LITERATURE REVIEW

E-Cigarette or Vaping Use-Associated Lung Injury (EVALI): A Literature Review

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ABSTRACT

Electronic cigarettes (e-cigarettes) are electronic tools designed to produce an inhalable aerosol from a liquid solution. Electronic cigarette or vaping use-associated lung injury (EVALI) describes any lung damage linked to the consumption of e-cigarettes or vaping products. The liquids and aerosols from e-cigarettes can include tobacco-related nitrosamines, aldehydes, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons, tobacco alkaloids from tobacco, flavor additives, and various medicinal compounds. Substantial evidence indicates that substances like propylene glycol, vitamin E acetate (VEA), and heavy metals such as lead and arsenic are significant constituents of e-cigarettes, contributing to lung harm. Patients with EVALI may present with sudden or gradually developing respiratory disease, presenting with non-specific signs, including breathlessness, coughing, chest discomfort, and sometimes coughing up blood. Radiological findings in EVALI are often non-specific. The most commonly observed pattern in EVALI is parenchymal organizing pneumonia (OP), identified in 56% of cases, whereby bilateral dominant ground-glass opacity (GGO) was identified, located in the inferior sections of the lungs or diffusely distributed with varying degrees of consolidation.

INTRODUCTION

Electronic cigarette/e-cigarette or vaping use-associated lung injury (EVALI) refers to a pulmonary disorder that develops following the use of e-cigarettes or vaping devices within the preceding 90 days. This condition is characterized by clinical manifestations, including productive cough, difficulty in breathing, and chest discomfort experienced by individuals who use e-cigarettes. Prolonged use can result in lung damage.[1,2] The use of e-cigarettes has harmful effects on the lungs, leading to the development of EVALI. Such devices, often referred to as e-cigs, mods, vapes, and electronic nicotine delivery systems (ENDS), operate on battery power to heat liquids containing nicotine and/or other chemicals, including flavoring agents, through a metal coil, producing an aerosol intended for inhalation.[3]

Electronic cigarettes were first introduced in the United States (US) in 2006, and subsequent generations of these products have produced newer versions capable of delivering higher concentrations of aerosol. Over 8,000 different flavoring agents and chemical constituents have been detected in e-cigarette formulations, with some identified as potentially carcinogenic.[4] In 2019, EVALI was recognized and named as a severe lung disease linked to the use of e-cigarettes or vaping devices.[4] In 2021, the American Thoracic Society (ATS) convened a workshop aimed at identifying and prioritizing research and regulations to address the EVALI epidemic.[5]

Lung injury connected to e-cigarette or vaping use was first detected in August 2019, with the number

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of identified cases rapidly increasing until December 2019. A link between EVALI and tetrahydrocannabinol (THC) was established within a few weeks. Tetrahydrocannabinol is the active compound produced by cannabis plants when heated to 100°C. The identification of vitamin E acetate (VEA) as a primary suspect took several months, although it has not yet been confirmed as the etiological agent. Fourteen percent of those affected used vaping products containing only nicotine-based e-liquids. Upon further analysis, these individuals were found to be older and exhibited less leukocytosis, suggesting that they might be suffering from a different vaping-related lung disease.[6]

In general, EVALI primarily impacts younger people, with the mean age of affected individuals being approximately 24 years old.[5,6] Among fatal cases, the median age was 49.5 years old, with patients' ages spanning from 15 to 75 years old.[5,6] This disease primarily affects males (66%), directly linked to the epidemiological patterns of THC vaping.[5,6] The mortality rate is relatively low, at 2.4% (a total of 68 deaths), with the highest death rates occurring among older e-cigarette users with pre-existing conditions.[5,6] By December 2019, nearly 47% of identified cases required intensive care unit (ICU) admission, while 22% necessitated intubation.[5,6]

REVIEW

ELECTRONIC CIGARETTES

Electronic cigarettes are marketed as harm-reduction tools for individuals attempting to quit smoking and are often portrayed as a safer and more convenient substitute for conventional tobacco use. However, evidence supporting their effectiveness over standard smoking cessation methods remains limited. The global use of e-cigarettes has rapidly increased, with a prevalence of 5.5% among adults in North America and the United Kingdom (UK).[7] Responses from tobacco regulatory officials have been mixed. Some promote the use of e-cigarettes to minimize the harm associated with tobacco smoking, while others advocate for nicotine market regulations that support established smoking cessation strategies. Nevertheless, the data supporting these marketing strategies remains limited.[7]

The population of e-cigarette users is diverse and includes individuals who have never smoked, former smokers who transitioned to e-cigarettes, and individuals who simultaneously use both traditional cigarettes and e-cigarettes. The role of e-cigarettes as smoking cessation tools is a subject of heated debate. Clinical trials have yielded mixed and inconclusive results. Electronic cigarettes containing nicotine tend to increase smoking cessation rates compared to non-nicotine ones. To date, evidence of harm attributed to nicotine-based e-cigarettes remains lacking.[7]

Electronic cigarettes are electrically powered devices that generate an inhalable liquid-based aerosol. The term "e-cigarettes" broadly encompasses all such devices, including ENDS, e-hookahs, e-pipes, vapes, dab pens, and personal vaporizers. Electronic cigarettes are further categorized based on their active ingredients, such as nicotine derived from tobacco or synthetic nicotine, which are currently regulated and monitored by the US Food and Drug Administration (FDA). It is equipped with microprocessor-controlled settings for adjustable voltage/wattage, transparent clearomizers, and replaceable dual-coil heads, as illustrated in Figure 1.[8]

Figure 1. Parts of e-cigarettes[9]

Electronic cigarettes operate on a simple principle: they convert liquid into aerosol (or "vapor") through the application of heat, a process referred to as "vaping." The heating medium consists of a metal coil wrapped in a cotton material capable of wicking the liquid base. The metal coil is heated by an electrical current from the battery, which, in turn, vaporizes the fluid base. The liquid typically contains solvents such as propylene glycol and vegetable glycerin, with added flavors, nicotine, and substances such as THC. When heated, propylene glycol and vegetable glycerin produce a dense vapor resembling smoke. Unlike traditional smoking, vaping bypasses harmful burning processes but still generates the thermal degradation of liquid base compounds, including low-molecular-weight

carbonyls (e.g., formaldehyde, acetaldehyde, and acetone) and tobacco-specific nitrosamines.[4,10]

Etiology and Pathophysiology of Electronic Cigarette or Vaping Use-Associated Lung Injury

The patterns of acute lung injury linked to EVALI show diverse pathological manifestations, such as acute fibrinous pneumonitis, organizing pneumonia (OP), and diffuse alveolar damage. The mechanisms of direct lung injury caused by inhalation of e-cigarette aerosols are illustrated in Figure 2. Certain chemicals added to e-liquids as flavorings, such as diacetyl, are known to cause airway inflammation and lung damage when inhaled. Diacetyl, for instance, can lead to bronchiolitis obliterans, a small airway obstruction disease presenting symptoms such as shortness of breath, productive cough, hemoptysis (coughing up blood), and chest pain.[11,12]

The processes responsible for lung damage in EVALI are depicted in Figure 2. Panel (A) illustrates two distinct pathways: on the left, a single chemical from inhaled e-cigarette aerosols damages lung cells, leading to epithelial and endothelial cell necrosis (yellow 'X'), whereas on the right side, inhaled aerosols containing propylene glycol, glycerin, nicotine, or THC trigger lung inflammation, transforming alveolar macrophages into a pro-inflammatory phenotype. Inflammatory cytokines (yellow circles) initiate a pathological inflammatory response. Panel (B) demonstrates how prolonged exposure to e-cigarette aerosols impairs lung immunity. Vitamin E acetate in e-cigarettes exerts cytotoxic effects on lung cells (yellow 'X'), resulting in necrosis, neutrophil recruitment and activation, ultimately causing lung injury and edema.[10,11]

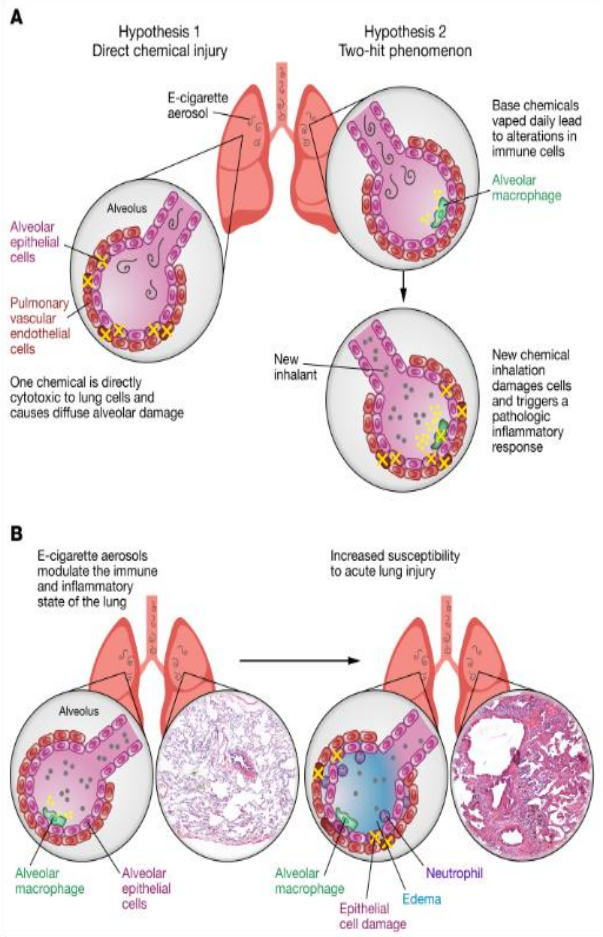

Figure 2. Underlying mechanisms of lung injury in electronic cigarette or vaping use-associated lung injury[13]

The vapor or aerosol inhaled from ENDS contains hydrocarbons, such as lipid oils. Flavoring agents in ENDS contribute substantially to the cytotoxic

properties of e-liquid and its aerosols.[11] Exposure to ENDS flavorings induces increased β-defensin gene expression in human bronchial epithelial (HBE) cells and interleukin-8 (IL-8) secretion by fibroblasts, which exhibit chemotactic effects on neutrophils. Electronic liquids with cinnamaldehyde have been shown to disrupt the immune responses of epithelial cells, neutrophils, and natural killer (NK) cells, leading to decreased macrophage phagocytosis and weakened antibacterial activity.[11] A study showed that exposure to ENDS extracts disrupts neutrophil chemotaxis, suppresses reactive oxygen species (ROS) generation, and consequently hinders the development of neutrophil extracellular traps (NETs).[11]

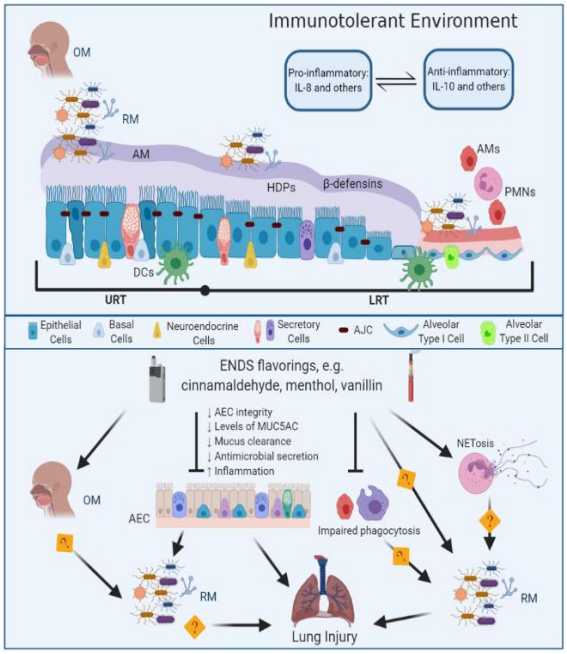

Figure 3. Effects of electronic nicotine delivery systems on airway innate immune cells[14]

The airway, from the nasal cavity to the bronchi, is lined by columnar ciliated epithelium, which transitions to cuboidal epithelium in the bronchioles and squamous epithelium in alveolar epithelial cells (AECs). Apical junctional complexes (AJCs) function as tight junctions, preserving epithelial integrity and blocking direct interaction between respiratory microbiota and phagocytic cells. Airway mucus (AM) is composed of two distinct layers: an apical aqueous layer that overlays the airway surface liquid, and a periciliary sol-phase layer that surrounds the epithelial cells.[10,11]

The composition of the respiratory microbiota (RM) is similar to that of the oral microbiota (OM). Respiratory microbiota depends on airway mucus as a source of nutrients, especially mucins like MUC5AC and MUC5B, and as a means of preventing direct contact with the epithelial surface, antigen-presenting cells, and phagocytic cells such as alveolar macrophages (AMs) and neutrophils (PMNs). The airway epithelium secretes β-defensin and other host defense peptides and proteins (HDPs). Beyond the epithelium, innate immune responses in the respiratory tract involve phagocytic cells, including dendritic cells, AMs, neutrophils, eosinophils, innate lymphoid cells, and NK cells.[12,15]

The liquid layer covering the airway serves as a habitat for respiratory microbiota, supplying key nutrients and influencing immune responses by facilitating interactions between the host's immune system and resident microbes. Flavor additives used in ENDS, such as cinnamaldehyde, menthol, and vanillin, may impair the clearance of microbes in the respiratory tract by undermining the structural integrity of AECs, reducing antimicrobial secretions, and provoking inflammatory responses, which collectively contribute to lung injury. These flavoring agents also impair the ability of alveolar macrophages and polymorphonuclear neutrophils to undergo phagocytosis. Additional studies are warranted to clarify how flavor-induced alterations in the OM, alveolar macrophage phagocytosis, and NETosis affect the RM and promote lung injury.[12,15]

Electronic cigarette devices and the aerosols they produce can contain numerous substances, such as tobacco-specific nitrosamines, aldehydes, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons, tobacco alkaloids, flavor additives, and even pharmaceutical agents. For example, a study identified propylene glycol, VEA, and metals such as lead and arsenic as key constituents of certain e-cigarettes.[11] For nicotine-based e-cigarettes, propylene glycol and vegetable glycerol act as diluents, whereas THC-containing formulations often use oils like medium-chain triglycerides for the same purpose.[11]

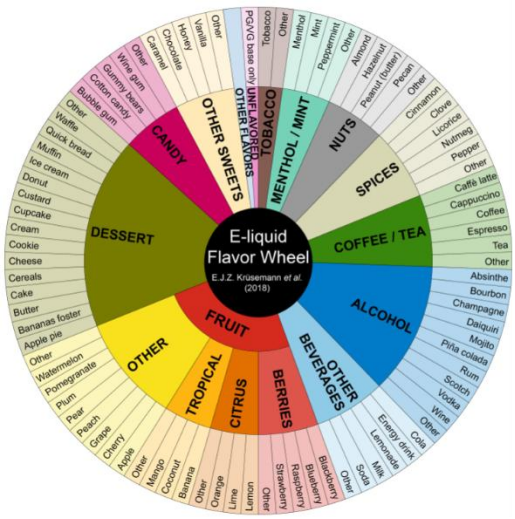

Figure 4. Variation of flavors in e-liquids[11]

Flavorings in ENDS consist of molecules involved in taste perception. Taste refers to the sensory experience of the flavor and aroma of e-liquids.

Currently, around 8,000 flavors are commercially available, many of which imitate traditional tobacco products (e.g., menthol or tobacco), fruits (such as berries, citrus, tropical, and tropical varieties), desserts (including coconut, cake, banana), alcoholic beverages (such as champagne, mojito, vodka, and rum), as well as sweets like caramel, chocolate, vanilla, cotton candy, and chewing gum (Figure 4).[11] The detrimental impact of inhaled flavoring chemicals on respiratory innate immunity remains poorly understood, with the underlying mechanisms and biomarkers for both short- and long-term effects yet to be clearly identified. Available data regarding the effects of ENDS flavoring agents and their possible role in modulating pulmonary innate immunity and respiratory microbiota are still limited.

Table 1. Effects of electronic liquid (e-liquid) flavorings on the lung innate immunity and respiratory microbiota[10,11]

Flavor	Chemical Substances Contained in E-Liquid Flavoring	Effects
Cinnamon	Benzaldehyde	- Suppresses interleukin (IL)-8 secretion in human bronchial epithelial (HBE) cells and human lung fibroblasts, leading to decreased transepithelial resistance in HBE (loss of alveolar epithelial cell/AEC integrity). - Reduces phagocytic activity and cell viability among alveolar macrophages, polymorphonuclear neutrophils, and natural killer cells, thereby inducing neutrophil extracellular trap activation and inflammation. - Does not regulate mucociliary clearance, thereby increasing susceptibility to infections.
	Cinnamaldehyde	
	Ethyl vanillin	
	Cinnamic acid	
	Methyl eugenol	
Tobacco	Butanoic acid	Tobacco-flavored e-liquids stimulate autophagy in human middle ear epithelial cells and increase mucin production.
	3-(1-Methyl-2-pyrrolidinyl)pyridine	
	β-Nicotyrine	
	3-Methyl-1-phenyl-1H-pyrazole	
Vanilla	Ethyl maltol	Vanilla stimulates IL-8 release in HBE cells and lung fibroblasts but has no impact on the barrier function of AEC.
	Piperonal	
	Vanillin	
	Isobutyl caproate	
Menthol	2,3,5-Trimethylpyrazine	The addition of menthol to cigarettes lowers microbial diversity and reduces the prevalence of human pathogenic bacteria.
	γ-Octalactone	Exposure to menthol-flavored e-liquids stimulates autophagic activity in human middle ear epithelial cells and elevates mucin production.
	DL-Menthol	In asthma, menthol has the potential to induce neurogenic inflammation through activation of the tumor necrosis factor receptor-associated protein 1 receptor.
	δ-Decalactone	Menthol demonstrates antimicrobial effects against *Staphylococcus aureus* and *Streptococcus epidermidis*.

DIAGNOSIS

There are no specific diagnostic tests that can definitively determine the condition in patients with EVALI. Multiple definitions have been developed by combining clinical characteristics with patient history. Individuals with EVALI can present with acute or subacute respiratory disease characterized by nonspecific symptoms, such as shortness of breath, persistent cough, chest discomfort, or coughing up blood. Most patients also experience digestive manifestations such as nausea, vomiting, or diarrhea, and/or systemic symptoms such as systemic complaints including fever, chills, tiredness, or unintended weight reduction. Such clinical signs may progress gradually, spanning from several days to weeks. The presentation of EVALI-VEA in adolescents may differ from that in adults. Several case reports have highlighted the requirement for venovenous extracorporeal membrane oxygenation as part of EVALI treatment in adolescents with underlying asthma. Individuals with EVALI may present with rapid heart rate, increased respiratory rate, and oxygen saturation levels falling below 95%. The physical exam should emphasize the cardiopulmonary system, with evaluation of vital signs and oxygen saturation to gauge the severity of respiratory distress and to detect alternative causes of respiratory disease (such as chronic lung disorders, heart failure, or community-acquired pneumonia). The most widely used diagnostic criteria are based on the Centers for Disease Control and Prevention (CDC) guidelines to aid in identifying suspected and confirmed cases, enabling standardized reporting and epidemiological case tracking.[8] The presence of pulmonary infiltrates on chest X-ray or computed tomography (CT) scans within 90 days of using e-cigarettes, without alternative causes identified after a comprehensive medical evaluation.

Table 2. Differences between suspected and confirmed cases

Confirmed Cases	Suspected Cases
Use of electronic cigarettes (e-cigarettes) within 90 days before the onset of symptoms. AND Pulmonary infiltrates, opacities on chest X-ray, or ground-glass opacities on computed tomography (CT) chest imaging. AND Lack of evidence of lung infection on the initial assessment. The basic criteria include: 1. Respiratory viral panel testing must yield a negative result 2. A negative result on an influenza polymerase chain reaction (PCR) or rapid diagnostic test, provided local epidemiological data warrant influenza testing 3. All other clinically indicated evaluations for respiratory infections should yield negative results (e.g., *Streptococcus pneumoniae* and *Legionella* antigens, sputum culture when productive cough is present, bronchoalveolar lavage if conducted, blood culture, and tests for opportunistic respiratory infections associated with human immunodeficiency virus) AND No evidence of alternative diagnoses in medical records (e.g., cardiac, rheumatologic, or neoplastic processes).	Use of e-cigarettes within the 90 days preceding symptom onset. AND Radiologic evidence of pulmonary abnormalities, including infiltrates, opacities on chest radiograph, or ground-glass opacities on CT imaging. AND Presence of an infection identified via culture or PCR, but the clinical team assesses that this infection does not explain the lung injury. OR Minimum criteria for excluding lung infection are not fulfilled (testing not conducted), yet infection is still judged unlikely to be the sole cause of lung injury. AND No evidence of alternative diagnoses recorded in the medical history (e.g., cardiac, rheumatologic, or neoplastic conditions).

This case definition does not incorporate variables regarding the specific e-liquid used, such as nicotine vs. THC-containing formulations, flavored vs. unflavored products, or the type of carrier liquid. It likewise omits requirements on the scope or methods of infection testing to be undertaken. Moreover, the criteria for confirmed and suspected cases are essentially the same, except for suspected cases where infection testing is inconclusive or where positive microbiological results do not fully account for the illness. The CDC's definition emphasizes acute respiratory disease linked to e-cigarette use but does not encompass chronic respiratory disorders or other conditions that may be initiated or aggravated by vaping.

Supportive Examinations

Supportive diagnostic evaluations for EVALI primarily aim to exclude alternative diagnoses. During influenza season, respiratory viral panel testing, including specific assays for influenza A and B antigens, should be considered. Testing for infectious diseases can involve identifying causes such as *Streptococcus pneumoniae*, *Legionella pneumophila*, fungal infections, human immunodeficiency virus/HIV, coronavirus disease (COVID-19), and opportunistic infections. Case reports show elevated inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leukocyte levels.[15] However, these inflammatory markers in EVALI patients are non-specific and may not be particularly useful for excluding other etiologies. Toxicology testing can assist in ruling out lung disease etiology triggered by other illicit substances.[15]

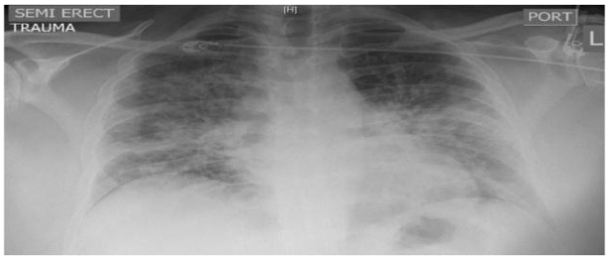

Figure 5. Chest X-ray image of an electronic cigarette or vaping use-associated lung injury patient showing bilateral patchy opacities[15]

Radiological findings in patients with EVALI are often non-specific. The most common pattern observed in EVALI is parenchymal OP identified in 56% of cases, with bilateral ground-glass opacities (GGO) predominantly affecting the lower lobes or appearing diffusely with varying degrees of consolidation, as shown in Figure 5.[15] Approximately 9% of EVALI patients exhibit diffuse centrilobular nodules with minimal or absent GGO, resembling a clinical lung disease caused by intravascular drugs.[16] However, centrilobular nodules in excipient lung disease are typically well-delfineld, and findings of right heart strain are common due to diffuse embolization of injected materials into the pulmonary arterioles.[16,17] This comparison is illustrated in Figure 6.

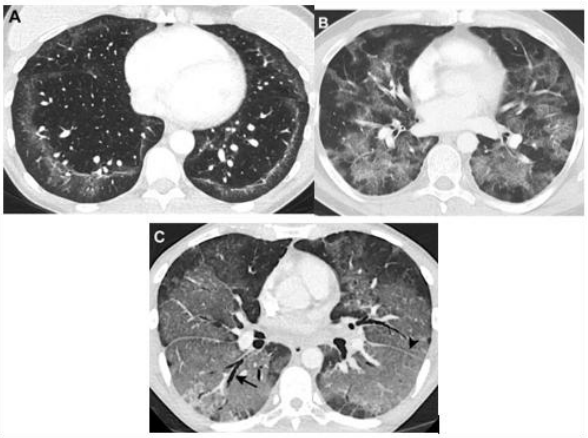

Figure 6. Chest computed tomography (CT) scans of patients with electronic cigarette or vaping use-associated lung injury. A) A CT scan of a 40-year-old female revelaed an organizing pneumonia (OP) pattern in the lower lobes, characterized by subpleural ground-glass opacity (GGO) bands, interpreted as mild degree of injury; B) A CT scan of a 31-year-old male demonstrated a diffuse GGO OP pattern, consistent with moderate lung injury and axial distribution of GGO; C) A CT imaging of a 36-year-old male, a daily user of vaporized tetrahydrocannabinol and nicotine, displayed severe pulmonary injury marked by diffuse subpleural GGO, mild displacement along the fissures (arrowhead), and multifocal bronchial dilation (arrow). The case was identified as consistent with a diffuse alveolar damage pattern.[18]

Around 20% of individuals present with a mixed OP pattern, characterized either by predominant centrilobular nodules in the upper lobes accompanied by diffuse GGO, or by lower-lobe, predominant involvement with mosaic-like regions. This imaging manifestation resembles hypersensitivity pneumonitis. Nevertheless, no histopathological confirmation of hypersensitivity pneumonitis has thus far been reported in EVALI patients.[16]

Conversely, in EVALI, centrilobular nodules are pathologically linked to OP centered around the airways. Among EVALI cases, diffuse alveolar damage constitutes the most severe form of pulmonary injury, occurring in approximately 4% of patients.[18] The radiological presentation is characterized by diffuse GGO with consolidation, accompanied by volume loss and airway dilatation secondary to alveolar collapse, as shown in Figure 7. Similar to other causes of diffuse alveolar damage, about ¼ of these cases have been reported as fatal.[17]

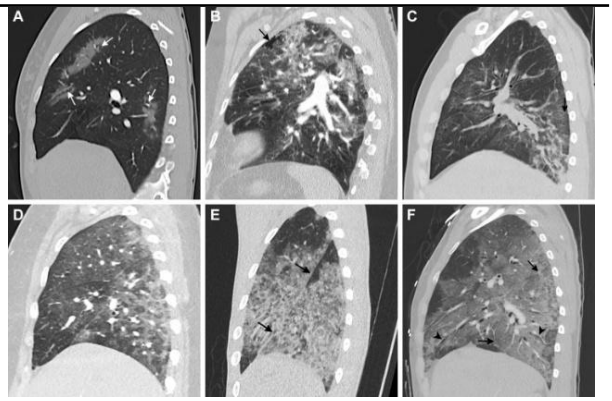

Figure 7. Illustrations of the varying severity of parenchymal injury patterns in electronic cigarette or vaping use-associated lung injury. A) A sagittal computed tomography (CT) scan of a 19-year-old female using tetrahydrocannabinol (THC) revealed an organizing pneumonia (OP) pattern with mild involvement, displaying peribronchovascular changes and ground-glass opacities (GGO) (arrow); B) A sagittal CT of a 59-year-old male with chronic nicotine use demonstrated an OP pattern predominantly affecting the upper lobes, together with diffuse GGO foci (arrow); C) A sagittal CT of a 31-year-old male using THC several times weekly showed severe parenchymal damage, evidenced by extensive consolidation and diffuse GGO (arrow); D) A sagittal CT of a 19-year-old male with daily THC use demonstrated severe pulmonary injury, characterized by diffuse GGO with subpleural and lobular distribution (arrow); E) Sagittal CT image of a 19-year-old male using both THC and nicotine showing severe injury with more extensive consolidation relative to GGO; F) Sagittal CT image of a 25-year-old male with daily THC use demonstrating diffuse GGO, inferior displacement of the right major fissure (arrow), and mild dilation of the subsegmental bronchi (arrowhead). The patient passed away three weeks later.[18]

Bronchoscopy is commonly employed to collect bronchoalveolar lavage (BAL) samples and tissue biopsies. Nonetheless, cytological assessment of BAL specimens provides limited diagnostic accuracy, as overlapping cellular features are often reported in EVALI cases. Lipid-laden macrophages are the most frequently observed finding in BAL samples from affected patients, as shown in Figure 8. Initially, this raised concerns of a diagnosis of lipoid pneumonia. Moreover, histopathological evaluation revealed foamy macrophages containing intracellular vacuoles within the alveolar spaces, but lacking filamentous

structures typical of lipoid pneumonia, such as vacuolated giant cells. Therefore, lipid-laden macrophages are considered an endogenous response to cigarette use.[11,19]

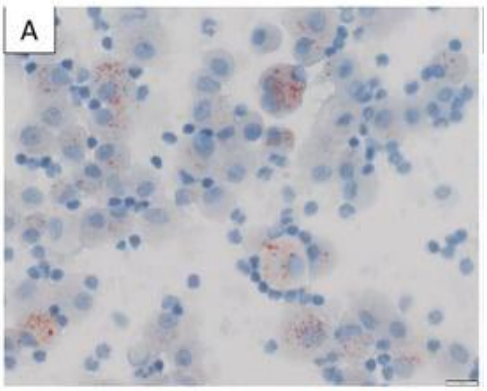

Figure 8. Bronchoalveolar lavage cytology from a patient with electronic cigarette or vaping use-associated lung injury (EVALI). The specimen, stained with Oil Red O and examined at 400x magnification, shows red-staining intracytoplasmic lipid droplets within alveolar macrophages, indicating lipid accumulation.[7]

Studies have also reported the prevalence of VEA in BAL specimens. In a study of 51 patients, 94% of EVALI patients had detectable VEA in their BAL, while none of the healthy control group did.[20] Although VEA has not been definitively established as a universal cause of injury, its detection in BAL fluid provides strong supporting evidence. Nonetheless, several factors may limit the interpretive value of negative findings, including the interval between the last e-cigarette use and bronchoscopy, differences in BAL collection techniques, and inadvertent dilution of alveolar fluid with saline. Furthermore, VEA testing is not routinely available in many clinical laboratories.[20]

Histopathology of Electronic Cigarette or Vaping Use-Associated Lung Injury

The histopathological characteristics of EVALI are largely non-specific. Lung biopsies most frequently demonstrate an OP pattern, which reflects sampling during the subacute stage of the illness. In contrast, cases presenting acutely or with more severe disease may reveal acute fibrinous lung inflammation or extensive alveolar injury. To date, no distinctive histopathological characteristics of EVALI have been established, although several observations point to possible underlying causes. Foam cells (macrophages) are almost universally present and indicate toxic injury, with changes typically being bronchiocentric. The majority of cases show protein-rich or pigmented granular debris within the injured regions, with marked neutrophilic inflammation commonly present, a finding that resembles infection and acute interstitial pneumonia.[19,21]

Early EVALI reports described lipid-laden macrophages in BAL fluid, which can be identified using Oil Red O histological staining. Although Oil Red O staining of BAL fluid was initially proposed as a diagnostic marker during the early EVALI outbreak, its specificity for EVALI is low. Oil Red O-positive macrophages can also occur in various other conditions, including COVID-19, other infectious diseases, drug-induced reactions, and autoimmune disorders, where lipid-laden macrophages accumulate as a result of cell membrane breakdown. Given its non-specificity, technical limitations, and the absence of robust sensitivity data, Oil Red O staining must be interpreted with caution, as shown in Figure 9.[19,21]

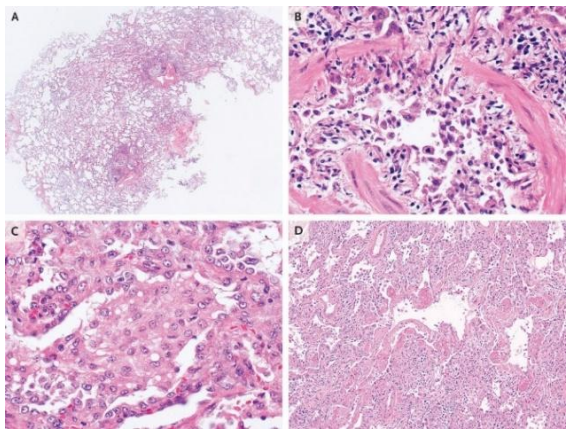

Figure 9. Microscopic tissue characteristics of lung injury linked to electronic cigarette or vaping use-associated lung injury (EVALI). A) Severe bronchiolitis characterized by mucosal edema, bronchiolar epithelial desquamation, and peri-bronchiolar organizing; B) All examined cases demonstrated foam-like or vacuolated macrophage accumulation within peribronchial airspaces accompanied by pneumocyte vacuolization; C) Four cases exhibited severe lung injury with diffuse alveolar damage and hyaline membranes formation; D) Follow-up revealed that two of the four patients passed away.[11]

ELECTRONIC CIGARETTE OR VAPING USE-ASSOCIATED LUNG INJURY MANAGEMENT

No randomized clinical trials have yet been conducted to assess treatments for EVALI. The majority of patients were admitted for inpatient care, with 68 deaths (2.4%) reported among 2,807 inpatient cases of EVALI.[4] Long-term data on patients who survived EVALI remain insufficient to determine therapeutic management. Prospective studies show that most patients diagnosed with EVALI experience persistent side effects, such as respiratory issues, as well as cognitive and mood disorders.[8] Reported therapies include supportive oxygenation,

supplemental oxygen, non-invasive ventilation (NIV), mechanical ventilation, and extracorporeal membrane oxygenation (ECMO).

There are two main types of ECMO: venoarterial (VA), offering combined cardiac and pulmonary assistance, and venovenous (VV), which is limited to respiratory support. Numerous clinical studies have demonstrated that ECMO improves survival outcomes in individuals with severe respiratory failure. Consequently, adults experiencing severe acute respiratory distress syndrome (ARDS) unresponsive to standard treatment should be evaluated for transfer to a facility equipped to perform ECMO. Lung transplantation may also be considered as a treatment option for these patients.

Extracorporeal carbon dioxide removal ($ECCO_2R$) is a method designed to eliminate carbon dioxide from the bloodstream using a gas-exchange membrane, with minimal impact on oxygenation. This approach requires significantly lower extracorporeal blood flow compared with that needed for oxygenation. Extracorporeal carbon dioxide removal techniques utilize pump-free arterio-venous circuits, low-flow venous systems adapted from hemodialysis technology, and venous circuits based on ECMO technology. This procedure has been shown to facilitate more protective ventilation for ARDS patients. The $ECCO_2R$ mechanism is illustrated in Figure 10.

Experimental data suggest the benefits of $ECCO_2R$ for patients with ventilator-induced lung injury, but there is no strong clinical evidence regarding improved outcomes. Extracorporeal carbon dioxide removal can also serve to avoid intubation and invasive ventilation in individuals experiencing acute COPD flare-ups when NIV fails to provide adequate relief. Complications from this procedure are mainly related to vascular access and hemostatic disturbances, leading to bleeding.[22]

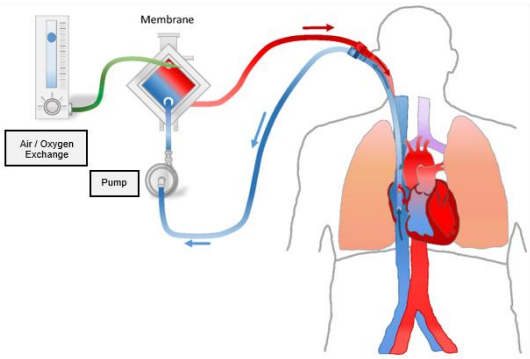

Figure 10. The working diagram of extracorporeal carbon dioxide removal[23]

Extracorporeal carbon dioxide removal is an effective technique for managing respiratory failure associated with hypercapnia and facilitates protective mechanical ventilation. However, strong evidence supporting its routine use remains limited. Further research, clinical guidelines, resources, and training are needed to ensure its safe and practical application. Innovations such as blood acidification, electrodialysis, and the latest pump/membrane technologies may enhance CO_2 removal efficiency through less invasive methods, making $ECCO_2R$ more accessible and not limited to referral hospitals. This review aims to establish a foundation for understanding the technology, defining its role within extracorporeal therapies, and encourage further research for targeted clinical use.[22]

The main therapeutic aims of mechanical ventilation include restoring oxygen levels, controlling acute respiratory acidosis, reducing respiratory distress, avoiding or treating atelectasis, providing rest and preventing fatigue of the respiratory muscles, decreasing systemic oxygen consumption and myocardial oxygen demand, lowering intracranial pressure via controlled hyperventilation, and stabilizing the chest wall.[24,25] Common indications for starting mechanical ventilation include slow breathing or apnea leading to respiratory arrest, acute lung injury and ARDS, rapid breathing with a rate over 30 breaths per minute, a vital capacity of less than 15 mL/kg, minute ventilation exceeding 10 L/min, an arterial oxygen pressure (PaO_2) to inspired oxygen fraction (FiO_2) ratio below 55 mmHg, and an alveolar–arterial oxygen gradient (A–a DO_2) greater than 450 mmHg while on 100% oxygen, respiratory muscle fatigue, depressed consciousness or coma, hypotension, acute hypercapnia with partial pressure of carbon dioxide ($PaCO_2$) exceeding 50 mmHg and arterial pH below 7.25, and neuromuscular disorders.[26]

Across multiple case reports, between 78% and 100% of patients required hospitalization, as EVALI-related respiratory failure often mimics the presentation of bacterial or viral pneumonia.[8] Moreover, both EVALI and viral infections like COVID-19 have been linked to severe disease progression necessitating intensive care and corticosteroid therapy. A case series reported that 67-90% of patients were treated with corticosteroids, though the appropriate dosing and treatment duration were inconsistent.[15] Nonetheless, numerous patients received only supportive care without corticosteroids and exhibited swift clinical recovery.[4,8]

The present strategy for pharmacological therapy is primarily based on case reports and small case series rather than evidence from systematic

clinical trials. The majority of EVALI patients have shown improvement when treated with high-dose systemic corticosteroids, such as intravenous methylprednisolone (0.5-1 mg/kg/day). A case series documented that corticosteroid therapy led to clinical improvement in 82% of patients.[15] Patients suspected of having other causes should not be given corticosteroids, such as those with fungal pneumonia. Managing patients with influenza co-infection is challenging, as corticosteroid therapy in influenza has been linked to higher mortality and an increased risk of hospital-acquired infections. Nevertheless, most existing evidence pertains to the use of high-dose corticosteroid regimens.[27]

Scott, *et al*. (2018) stated that the condensate formed from e-cigarette vapor is significantly more harmful to alveolar macrophages compared to the liquid form of e-cigarettes that has not been vaporized.[28] In vitro studies indicate that the antioxidant N-acetylcysteine (NAC) has been shown to reduce both the toxic and cell death-inducing effects caused by e-cigarette vapor condensate. Choe, *et al*. (2020) reported that treatment with inhaled NAC, administered for its mucolytic effects, resulted in a favorable clinical outcome.[29] Further research on the use of NAC in EVALI management is still needed, although NAC has shown benefits for treating EVALI.[29]

The primary and most important measure in managing EVALI is stopping the use of e-cigarettes entirely. Recurrent cases of EVALI continue to be reported among individuals who persist in using e-cigarettes. The addictive properties of nicotine in these products, however, often make cessation challenging. The CDC advises that patients be provided with, or referred to, cessation programs for cigarette use, whether in inpatient or outpatient care settings.[8] A significant number of patients have been found to use e-cigarettes containing cannabinoids, and discontinuation of such products is strongly recommended. Currently, evidence regarding effective strategies for nicotine or cannabis cessation among adolescents and young adults remains limited.[4,8,29]

Patient Follow-Up and Prognosis

The prognosis for patients with EVALI is relatively favorable, even in severe cases. The average duration of hospitalization is 6-7 days, whereas for patients aged 51 years and older, it is 14.8 days.[15] Uncertainty remains regarding the long-term prognosis of EVALI, the likelihood of relapse, and possible influencing elements like genetic predisposition. Cases of recurrence have been reported both during corticosteroid tapering and following the resumption of e-cigarette use (personal communication). Some patients may require endocrinological follow-up after prolonged corticosteroid therapy to assess adrenal function. Although post-discharge monitoring could provide valuable insights into long-term outcomes, such data have not yet been established.[15,30]

Before discharge to outpatient care, it is crucial to confirm that a patient's dyspnea has resolved and that vital signs, including oxygen saturation, have remained stable for 24 to 48 hours. Data on the risk of EVALI recurrence among individuals who continue e-cigarette use are limited. In a multicenter, prospective observational study conducted within an integrated healthcare system in Utah, US (27 June-4 October 2019), six of 60 patients (10%) required ICU or hospital readmission within two weeks, and 30 patients (50%) experienced recurrence associated with continued e-cigarette use.[31] The precise risk factors and underlying mechanisms for EVALI recurrence remain unknown. Consequently, complete cessation of e-cigarette use is imperative, and comprehensive smoking cessation counseling should be incorporated into discharge planning.[32] Table 3 outlines the management steps for EVALI.

Table 3. Management of lung injury linked to electronic cigarette or vaping use

Clinical	History (e.g., e-cigarette products, respiratory/cardiovascular/gastrointestinal symptoms) Physical Examination (e.g., peripheral oxygen saturation/SpO_2, signs of bronchiolitis)
Diagnosis (Non-Invasive)	a. Laboratory examination (e.g., C-reactive protein, procalcitonin, complete blood count, liver function tests, blood glucose, human immunodeficiency virus serology, blood culture, urine for *Legionella* and *pneumococcus*, blood gas analysis) b. Gram staining and sputum culture, polymerase chain reaction for respiratory viruses, influenza c. Chest X-ray, chest computed tomography (CT) scan
Diagnosis (Invasive)	a. Bronchoscopy with bronchoalveolar lavage (Oil Red O or Sudan Black staining to identify lipid-laden macrophages, and Prussian Blue staining for iron) b. Lung biopsy
Treatment (Empirical)	a. Discontinuation of e-cigarette use b. Consideration of antibiotic administration (e.g., ceftriaxone and azithromycin, and/or antiviral treatment such as for influenza) c. Consideration of systemic steroid administration (e.g., methylprednisolone 250-500 mg initial dose, then 0.5-1 mg/kg/day) d. Adequate oxygenation (e.g., nasal oxygen cannula, high-flow nasal cannula, non-invasive and invasive ventilators, extracorporeal membrane oxygenation)
Outpatient Care	a. Follow-up 24-48 hours after discharge (SpO_2 examination, patient education on the 50% risk of recurrence with e-cigarette use) b. Follow-up visit 1-2 weeks (with SpO_2 examination and periodic chest X-rays) c. Follow-up visit 1-2 months (with SpO_2 examination, spirometry, diffusing capacity of the lungs for carbon monoxide, chest X-ray, and/or chest CT scan if there is a strong indication)

Patients with comorbidities who undergo hospitalization often require follow-up care after discharge. This necessity arises due to the significantly higher rates of hospital readmission and mortality observed among older patients and individuals with underlying health conditions. Recognizing the importance of post-discharge monitoring, the CDC has updated its recommendations, shortening the follow-up period from two weeks to two days after hospital discharge.[31] However, considerable uncertainty remains regarding the long-term residual symptoms associated with the disease process, extending beyond the immediate short-term complications following an EVALI diagnosis. Therefore, a well-structured follow-up evaluation, combined with addiction counseling, can be designed within a multidisciplinary program to ensure comprehensive care for patients diagnosed with EVALI.[31,32]

SUMMARY

Electronic cigarette or vaping use-associated lung injury represents an acute lung condition caused by inhaling aerosolized substances from e-cigarettes or vaping devices. It is characterized by diverse histopathological patterns and nonspecific symptoms such as dyspnea, cough, and chest pain. Patients, especially those with comorbidities or of advanced age, face increased risks of hospital readmission and mortality, necessitating post-discharge monitoring and structured follow-up care. To reduce health risks, healthcare providers should enhance public awareness, promote early detection, and implement screening and education strategies targeting at-risk populations.

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Conflict of Interest
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