabolizing this substance. This results in impaired alveolar function and the development of lipoid pneumonia [14][15][16].

Despite the strong correlation between VEA and EVALI, there is no conclusive evidence that lipoid pneumonia is the sole pathogenic mechanism. Larsen et al. [17] question the direct toxicity of VEA, suggesting that lipid-laden macrophages in BALF may reflect exposure to e-cigarette substances rather than direct toxicity. EVALI encompasses various forms of lung injury, including acute eosinophilic pneumonia and organizing pneumonia [18][19].

The leading hypothesis in EVALI pathogenesis remains the toxicity of VEA degradation products - when exposed to high temperatures, VEA may convert into reactive ketenes that damage the lung epithelium [20].

Other Substances

Other substances suspected in EVALI pathogenesis include flavoring agents used in e-cigarettes. Despite their GRAS (Generally Recognized As Safe) status for oral use, inhalation may pose risks. Heating liquids generates toxic thermal degradation products (e.g., propylene glycol adducts) and interactions between components. Certain flavorings, such as diacetyl (linked to "*Popcorn Worker's Lung*," a form of bronchiolitis obliterans) and pulegone (a genotoxic component in mint-flavored liquids), exhibit documented respiratory toxicity. Additionally, natural extracts (e.g., tobacco-derived) have unpredictable compositions, complicating safety assessments.

Currently, there is insufficient evidence to confirm the role of specific substances in EVALI mechanisms due to limited studies on their genotoxicity, inhalational toxicity, and allergenic effects. Urgent implementation of interdisciplinary regulations and standardization of liquid composition are critical to minimizing potential risks [21][22][23][24].

Clinical Picture

The clinical picture is varied and nonspecific, and differentiation requires excluding infections, as the clinical presentation (signs and symptoms) alone is not sufficiently characteristic. It is characterized by a broad spectrum of respiratory, systemic, and gastrointestinal symptoms.

Symptoms

Among the reported symptoms, those involving the respiratory system are most dominant (frequency of occurrence 95% - based on the interview of 339 EVALI patients):

- **Shortness of breath – reported most frequently, frequency of occurrence 85–100% [3].**

Additionally, patients report:

- **Cough – frequency of occurrence 60–85% [3],**
- **Chest pain – frequency of occurrence 30–52% [3],**
- **Hemoptysis – frequency of occurrence approximately 8% [25].**

Systemic symptoms are also reported (frequency of occurrence 85% - based on the interview of 339 EVALI patients):

- **Fever – frequency of occurrence 57–84% [3],**
- **Weight loss – frequency of occurrence 12–26% [3],**
- **Fatigue – frequency of occurrence 34–48% [3],**
- **Muscle pain – frequency of occurrence 17–42% [25].**

The disease is often accompanied by gastrointestinal symptoms (frequency of occurrence 77% - based on the interview of 339 EVALI patients):

- **Nausea – frequency of occurrence 57–75% [3],**
- **Vomiting – frequency of occurrence 33–72% [3],**
- **Abdominal pain – frequency of occurrence approximately 66% [25],**
- **Diarrhea – frequency of occurrence 14–44% [3].**

Other reported symptoms:

- **Headaches – frequency of occurrence approximately 30% [26].**

Signs

In most patients, tachycardia (in 55% of cases) and tachypnea (in 45% of cases) [26] are observed, along with signs of respiratory failure with oxygen saturation <95% in patients not receiving passive oxygen therapy (in 57% of cases) [25].

There are no characteristic changes (crackles or wheezing are observed) during auscultation of patients suffering from EVALI [27].

Atypical clinical presentations include neurological symptoms (headaches), hypoxemia without a sensation of shortness of breath, and a disease course manifesting as acute respiratory failure requiring ECMO in the patient [28].

Differentiating factors for EVALI compared to other respiratory diseases include the frequent co-occurrence of gastrointestinal symptoms (requiring differentiation from, among others, COVID-19) and the use of e-cigarettes or vaping products - a key element of the medical history, characteristic of EVALI (one of the diagnostic criteria).

Natural Course and Prognosis

The vast majority of EVALI patients require hospitalization - approximately 95%, with one-third of them receiving non-invasive mechanical ventilation. Another one-third of hospitalized patients required intubation [25].

Mortality among confirmed EVALI cases in the United States is estimated at approximately 2.5% [5].

Diagnosis – Diagnostic Criteria, Additional Tests

Diagnostic Criteria

The disease definition and criteria do not have a unified version. According to the CDC, which is the most frequently cited source, a confirmed case can be diagnosed when the following criteria are met:

1) **Infiltrative changes in the lungs on chest radiograph (X-ray) or computed tomography (CT).**
2) **Use of e-cigarettes (vaping) within <90 days before symptom onset.**
3) **No clinical evidence indicating another cause of the lung changes (e.g., cancer, heart failure, rheumatic diseases, etc.).**
4) **Infection has been excluded (negative test results for influenza and other respiratory viruses, negative results from all microbiological tests, including cultures and immunological assays).**

A probable diagnosis can be made if criteria 1–3 are met, even if an infection is confirmed, but the overall clinical picture does not suggest it is the sole cause of the illness.

The American Lung Association (ALA**)** has also established its diagnostic criteria, defined as the onset of pulmonary infiltrates on chest X-ray or CT occurring within 90 days of e-cigarette use, with no alternative cause identified after medical evaluation. However, it should be noted that most patients (>90%) used e-cigarettes within <7 days before the onset of subjective symptoms [5].

It is also proposed to expand the criteria [29] to include a broader differential diagnosis depending on the clinical presentation. Examples include fungal infections, HIV, rheumatologic diseases, cardiac conditions, or oncologic diseases.

Imaging Studies

As mentioned above, imaging is necessary for a definitive diagnosis of the disease according to the CDC and ALA. In most patients with an X-ray, ground glass opacities (GGO) are visible, and in patients who undergo high resolution computed tomography (HRCT), GGO are present in every examined individual. The distribution of changes is varied. Sometimes, characteristic radiological patterns present in patient studies can be distinguished (Table 1).

Main radiological patterns on chest CT according to Kligerman et al. (2020):

1. Organizing pneumonia (OP) – the most common pattern, observed in 76% of histopathological studies:
   - **Bilateral ground glass opacities (GGO) with dominance in the lower lobes.**
   - **Characteristic *subpleural sparing* and *peribronchovascular sparing*.**
   - **Thickening of interlobular septa, forming a "*crazy paving*" pattern.**
   - **On chest X-ray: diffuse opacities with sparing of the heart borders and peripheral lung regions.**

2. Diffuse alveolar damage (DAD) – occurs in 24% of patients, mainly in severe cases:
    - **Consolidations and GGO predominantly in the lower lobes, often with accompanying septal thickening.**
    - **In the organizing phase: fibrotic changes, bronchiectasis.**

3. Acute eosinophilic pneumonia (AEP) – a rare pattern, with several cases described in the literature:
    - **Diffuse GGO with pleural effusion and septal thickening (resembling pulmonary edema but without left ventricular dysfunction).**

4. Diffuse alveolar hemorrhage – reported in isolated cases:
    - **Asymmetric consolidations and/or nodules on CT.**

Other rare changes:

- **Pneumothorax, mediastinal emphysema, pleural effusion.**
- **Centrilobular nodules, resembling changes seen in drug-induced lung disease or hypersensitivity pneumonitis (HP).**

In most EVALI cases, OP and DAD patterns are present (combined >80%), and radiological changes often overlap (e.g., OP with a DAD component in severe cases) [30].

Radiological pattern	Frequency of occurrence
Organizing pneumonia	76%
Diffuse alveolar damage	24%
Acute eosinophilic pneumonia	<1%
Diffuse alveolar hemorrhage	<1%

Table 1. Types and frequency of radiographic patterns in EVALI [30].

Laboratory Tests Typically, leukocytosis with neutrophilia is observed. Elevated inflammatory markers have also been noted: C-reactive protein (CRP) >30 mg/L in 90% of cases; erythrocyte sedimentation rate (ESR) >60 mm/h, and procalcitonin [25].

Bronchoscopy

Neutrophils in bronchoalveolar lavage (BAL) – dominate in bronchoalveolar lavage fluid in patients with EVALI (median 65%), as confirmed in cohort studies [25]. Eosinophils in BAL – rare cases with eosinophil predominance (up to 40% in BAL), reported in individual case studies [31]. Foamy macrophages – present in >80% of patients with EVALI, indicative of toxic lung injury [32]. Lipid macrophages (Oil Red O staining) – common but nonspecific; absence of fat on computed tomography (CT) rules out lipoid pneumonia [33]. Microbiology (BAL fluid cultures) – negative results are a requirement for diagnosing EVALI [34].

Histopathology

Main patterns of injury in histopathological examinations:

1. Organizing pneumonia (OP):
    - **Presence of fibrin plugs in the lumens of bronchioles and alveoli.**
    - **Focal inflammatory infiltrates of mononuclear cells.**
2. Diffuse alveolar damage (DAD):
    - **Acute phase: Edema, hyaline membranes within alveoli.**
    - **Organizing phase: Fibroblast proliferation and fibrosis.**
3. Acute fibrinous pneumonia (AFOP):
    - **Clumps of fibrin in alveolar lumens.**

Other histological features:

- **Macrophages with abundant cytoplasm (vacuolated, "*foamy*") – positive on Oil-Red-O staining, but nonspecific for EVALI.**
- **Bronchiolitis with mucosal ulceration.**
- **Absence of classic features of exogenous lipid pneumonia (ELP) – no lipid deposits in the tissue.**

In the histological examination of lung biopsies, no features specific to EVALI were identified; the most common finding was organizing pneumonia [30].

Other tests

Diagnosis of EVALI requires exclusion of viral (e.g., influenza, SARS-CoV-2, RSV), bacterial, and fungal infections. According to CDC guidelines, the following are necessary:

- **Molecular tests for viruses (e.g., PCR for influenza, SARS-CoV-2).**
- **Cultures of BAL fluid and blood for atypical bacteria (e.g., *Legionella*, *Mycoplasma*) and fungi.**
- **Serological testing in selected cases (e.g., HIV) [34].**

Due to the strong association of EVALI with the use of THC-containing products, urine testing for its metabolites (e.g., 11-nor-9-carboxy-THC) is recommended. In one study, 86% of EVALI patients admitted to vaping THC [25].

Differential Diagnosis

In differential diagnosis, it is necessary to first exclude respiratory infections: COVID-19, influenza, pneumonia. PCR tests for SARS-CoV-2, BAL cultures, and blood cultures (atypical bacteria, fungi) are required [34].

Additionally, other rarer diseases should be considered, such as:

- **Acute eosinophilic pneumonia (AEP) – eosinophilia in BAL (>25%) is present, but no infection is found [31].**
- **Hypersensitivity pneumonitis (HP) – CT imaging may resemble HP, but there is no histopathological confirmation [35].**
- **Lipid pneumonia (ELP) – lipid-laden macrophages in BAL do not confirm ELP in EVALI, as typical fat features are absent on CT [33].**
- **Organizing pneumonia – OP is the dominant histopathological pattern in EVALI, requiring differentiation from idiopathic organizing pneumonia [30].**

Treatment

Currently, no causal treatment for EVALI is known. Management is based on symptomatic and supportive therapy due to the lack of randomized clinical trials defining optimal protocols. The main components of management include: oxygen therapy, antibiotic therapy, glucocorticosteroids, cessation of e-cigarette use, as well as post-treatment monitoring and follow-up.

Oxygen therapy: Passive oxygen therapy, high-flow nasal oxygen therapy, non-invasive and invasive ventilation support.

Antibiotic therapy: Antibiotics are typically administered empirically (spectrum as for severe community-acquired pneumonia) due to the similarity of symptoms to bacterial or viral pneumonia.

Glucocorticosteroids: Used in 67–90% of patients, though the dosing regimen and duration of therapy varied.

Cessation of e-cigarette use: A key element of treatment. The CDC recommends offering smoking cessation support in both hospital and outpatient settings, with particular attention to nicotine or THC dependence.

Post-treatment monitoring and follow-up: A follow-up within 48 hours of discharge is recommended due to the risk of relapse. Long-term observation includes assessment of lung function (e.g., spirometry) and imaging (X-ray/CT), which typically show improvement after discontinuing vaping.

Prospective studies are necessary to develop unified algorithms [36].

Prevention and recommendations

The best way to prevent EVALI is complete cessation of e-cigarettes and vaping, as cases of disease recurrence have been reported with continued e-cigarette use [37].

The CDC and the Food and Drug Administration (FDA) strongly advise against the use of e-cigarettes or vaping products, particularly those obtained from unverified sources, because they may be contaminated. Special attention should be given to products containing THC (risk of VEA presence).

The addition of vitamin E acetate to any vaping products is strictly prohibited. Furthermore, modifying product contents by introducing substances not specified by the manufacturer is unacceptable.

Adults Replacing Traditional Cigarettes - individuals using nicotine-containing e-cigarettes as an alternative to tobacco smoking are advised against resuming cigarette use. For those opting for e-cigarettes as a transitional measure, complete replacement of tobacco products is necessary. In cases of difficulty discontinuing tobacco or e-cigarette use, or if symptoms suggestive of EVALI (e-cigarette or vaping product use-associated lung injury) arise, immediate consultation with a healthcare provider is required.

Groups Subject to Strict Restrictions:
The use of vaping products (both nicotine- and THC-containing) is strictly contraindicated for: adolescents and individuals in early adulthood, pregnant women, individuals who have not previously used tobacco products.

SUMMARY
E-cigarette or vaping product use-associated lung injury (EVALI) is a severe lung disease that in recent years has become a significant public health issue, particularly among young adults. Although its etiology has not been fully explained, epidemiological and laboratory data point to the key role of vitamin E acetate (VEA) - a substance used as a thickener in illegal THC-containing liquids. The pathogenic mechanisms of EVALI are complex and include direct toxicity of VEA degradation products leading to destabilization of pulmonary surfactant.
The clinical presentation of EVALI is non-specific, which complicates rapid diagnosis. Respiratory symptoms (dyspnea, cough) and systemic symptoms (fever, weight loss) dominate, often coexisting with gastrointestinal complaints. Diagnosis requires ruling out infections (e.g., COVID-19, influenza) and other lung diseases, such as organizing pneumonia or eosinophilic pneumonia. A history of e-cigarette use, particularly THC-containing products, is critical.
Treatment of EVALI is symptomatic and includes oxygen therapy, empirical antibiotic therapy, and glucocorticoid use, though there is a lack of randomized studies confirming their efficacy. An absolute condition for improvement is discontinuation of e-cigarette use. The long-term prognosis remains uncertain - some patients exhibit permanent lung function impairment, underscoring the need for further research into the health consequences of vaping.
Prevention of EVALI should focus on educating youth and adults about the risks of using illegal products, tightening legal regulations on liquid composition (e.g., banning VEA), and promoting support programs for individuals addicted to nicotine or THC.

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