Radiology

REVIEWS AND COMMENTARY • REVIEW

Radiologic, Pathologic, Clinical, and Physiologic Findings of Electronic Cigarette or Vaping Product Use–associated Lung Injury (EVALI): Evolving Knowledge and Remaining Questions

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Proposed as a safer alternative to smoking, the use of electronic cigarettes has not proven to be innocuous. With numerous deaths, there is an increasing degree of public interest in understanding the symptoms, imaging appearances, causes of, and treatment of electronic cigarette or vaping product use–associated lung injury (EVALI). Patients with EVALI typically have a nonspecific clinical presentation characterized by a combination of respiratory, gastrointestinal, and constitutional symptoms. EVALI is a diagnosis of exclusion; the patient must elicit a history of recent vaping within 90 days, other etiologies must be eliminated, and chest imaging findings must be abnormal. Chest CT findings in EVALI most commonly show a pattern of acute lung injury on the spectrum of organizing pneumonia and diffuse alveolar damage. The pathologic pattern found depends on when in the evolution of the disease process the biopsy sample is taken. Other less common forms of lung injury, including acute eosinophilic pneumonia and diffuse alveolar hemorrhage, have also been reported. Radiologists and pathologists help play an important role in the evaluation of patients suspected of having EVALI. Accurate and rapid identification may decrease morbidity and mortality by allowing for aggressive clinical management and glucocorticoid administration, which have been shown to decrease the severity of lung injury in some patients. In this review, the authors summarize the current state of the art for the imaging and pathologic findings of this disorder and outline a few of the major questions that remain to be answered.

Online supplemental material is available for this article.

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Learning Objectives:

After reading the article and taking the test, the reader will be able to:

- Describe the symptoms most often associated with e-cigarette or vaping acute lung injury (EVALI)
- Identify the radiographic and CT patterns of disease seen in patients with EVALI
- List the common pathologic patterns of lung injury that have been described in biopsy specimens of patients with EVALI

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Over the past few millennia, nicotine and marijuana were smoked through chemical combustion. In the 20th century, it became widely recognized that inhalation of toxic particles associated with smoking led to a proliferation of diseases including chronic obstructive pulmonary disease, lung cancer, and cardiovascular disease. In 2003, a Chinese pharmacist whose father died of lung cancer and who himself was a smoker invented the modern electronic cigarette (hereafter, e-cigarette) in an effort to develop a "safe" alternative to traditional forms of smoking (1–3).

Since being introduced into Europe in 2006 and the United States in 2007, the number of users of e-cigarettes (also known as *vapers*) has continued to skyrocket, with an increase from 7 million in 2011 to 41 million in 2018 (4). While this increase has occurred across almost all demographics, the most dramatic rise has been in adolescents. Between 2017 and 2018, there was an increase of 48% and 78% in middle school and high school students who reported vaping, respectively (5). This 1-year growth represents the largest increase of any substance tracked (by using survey results) by the

Abbreviations

DAD = diffuse alveolar damage, ELP = exogenous lipoid pneumonia, EVALI = electronic cigarette or vaping product use–associated lung injury, HP = hypersensitivity pneumonitis, OP = organizing pneumonia, THC = tetrahydrocannabinol

Summary

In most cases, both the imaging and pathologic findings of electronic cigarette or vaping product use–associated lung injury are that of organizing pneumonia and diffuse alveolar damage, with acute eosinophilic pneumonia and diffuse alveolar hemorrhage being less common.

Essentials

- The dramatic increase in vaping in middle school and high school students over the past year represents the largest increase in use of any illicit substance tracked by the National Institute of Drug Abuse over the last 44 years.
- The acute lung injury associated with vaping, termed electronic cigarette or vaping product use–associated lung injury (EVALI), is a diagnosis of exclusion and abnormal pulmonary findings at imaging are required to suggest the diagnosis.
- EVALI, characterized primarily by acute lung injury consisting of histopathologic and imaging patterns of organizing pneumonia, diffuse alveolar damage, or both, has emerged as a serious and sometimes fatal complication of vaping.
- Both nicotine and tetrahydrocannabinol products have been associated with EVALI, and although vitamin E acetate has been found in bronchoalveolar lavage fluid in many patients with EVALI, it is unclear whether this represents the cause of injury or merely a marker of exposure.

Monitoring the Future program over the last 44 years (6). This National Institute on Drug Abuse–funded program tracks drug use in the U.S. population by using survey results (see *https://www.drugabuse.gov/related-topics/trends-statistics/infographics/monitoring-future-2018-survey-results*).

Vape Pen Design and Function

E-cigarettes are products that aerosolize (or vaporize) a substance for inhalation. Many other colloquial names including *e-cigs, cigalikes*, *e-hookahs, mods, vape pens, vapes, tank systems, e-vaporizers*, and *electronic nicotine delivery systems* have been used by various publications and manufacturers, but refer to the same basic device (7). E-cigarettes consist of three main components: a battery, a reservoir containing the substance to be vaped, and the heating element that vaporizes the substance (7). Some modern devices now have Bluetooth connectivity for mobile apps that track vaping habits.

Each component is a separate variable, and thus e-cigarettes are almost infinitely customizable. For instance, batteries of different strengths may produce different combustion temperatures leading to different byproducts of combustion (7). Particle size has been shown to dramatically vary depending on the power of the atomizer. Increasing power causes a shift from nano-sized particles to micron-sized particles, likely due to coagulation of small particles inside the oral cavity (8). Both particle sizes reach the alveoli, although their deposition patterns are different. The heating element may be constructed of various heavy metals, and traces of these metals known to cause lung disease have also been found in aerosol samples from vaping devices (9). However, the reservoirs—and more specifically, the substances they contain—are the most variable. Thousands of different flavoring agents are available. There is little, if any, governmental or regulatory oversight for these tobacco agents in the United States. There is an additional problem as well: illegally manufactured vaping liquids that contain toxic chemicals may also be present in these vaping mixtures. Lastly, there are numerous end-user variables including puff duration, volume, flow rate, number of daily sessions, and puffs per session. In a study of just 22 vapers, the puff duration, puff volume, and puff flow rate ranged from 0.7–6.7 seconds, 29–388 mL, and 23–102 mL/sec, respectively (10). In this same cohort, daily exposure dramatically varied with the number of vaping sessions, total puffs, and total volume of inhaled aerosol ranging from five to 59 sessions, 24–1091 puffs, and 1553–182 147 mL, respectively (10).

Vape Products

Most vaping devices feature refillable tanks with reusable or disposable pods. Nicotine e-liquids consist of liquid nicotine often dissolved in glycerin or propylene glycol. Although the nicotine compounds can be vaped by themselves, most people who use e-cigarettes opt to inhale nicotine mixed with various aldehydes and alcohols to create numerous sweet and sour flavors, or *juices*. Although banned in traditional cigarettes, these flavors are more commonly vaped by new and younger users (11) and are believed to be a major driver of adolescent vaping (12). Given increasing economic demand, as of 2017 there were 288 models of e-cigarettes on the market with over 15 500 distinct flavors (13). Although vaping products can be purchased legally (eg, vape shops, gas stations, and convenience stores), black-market and homemade vaping mixtures are also

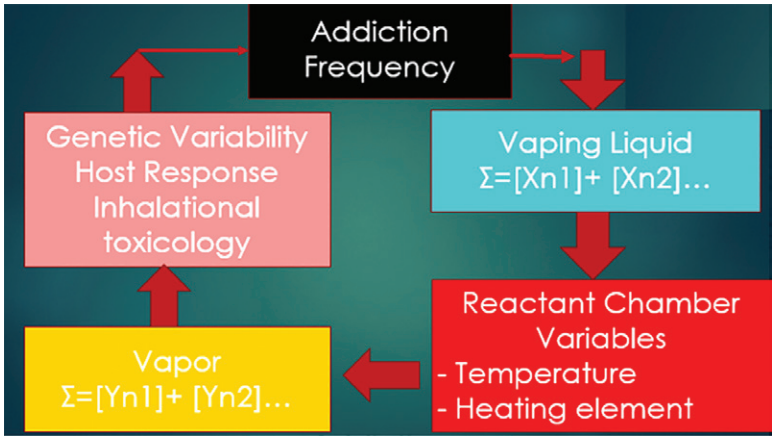


Figure 1: Diagram demonstrates host factors that influence lung injury response to vaping. Factors are dependent both on personal behavior (addiction frequency), what vaping agents (reactants) are used ([Xn1] + [Xn2]...), temperature of heating filament and temperature of walls of reactant chamber, what new chemicals (products) are made in filament chamber ([Yn1 + [Yn2]...), and host response to these chemicals.

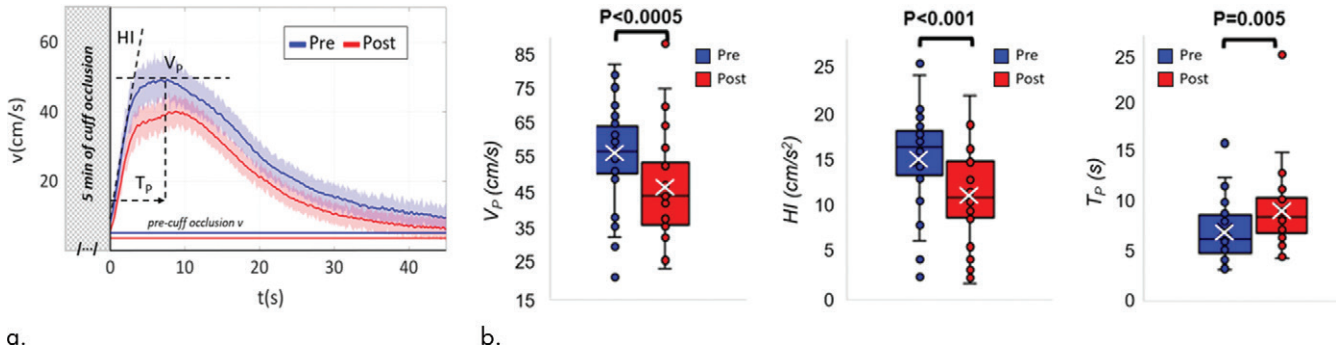


Figure 2: Graphs show blood flow velocity in femoral artery during reactive hyperemia before versus after nonnicotine electronic cigarette vaping. **(a)** Solid lines represent averages (31 subjects) of time-course data, along with standard errors. Cuff was released at time (*t*) of 0, after 5 minutes of occlusion (shaded area). Horizontal lines indicate baseline values of arterial blood flow velocity, acquired precuff occlusion (extended to entire time-course to facilitate visualization of hyperemic effects). Slope of curve (hyperemic index [HI]), peak velocity (V_p), and time to peak (T_p) are indicated. **(b)** Comparison of extracted parameters illustrates highly significant acute effects of vaping a single denicotinized e-cigarette. Source.—Reference 31.

commonly used (14). As a result, the exact components of vaping mixtures are often unknown and may contain unwanted contaminants. Given the many variables, including the heterogeneity of vaping compounds and patient-specific responses, it is no surprise that the biologic effects of vaping and e-cigarette or vaping product use–associated lung injury (EVALI) are poorly understood (Fig 1).

The growth in the use of e-cigarettes cannot be attributed only to flavored nicotine. With an increasing number of states legalizing marijuana and an ever-present black-market supply, the use of vape pens to smoke marijuana and its tetrahydrocannabinol (THC) derivatives has also increased in both adolescents and adults (15–17). In addition to aerosolizing plant material, vape pens can be used to inhale marijuana-derived oils and waxes, a practice termed *dabbing*. In most instances, these oils or waxes come prepackaged in cartridges or pods. Cannabinol oils have no THC and are used for purposes other than getting high. The number of proposed uses for cannabinol oils is large and growing each day. The science for the use of these agents is slowly catching up to the public's enthusiasm. Because of a decrease in the typical marijuana odor, vape pens offer a "discreet" way to smoke in public, which has been reported as the leading reason why young adults choose to vape THC products (18). In one recent study (19), 61% of marijuana users have vaped marijuana or its derivatives at some point, with 37% doing so in the last month.

Pathophysiology of Vaping

E-cigarettes have been shown to yield mainstream aerosols with particle concentrations similar to or even higher than those emitted by conventional cigarettes (20). In fact, vapers repeatedly inhale high concentrations of propylene glycol, glycerol, volatile organic compounds, and ultrafine particles (<100 nm in diameter) (21), as well as free radicals (22,23). Because e-cigarettes do not burn tobacco, it has falsely been conjectured that vape pen aerosols contain very low levels of free radicals (which are abundant in cigarette smoke and are well known to suppress the endogenous activation of nitric oxide and lead to endothelial dysfunction, the prime promoter of atherosclerotic cardiovascular disease) (24). However, e-cigarette vaping aerosols do indeed have high levels of free radicals and are not better than cigarettes in this regard.

Current noninvasive tools available for detecting the earliest presymptomatic vascular changes, brought about by endothelial dysfunction, are relatively limited. They are largely US-based and include brachial artery reactivity through flow-mediated dilation (25), aortic pulse-wave velocity (26), and carotid intima-media thickness (27). A few studies demonstrating the effect of tobacco cigarette use on systemic vascular dysfunction in the chronic setting based on advanced imaging techniques have appeared during recent years (28). However, similar work focusing on e-cigarettes is sparse (29–31). Carnevale et al (29) investigated acute effects of both electronic and tobacco cigarettes in both smokers and vapers and in nonsmokers and nonvapers by means of brachial artery flow-mediated dilation. The authors demonstrated a reduction in this parameter overall with both groups pooled as well as in each of the groups, along with a detectable increase in oxidative stress, but the magnitude of the flow-mediated dilation reduction was greater for tobacco cigarettes. Vlachopoulos et al (30) found aortic stiffness measured as carotid-femoral pulse-wave velocity at 30 minutes to be increased comparably following a single episode of smoking cigarettes or vaping e-cigarettes. Both studies involved nicotinized e-cigarettes, so it is unclear whether the effect was caused by aerosol inhalation or the action of nicotine.

Very recently, researchers examined smoking and vaping–naive participants to a battery of quantitative MRI tests (31). Of note, in this study nicotine-free e-cigarette aerosol was inhaled to eliminate potential confounding effects of nicotine (31). These included flow-mediated dilation of the femoral artery (motivated by atherosclerosis being far more common in lower-extremity vessels) and pulse-wave velocity and hyperemic response to upper leg cuff occlusion (measuring both arterial parameters and changes in transient venous hemoglobin saturation by using oxygenated hemoglobin as an endogenous tracer) (Movie E1 [online]) prior and following a single episode of vaping (31). Of note, the e-cigarette brand used contained no nicotine to eliminate potential confounding effects of nicotine. The authors observed highly significant changes before and after vaping (Fig 2) suggestive of transient vascular impairment indicative of endothelial dysfunction, previously found in tobacco cigarette

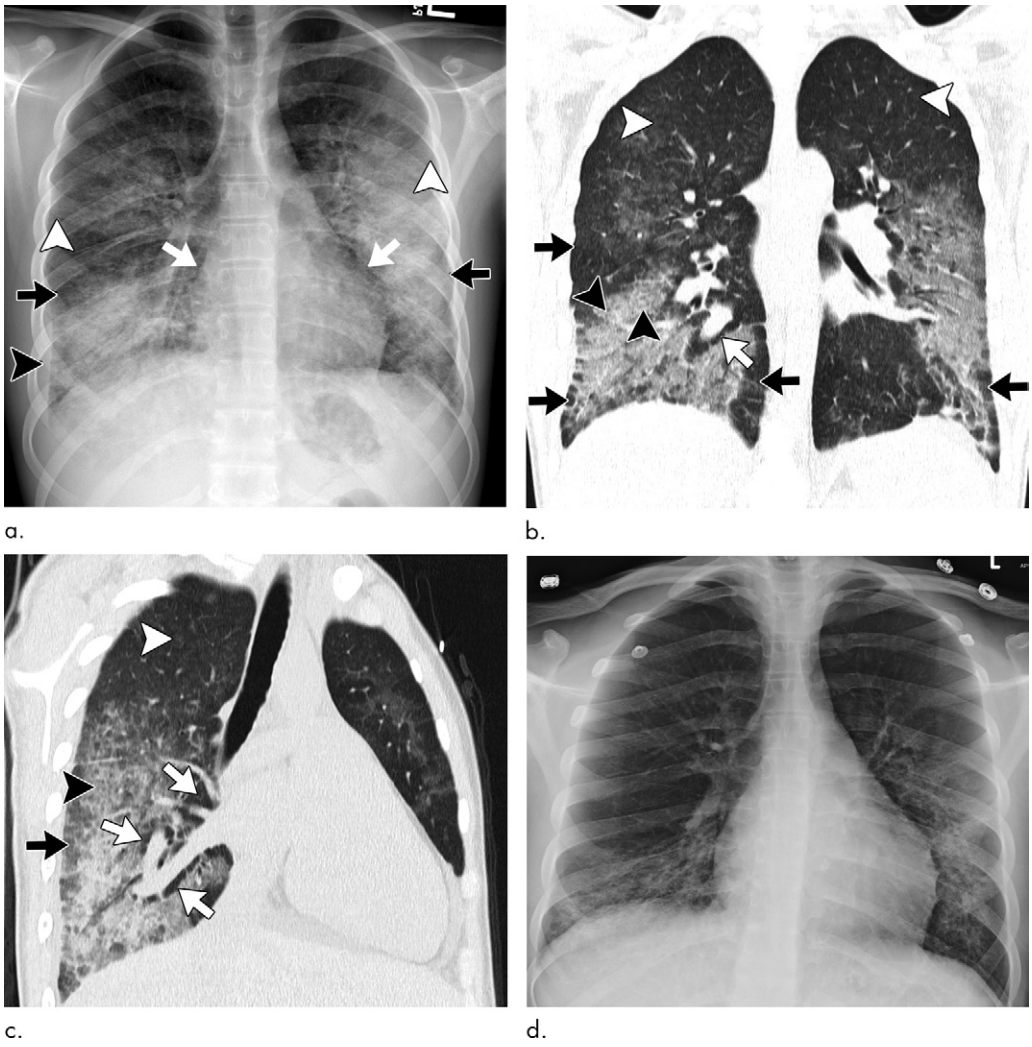


Figure 3: Images show electronic cigarette or vaping product use–associated lung injury with organizing pneumonia pattern secondary to vaping tetrahydrocannabinol in an 18-year-old man. **(a)** Posteroanterior radiograph shows midlung and lower lung consolidation and opacity bilaterally. Small right pleural effusion (black arrowhead) and septal thickening (white arrowhead) are seen. There is conspicuous sparing of cardiac borders (white arrows) as well as subpleural portions of lung (black arrows). **(b)** Coronal and **(c)** sagittal oblique images from CT nicely illustrate radiographic findings with mild and lower lung–predominant ground-glass opacity with few areas of consolidation. Prominent subpleural and perilobular sparing is present (black arrows). In addition, there is conspicuous sparing of peribronchovascular interstitium, best illustrated around larger pulmonary arteries and veins (white arrows). Hazy upper lobe–predominant ground-glass centrilobular nodules are present bilaterally (white arrowheads). In addition to thickening of interlobular septa, there are few areas with thickening of intralobular septa creating "crazy paving" pattern (black arrowheads). **(d)** Three days after initiation of steroids, patient showed dramatic clinical and radiographic improvement.

smokers in comparison to nonsmokers (28). In a parallel article, using the same vaping paradigm and study population, Chatterjee et al (32) found serum markers of inflammation, oxidative stress, and nitric oxide bioavailability to be transiently impaired. It is not currently known what toxins in the well-characterized brand of e-cigarettes caused the observed immune response, a question whose resolution is particularly urgent given the alarming reports of morbidity and death in some e-cigarette users (33).

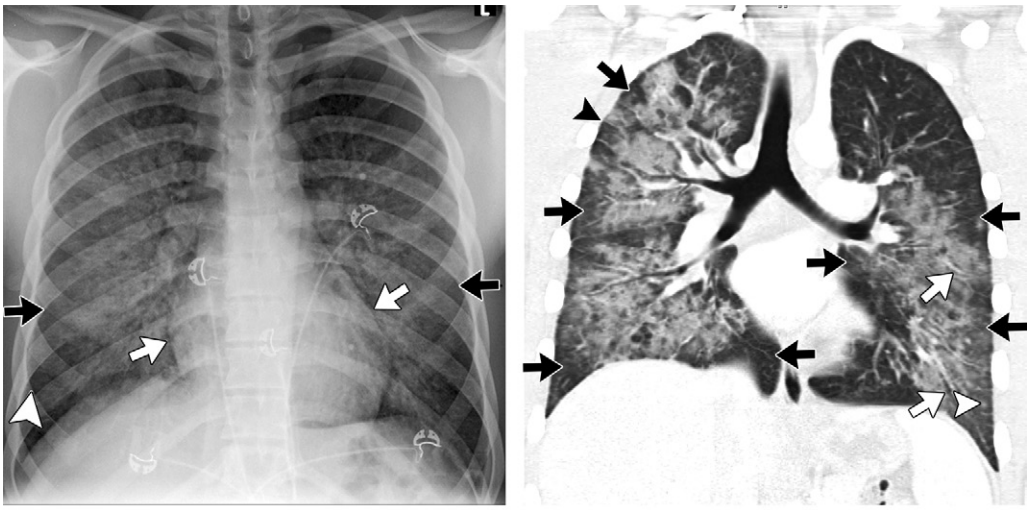
Recently, George et al (34) showed that female cigarette smokers demonstrated improved vascular health when compared with male cigarette smokers within 1 month of switching from tobacco cigarettes to e-cigarettes (34). They measured the changes in vascular function by using flow-mediated dilation (endothelial function) and pulse-wave velocity (vascular stiffness). After 1 month of switching from cigarettes to vaping (with or without nicotine), there was an improvement in vascular stiffness of −0.53 m/sec (95% confidence interval: −0.95, −0.11; $P = .01$) and better endothelial function (linear trend $\beta = .73\%$; 95% confidence interval: 0.41, 1.05; $P < .0001$) (34). Thus, not all physiologic changes are worse with e-cigarettes when compared with cigarette smoking. Why these improvements are seen more often in women than men is not well understood.

Addiction of Nicotine and THC Derivatives

Drug addiction results from complex relationships among pharmacokinetics, pharmacodynamics, learned or conditioned behaviors, environmental and social factors, and genetics (35). Nicotine is particularly addictive because of rapid-onset pleasurable effects from dopamine release (36) and rather rapid onset of withdrawal symptoms on cessation (37). Children and adolescents are particularly prone to developing nicotine addiction compared with adults, with the majority of adult smokers beginning in childhood (35).

Addiction to cannabis is thought to have similar mechanisms as other drugs. THC, which also increases dopamine release, is the likely agent driving addiction, or cannabis use disorder (38). In contrast to tobacco, for which 20%–25% of young people become addicted (39,40), cannabis use disorder develops in about 9% of users (41).

Because the amount of nicotine or THC in e-cigarette solutions varies and may exceed the labeled amount (42), e-cigarette use may increase the risk of addiction. Furthermore,



a. b.

Figure 4: Images show electronic cigarette or vaping product use–associated lung injury with organizing pneumonia pattern in an 18-year-old man who vaped nicotine and tetrahydrocannabinol with fever of 103°F, vomiting for 3 days, and negative workup for infection and rheumatologic disease. **(a)** Posteroanterior radiograph shows perihilar predominant hazy opacity with conspicuous sparing of both heart border (white arrows) and periphery (black arrows). Septal thickening is present (arrowhead). **(b)** Corresponding CT image shows perihilar predominant ground-glass opacity with prominent sparing of subpleural interstitium both peripherally and centrally (black arrows) with intermixed areas of lobular sparing. In addition, there is sparing of peribronchovascular interstitium (white arrows). Septal thickening (black arrowhead) and scattered centrilobular nodules are present (white arrowhead). Patient rapidly improved after administration of steroids.

studies have shown users of e-cigarettes are up to 3.6 times more likely to report traditional cigarette use than are nonusers (43,44).

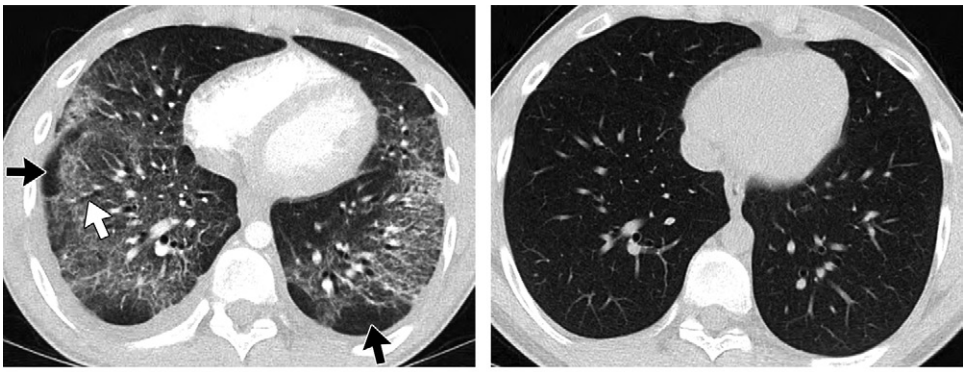
EVALI: Clinical Considerations and Diagnosis

In 2019, physicians, the U.S. Centers for Disease Control and Prevention, or CDC, the U.S. Food and Drug Administration, and state and local health departments identified an outbreak of a respiratory illness in patients with a history of vaping. This disease was associated with lung injury at imaging and histopathologic evaluation and ultimately given the name *e-cigarette or vaping product use–associated lung injury*. From a clinical standpoint, EVALI most often manifests as a relatively acute disease that mimics a viral illness. In a review of 323 patients with EVALI submitted to the CDC, 95% had respiratory symptoms, 77% had gastrointestinal symptoms, and 85% had constitutional symptoms (45,46).

Because these symptoms are nonspecific, these patients are often thought to have an infection, but testing demonstrates no offending pathogen. To date, EVALI remains a diagnosis of exclusion and depends on eliciting a history of vaping (within 90 days of onset of symptoms but preferably more recently), identifying an abnormality at chest imaging, and excluding other potential causes of the patient's symptoms including infections, other exposures, malignancy, and autoimmune disease (47). Given the importance of identifying a pulmonary abnormality at chest imaging, radiologists play an important role in supporting this diagnosis. In cases in which a pulmonary abnormality is not seen or certainly identified at chest radiography, or when further characterization of the chest radiograph findings is needed to evaluate for another potential cause of the patient's symptoms, a noncontrast chest CT can be obtained. However, a CT pulmonary angiogram could be considered in the appropriate clinical setting.

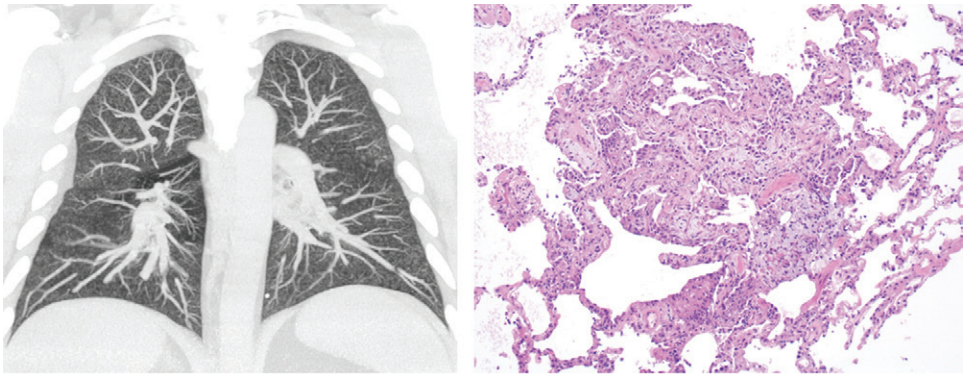
Surprisingly, EVALI has not been reported in Europe. The reason for this is unknown; however, the tobacco market and vaping devices in Europe are tightly regulated by the Tobacco Products Directive. In the United States, as of December 2019, 2506 cases of EVALI with 54 deaths have been reported to the CDC in all 50 states, the District of Columbia, and two U.S. territories (48). EVALI is more common in younger patients, with a median age of 24 years and 79% of reported patients being younger than 35 years (47). Although the number of deaths is small, the available data suggest worse outcomes for older patients, as the median age of deceased patients is 53 years (49). Particularly when recognized in the early stages, most patients with EVALI improve and return to baseline with cessation of vaping, supportive measures, and administration of glucocorticoids (49). Some patients, however, have a more progressive course. In these patients, death can occur due to respiratory failure. If these patients do survive, then EVALI can lead to severe pulmonary scarring and chronic dysfunction, with one recent case requiring bilateral lung transplantation (50). Radiologists are integral in the follow-up of these patients because imaging studies can be used to evaluate for improvement or worsening of the patient's pulmonary disease, in addition to superimposed complications. In addition to organizing pneumonia (OP) and diffuse alveolar damage, other short-term complications of EVALI for the radiologist to be aware of include superimposed infection, bullae formation, and pneumothorax.

In the EVALI cases reported to the CDC, 86% reported using products containing THC, with 34% exclusively using products containing THC. Sixty-four percent of patients reported using products containing nicotine, with 11% exclusively using products containing nicotine (49). These data suggest that while EVALI is more strongly associated with products containing THC, one or more causative agents may be at play. The identification of a causative agent is also problematic given the extensive heterogeneity of compounds in vaping mixtures, the fact that users often cannot report the specific mixtures they vaped, and—particularly in black-market mixtures—components and contaminants are often unknown. Users may also be reluctant to give a complete history of their vaping use in those states where



a. b.

Figure 5: Images show electronic cigarette or vaping product use–associated lung injury with organizing pneumonia pattern in a 20-year-old man who vapes nicotine and tetrahydrocannabinol products daily and who presented to community health clinic with fever, weakness, and chills. He was initially diagnosed with community-acquired pneumonia, but his symptoms continued to progress despite antibiotic therapy. Extensive work-up for infection and rheumatologic disease was negative during hospital admission. **(a)** Axial CT image shows peribronchiolar ground-glass opacity with subpleural sparing both centrally and peripherally (black arrows). Few areas of bronchial dilation are present in areas of ground-glass opacity (white arrow). Bronchoscopic biopsy yielded result of organizing pneumonia. **(b)** Four weeks after initiation of steroid therapy, patient's CT scan was normal.



a. b.

Figure 6: Images show electronic cigarette or vaping product use–associated lung injury in a 32-year-old man with history of vaping who presented with fevers and night sweats for 1 week. **(a)** Coronal maximum intensity projection image shows diffuse centrilobular nodularity. **(b)** Histologic sections of his transbronchial cryobiopsy showed distinctive micronodular pattern of airway-centered organizing pneumonia, corresponding to centrilobular nodularity seen at CT. Similar imaging and pathologic findings have been described in patients with smoke synthetic cannabinoids.

marijuana and/or THC products have not been legalized. Recently, vitamin E acetate was isolated from 29 of 29 bronchoalveolar lavage specimens submitted to the CDC from patients with EVALI, but its role in the pathogenesis is still under investigation (51). This finding could be related to confirmation bias, wherein an inert substance (vitamin E) is blamed for being the causative agent, but is merely associated with another agent(s) that were not found at the initial toxicologic evaluation of the bronchoalveolar lavage material (eg, a so-called red herring).

Improved Understanding

Given that many patients who meet the clinical criteria for EVALI do not require a lung biopsy, it is imaginable that the pathologic understanding of EVALI has lagged. Early reports suggested that a variety of pathologic patterns of injury and inflammation could be encountered in EVALI, including OP (52,53), diffuse alveolar damage (DAD) (46), diffuse alveolar hemorrhage (54), mild nonspecific inflammation (46), granulomatous pneumonitis (46), exogenous lipoid pneumonia (ELP) (55), and respiratory bronchiolitis (56). However, many of these early reports did not include illustrations of the pathologic findings, and the patient reported to have respiratory bronchiolitis was also a cigarette smoker (56), an important confounder.

Similarly, described imaging patterns of lung injury due to vaping included OP (52,53), DAD (46), acute eosinophilic pneumonia, (57), diffuse alveolar hemorrhage (54), hypersensitivity pneumonitis (HP) (58), ELP (59), and giant cell interstitial pneumonia (60). With an increasing number of cases and the publication of larger pathologic studies (61,62), both the radiologic and pathologic understanding of EVALI has improved. In most cases, both the imaging and pathologic findings of EVALI are that of OP and DAD, with acute eosinophilic pneumonia and diffuse alveolar hemorrhage being less common.

Some of the previously suggested mechanisms described in vaping-related lung disease still have an unclear role or are thought to be rare associations with vaping that are not typical of EVALI. For example, although imaging patterns of HP in vapers has been described, to date, to our knowledge, no biopsy-confirmed cases have been described. In cases of presumed ELP, both pathologic and radiologic findings are atypical for the classically described entity. Therefore, inclusion of HP and ELP into the spectrum of EVALI is controversial and will be discussed separately below. The case of vaping-related giant cell interstitial pneumonia was related to cobalt found in the patient's vape pen (59). Because giant cell interstitial pneumonia is a chronic process that occurs over months to years, it should not be categorized as EVALI.

Patterns of Lung Injury

OP and DAD.— OP and DAD are common pathologic patterns of acute lung injury (62). Whereas the imaging pat-

terns associated with the pathologic finding of OP are numerous and variable, ranging from a focal nodule to diffuse ground-glass opacity (63), the pattern of OP encountered in EVALI appears to be less heterogenous. At chest radiography, patients often present with diffuse hazy opacity that is most pronounced centrally, although there is usually conspicuous sparing of the heart border and subpleural portions of the lung (Figs 3, 4). Both upper lung, midlung, and lower lung–predominant abnormality can occur. Kerley B lines due to septal thickening can be seen. Radiographic findings often mirror what is seen at CT with diffuse ground-glass opacities, which are often bilateral and relatively symmetric. If present, then consolidation is usually mild. An extremely common finding is subpleural sparing that is seen both centrally and peripherally, as well as areas of lobular sparing (Figs 3, 4) (46,53,59,60). In addition, in some cases there is pronounced sparing along the peribronchovascular interstitium (Figs 3, 4). Interlobular septal thickening is common, and in some instances associated with intralobular lines creating a "crazy paving" pattern (Fig 3) (64). The reverse halo and atoll signs are highly suggestive of OP, although in our experience this is not a common finding in EVALI (but has been observed). Once the diagnosis of EVALI is suspected, most patients with this pattern of injury rapidly improve after corticosteroids are initiated (Figs 3, 5) (47).

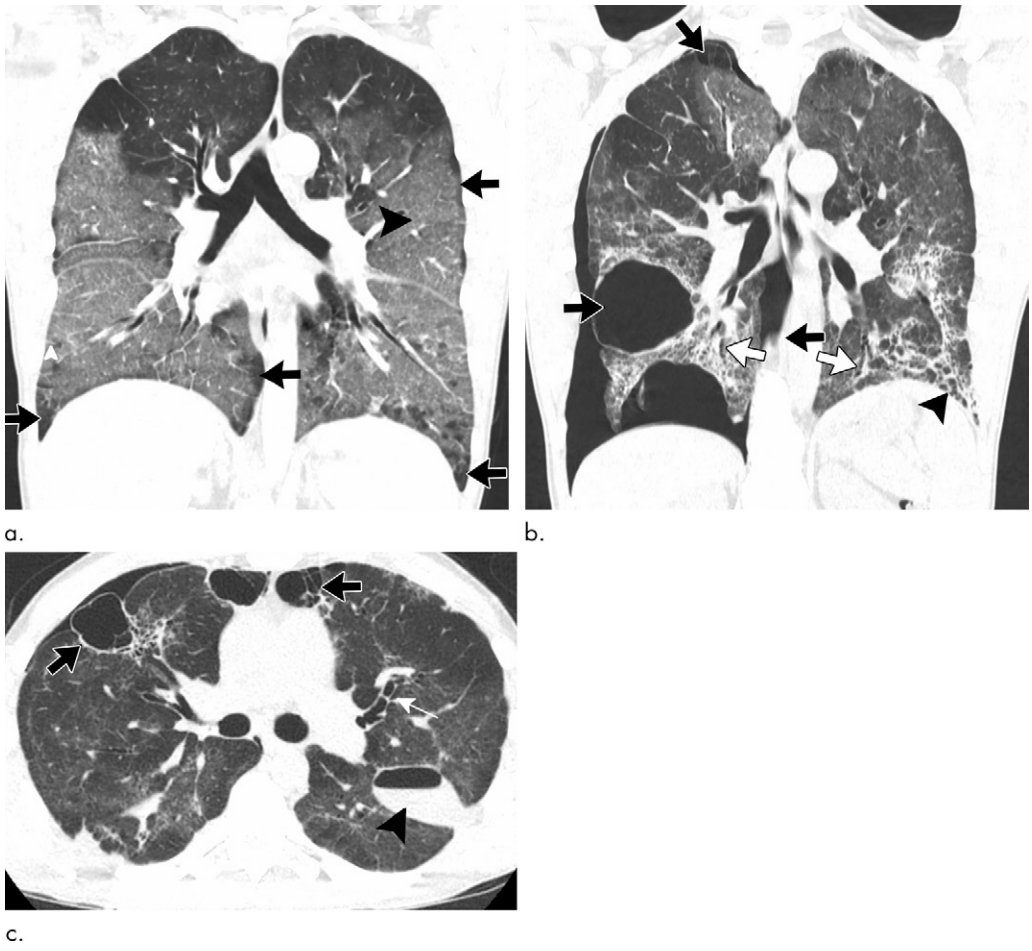


Figure 7: Images show electronic cigarette or vaping product use–associated lung injury in a 37-year-old man with history of vaping tetrahydrocannabinol products daily. **(a)** Coronal CT image shows diffuse ground-glass opacity with subpleural sparing (arrows) and interlobular and intralobular septal thickening creating "crazy paving" pattern (arrowhead). At initial CT, it is unclear whether this represents organizing pneumonia or early exudative phase of diffuse alveolar damage. Patient's condition dramatically worsened with progressive consolidation and volume loss requiring intubation. **(b)** Coronal and **(c)** axial CT images 14 days after initial study show improvement of ground-glass opacity with interval development of lower lobe–predominant fibrosis with reticulation (black arrowhead in **b**), bronchiectasis (white arrows), and volume loss. Additionally, there has been development of numerous bullae of varying sizes bilaterally (black arrows), moderate-size right pneumothorax, and loculated hydropneumothorax along left major fissure (black arrowhead). (Images courtesy of Tan-Lucien Mohammed, MD, Professor of Radiology, University of Florida.)

Centrilobular nodules are a common finding in EVALI and likely reflect the bronchiolocentric distribution of injury. If present, then they are often a relatively minor finding and tend to be upper lobe predominant, similar to other inhalational injuries (65). Possible etiologies for the centrilobular nodules include airway-centered foci of OP, pulmonary hemorrhage, or even a hypersensitivity reaction, as discussed below. However, in a minority of cases of EVALI, centrilobular nodularity is the dominant finding (Fig 6). An almost identical pattern has been described with synthetic cannabinoid pulmonary injury (66). In both synthetic cannabinoid injury and this subset of EVALI cases, the diffuse centrilobular nodularity corresponds to airway-centered OP at pathologic analysis. There are various possible explanations. The similarities may be related to the size of the inhaled or aerosolized particles. Alternatively, a recent discovery that some black-market vape pens are "spiked" with synthetic cannabinoid may provide another plausible explanation (67). It should also be noted that this pattern of lung injury may be radiologically indistinguishable from excipient lung disease, also termed *intravenous talcosis*, which occurs when particulates from intravenously injected crushed oral tablets embolize into pulmonary arterioles causing a granulomatous reaction (68). Findings of pulmonary hypertension and/or right heart strain (ie, right ventricle enlargement, pulmonary artery dilation) may help to differentiate excipient lung disease. Regardless whenever this diffuse centrilobular

nodular pattern is encountered, a detailed drug use history should be obtained.

Compared with OP, the imaging findings in patients with DAD often reflect the greater severity and extent of the pulmonary injury. These patients are extremely ill and frequently will require ventilatory support or even extracorporal membrane oxygenation. During the acute exudative phase of DAD, both chest radiography and CT commonly show volume loss with lower lobe–predominant consolidation and ground-glass opacity. Similar to OP, septal thickening or a crazy paving pattern can be present (Fig 7). As the injury progresses to the organizing phase, volume loss, reticulation, and bronchial dilation increase (Fig 8) (63). Although the extent of injury is more severe in DAD, the imaging appearances and clinical course of OP and DAD can overlap. In patients with EVALI who demonstrate a progressive course, areas of organizing DAD can evolve on a background of OP. As such, radiologists need to describe findings of developing organizing DAD because they are often reflective of an underlying worsening degree of injury that may require mechanical ventilation or extracorporeal oxygenation (11,62).

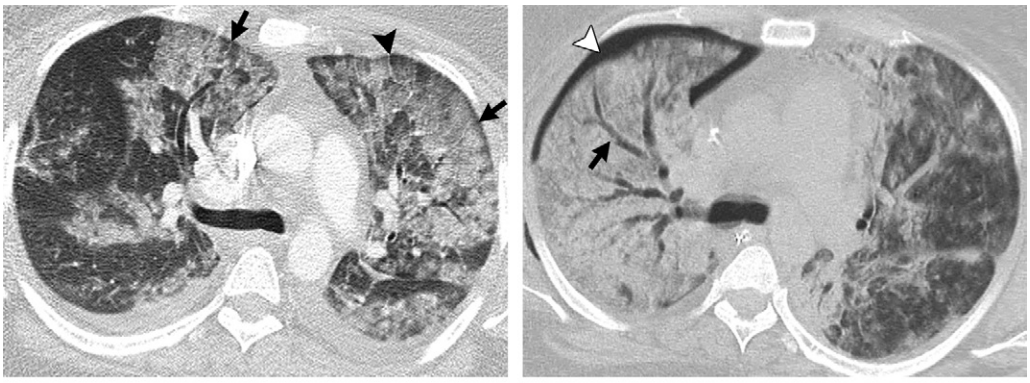


Figure 8: Images show electronic cigarette or vaping product use–associated lung injury with diffuse alveolar damage pattern in a 35-year-old woman who vaped tetrahydrocannabinol. Work-up for infection and rheumatologic disease was negative. **(a)** Axial CT scan shows ground-glass opacity, left greater than right, with areas of consolidation. Subpleural and perilobular sparing is present (arrows). Septal thickening is present (arrowhead). **(b)** CT scan 2 weeks later shows extensive right lung consolidation with areas of bronchial dilation (arrow) and internal development of right pneumothorax (arrowhead). Ground-glass opacity in left lung has improved with residual centrilobular nodularity. Patient died 5 days later.

Several recent pathologic studies have detailed the spectrum of

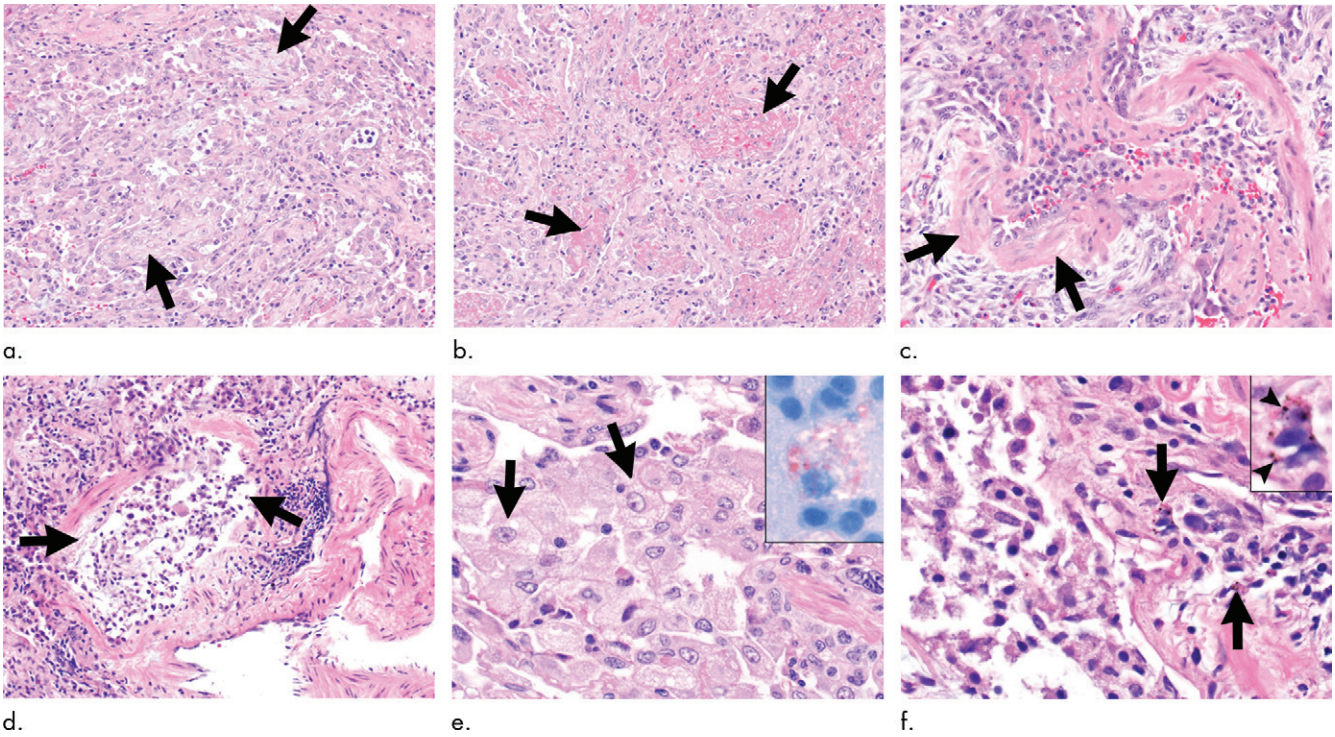


Figure 9: Images show histopathologic findings of vaping-associated lung injury. Representative photomicrographs of lung biopsies from patients with electronic cigarette or vaping product use–associated lung injury show variety of acute injury patterns including **(a)** organizing pneumonia (arrows), **(b)** acute fibrinous pneumonitis with balls of intra-alveolar fibrin (arrows), and **(c)** diffuse alveolar damage with hyaline membranes (arrows). Other common findings include **(d)** bronchiolitis with bronchiolar mucosal ulceration (arrows) and **(e)** accumulation of foamy lipid-laden macrophages in alveolar spaces (arrows) that can be detected in bronchoalveolar lavage fluid with Oil-Red-O lipid stain (inset image). **(f)** Occasional scattered macrophages (arrows) may also contain brown or black pigmented particles (arrowheads, inset image) in some cases, which can be a helpful clue particularly when patient is a nonsmoker.

Table 1: Summary of Histopathologic Features in Vaping-associated Lung Injury

Feature	Cases
Injury pattern(s)	
Organizing pneumonia	19/25 (76)
Acute fibrinous pneumonitis with organization	12/25 (48)
Diffuse alveolar damage, acute and organizing	6/25 (24)
Other histologic features	
Foamy or vacuolated macrophages	21/25 (84)
Foamy or vacuolated pneumocytes	17/17 (100)
Intra-alveolar fibrin	22/25 (88)
Bronchiolitis	7/9 (78)
Bronchiolar mucosal ulceration	6/9 (67)
Interstitial edema	11/17 (65)
Neutrophilic inflammation	10/25 (40)
Chronic interstitial inflammation	14/25 (56)
Pigmented macrophages	7/17 (41)
Eosinophils, rare	7/25 (28)
Granulomas	0/25 (0)
Exogenous lipoid pneumonia	0/25 (0)

Note.—Based on two largest reported series of patients with lung biopsies. Numerators are the number of cases with the feature and denominators are the total number of cases, with percentages in parentheses. Source.—References 61, 62.

histopathologic changes seen in EVALI, providing greater insight into this problem and the potential mechanism(s). The first systematic review of the histologic features of EVALI revealed a spectrum of pathologic patterns of acute lung injury in lung biopsies from 17 patients at various stages of organization and repair, including DAD, acute fibrinous pneumonitis, and OP (61). These findings were corroborated by a second series of eight patients with EVALI published more recently by an independent group of pathologists (62), who observed nearly identical histopathologic changes in lung biopsies including accumulation of foamy macrophages but no evidence of ELP. This is not surprising, because the lung has a relatively limited repertoire of responses to acute injury regardless of cause, and the histopathologic findings of acute lung injury depend largely on the timing of the biopsy relative to the time of injury and the relative severity thereof.

Most biopsies in patients with EVALI have shown injury accentuated around small airways with bronchiolitis, a common finding in inhalational lung injuries. More notably, all biopsies revealed prominent accumulation of finely vacuolated macrophages in airspaces and cytoplasmic vacuolization of pneumocytes. These are nonspecific findings, but they are characteristic of toxic exposures and closely resemble what is seen with amiodarone toxicity or noxious chemical fume exposures, where increased surfactant turnover and impaired removal due to epithelial injury lead to intracytoplasmic accumulation of surfactant and foamy cytoplasmic change. The striking histologic similarity of EVALI to these other forms of toxic injury is intriguing and suggests a similar mechanism, which is further supported by work in an animal model of vaping (69). Representative histopathologic findings in EVALI are illustrated in Figure 9, and the spectrum of histologic findings in these two studies is summarized in Table 1.

Acute eosinophilic pneumonia.—Acute eosinophilic pneumonia is an acute lung injury that pathologically manifests as a combination of DAD with interstitial and alveolar eosinophils (70). Eosinophilic degranulation exacerbates this injury by increasing vascular permeability causing edema within the alveolar spaces, alveolar walls, and interstitium (71). Although there are numerous causes of acute eosinophilic pneumonia, it is highly associated with patients who have started smoking or have changed their smoking habits (72,73). Given this association, its occurrence in EVALI is not surprising, although in the authors' experience it is much less common than are the OP and DAD patterns (57,59). At CT, acute eosinophilic pneumonia usually manifests with bilateral and often symmetric ground-glass opacity, consolidation, or both, and can have a similar imaging appearance to DAD and OP. However, due to the increase in vascular permeability, acute eosinophilic pneumonia should be included in the differential diagnosis when there are superimposed findings of fluid overload, such as pleural effusions and prominent septal thickening, in the absence of left heart dysfunction (Fig 10) (70). Acute eosinophilic pneumonia can be a difficult radiologic and clinical diagnosis because peripheral eosinophilia is often absent at presentation. The disease can be confirmed when the following clinical criteria are met: duration of acute febrile illness of fewer than 5 days, progression to hypoxemic respiratory failure, abnormal finding at chest imaging, bronchoalveolar lavage eosinophils exceeding 25%, prompt response to steroid therapy, and absence of underlying infection (73).

Pulmonary hemorrhage.—Diffuse alveolar hemorrhage has been reported with vaping (54,60). Patients with diffuse alveolar hemorrhage typically present with recent onset of cough, fever, and dyspnea. Hemoptysis, although common, may be absent in up to one-third of patients. Findings on chest radiographs include focal or diffuse airspace opacities that can be unilateral or bilateral, but is often more asymmetric than what is seen with OP and DAD patterns. Imaging findings in diffuse alveolar hemorrhage at CT are often nonspecific and include consolidation and ground-glass opacity that can spare the lung periphery (Fig 11a). Nodules, often in a centrilobular or tree-in-bud configuration, can be seen when blood products are aspirated or retained in distal bronchioles (Fig 11b). Over time, septal thickening becomes more pronounced as macrophages clear blood products. Sequential bronchoalveolar lavage with persistent or increasingly bloody aliquots confirms the diagnosis.

Controversies

Exogenous lipoid pneumonia.— ELP is an inflammatory response to inhaled or aspirated lipids and can be due to a wide range of substances including laxatives, petroleum-based lubricants, ophthalmic drops, mineral oils, and hydrocarbons

(74). In most cases, ELP is a chronic process where impairment of the normal mucociliary clearance mechanisms leads to failure to clear exogenous lipid, secretions, and other cellular debris. Patients are often asymptomatic or mildly symptomatic (74). Acute presentations of ELP do occur and patients can present with low-grade fever, cough, and dyspnea. In both settings, imaging often shows a lower lobe–predominant pattern of abnormality with consolidation and ground-glass opacity with or without septal thickening. Rarely, ELP can appear as spiculated nodules and mimic malignancy. The diagnosis can be made when there are areas of macroscopic fat attenuation (less than −30 HU) within the consolidation or nodules at CT, a finding which is present in most, but not all, of acute and chronic cases (73,74).

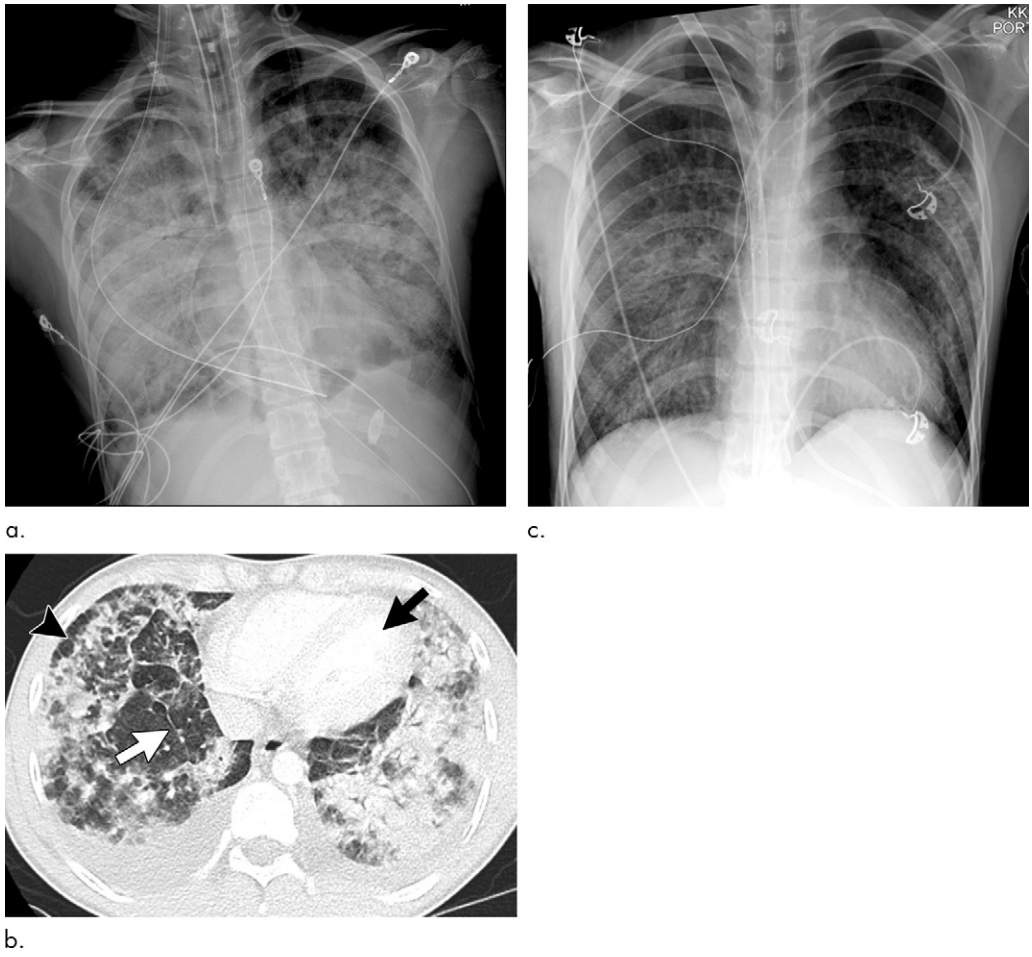
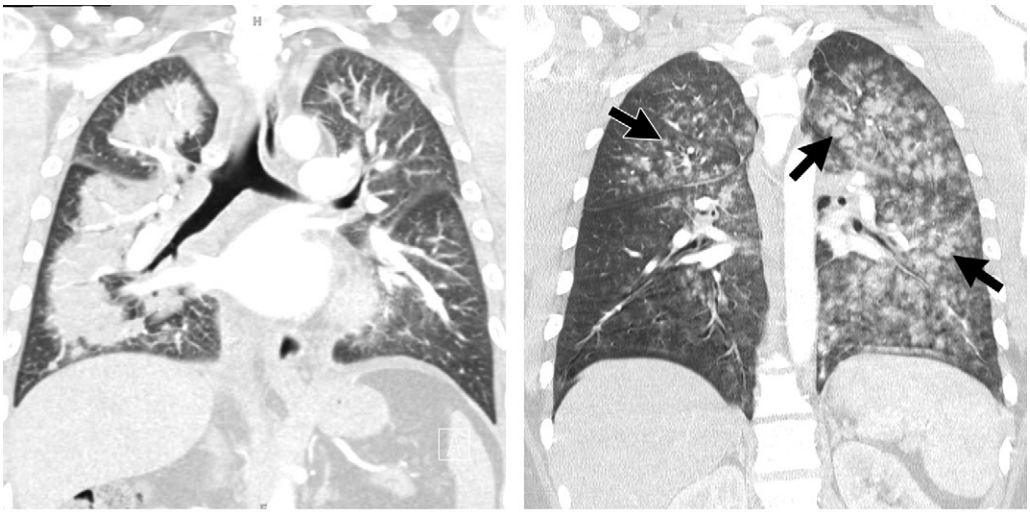


Figure 10: Images show electronic cigarette or vaping product use–associated lung injury secondary to acute eosinophilic pneumonia in a 21-year-old man who had been vaping nicotine and tetrahydrocannabinol products daily. **(a)** Posteroanterior radiograph 2 days after admission shows extensive consolidation. **(b)** Although imaging findings are often nonspecific, presence of extensive consolidation with areas of lobular and subplerual sparing (black arrowhead), such as that seen with diffuse alveolar damage, with associated prominent septal thickening (white arrow), moderate to large bilateral plerual effusions, and normal appearing left ventricle (black arrow), should raise possibility of acute eosinophilic pneumonia. Clinical diagnosis is also difficult because peripheral eosinophils are often not elevated until many days after start of symptoms. Patient's clinical condition and radiographic imaging continued to worsen and he was subsequently started on extracorporeal membrane oxygenation. Patient subsequently underwent bronchoscopy, which showed large percentage of eosinophils. **(c)** Three days after initiation of steroids, chest radiograph has significantly improved. (Images courtesy of Howard Mann, MBBCh, Professor of Radiology, University of Utah.)

In a recent press release, the CDC reviewed bronchoalveolar lavage specimens from 29 patients with EVALI from 10 states (51). All 29 patients had vitamin E acetate, which is a lipid, in their bronchoalveolar lavage fluid. These findings have generated much enthusiasm among physicians, but the reported histopathologic findings in EVALI suggest that more caution is warranted. In addition to the strong association with vitamin E acetate, many studies describe lipid-laden macrophages in pulmonary fluid amd tissue that stain positive with Oil-Red-O, a dye used to stain lipids (76,77). It is well recognized that Oil-Red-O–positive lipid-laden macrophages in bronchoalveolar lavage fluid are nonspecific and can be seen in various forms of lung injury (78,79). In addition, a recent study (69) showed that chronic e-cigarette exposure alters lipid homeostasis in mice and may lead to both increased intracellular and extracellular propylene glycol and vegetable glycerin, contributing to an increase in Oil-Red-O staining in EVALI.

Whether the lipid-laden macrophages are filled with vitamin E acetate or other lipid is unknown at this point. Additionally, it is unclear if one or more lipid substances, such as vitamin E acetate or byproducts produced by heating, are acting as a toxin or if lipids are simply a marker of exposure. The histopathologic changes in EVALI suggest that there is more to the story than simply lipid accumulation in the lung, and to date, to our knowledge, no reported cases have shown histologic evidence of exogenous lipoid pneumonia as this disorder is classically defined. Therefore, until more data accumulate, these findings alone should not be relied on to make the diagnosis of EVALI without additional evidence.

There are other inconsistencies with accepting EVALI as a type of ELP. First, the mechanics of the injuries are different, as EVALI is secondary to the superheating and aerosolization of a chemical cocktail usually containing lipids causing an acute inhalational lung injury. Second, even in cases of acute ELP, symptoms are usually mild and patients recover with supportive therapy (74), whereas there have been multiple deaths associated



a. b.

Figure 11: Images show electronic cigarette or vaping product use–associated lung injury presenting as diffuse alveolar hemorrhage. **(a)** Coronal CT in a 41-year-old man who makes his own nicotine flavoring and vapes more than 50 times a day shows asymmetric consolidation on right greater than left. Subpleural sparing is present. **(b)** Coronal CT image in a 21-year-old man who vapes nicotine and tetrahydrocannabinol products show asymmetric, left greater than right, large "fluffy" centrilobular nodules filling much of secondary lobule (black arrows), and appearance commonly seen with pulmonary hemorrhage. This degree of asymmetric consolidation and/or nodularity would be atypical for organizing pneumonia or diffuse alveolar damage. Diffuse alveolar hemorrhage was confirmed with bronchoalveolar lavage in both cases.

with EVALI (47). Third, the imaging findings in these cases of EVALI with lipid-laden macrophages mirror those seen in the classic forms of acute lung injury (OP, DAD, acute eosinophilic pneumonia) and to date, to our knowledge, no case has shown areas of fat attenuation at CT (Fig 12). Therefore, although some cases are being labeled as ELP, it does not appear to be so from a radiologic or pathologic perspective.

Hypersensitivity pneumonitis.—Acute HP is uncommon and occurs when a genetically susceptible individual inhales a large dose of a specific antigen leading to an immunologic response dominated by a type III hypersensitivity reaction (80). Patients develop fever, malaise, cough, and dyspnea within a few hours of exposure, often mimicking infection. Symptoms often rapidly improve after removal of the antigen, and in severe cases, the initiation of systemic steroids. Although biopsy is rarely performed, a bronchiolocentric pattern of disease with superimposed findings of acute lung injury is often encountered (80,81). Typical imaging findings suggestive of an acute HP pattern include symmetric upper lung–predominant centrilobular nodules, which are often poorly defined. Ground-glass opacity and consolidation can be present in the midlung and lower lung zones (82); superimposed septal thickening may be present due to areas of pulmonary hemorrhage or edema (81,83).

Patients with the more commonly seen subacute and chronic forms of hypersensitivity pneumonitis present with symptoms that develop over weeks to months from prolonged exposure to smaller antigen loads. Imaging findings are similar to acute HP, although consolidation is usually absent and the degree of ground-glass opacity in the lower lung is less pronounced. These forms of HP are also classically associated with mosaic attenuation and air trapping due to small airway injury. As the disease progresses, overt honeycombing with or without fibrosis can develop (84).

In the literature, acute HP from vaping has been described in a case report (58). No imaging was shown but the description of the imaging (dependent consolidation with septal thickening and bilateral pleural effusions), normal left ventricular function on echocardiogram, 22% eosinophils at bronchoalveolar lavage, and rapid decompensation with quick improvement after steroid initiation are suggestive of acute eosinophilic pneumonia. However, the authors have encountered cases with typical imaging findings of both acute HP and subacute HP (Fig 13) with expected clinical improvement after antigen removal and steroid initiation. However, to date, no cases have pathologic confirmation; therefore, it is unclear whether the centrilobular nodules in these cases represent the sequela of a hypersensitivity reaction, foci of organization around injured respiratory bronchioles (as discussed above), or other etiologies (59,60,66). If pathologic confirmation does occur, then HP may be incorporated into the imaging spectrum of EVALI.

Preliminary Evidence for the Deleterious Longitudinal Effects of Vaping

We are beginning to understand that vaping induces pulmonary inflammation (85–87), affects endothelial function (31), and causes coronary artery vascular dysfunction (88). A longitudinal analysis of e-cigarette use was recently published (89) showing that there is a higher incidence of self-reported respiratory disease in users of e-cigarettes than in nonsmokers and that the combined use of cigarettes and e-cigarettes was worse for lung health than either alone. This same research group has also studied the effects of e-cigarettes on the incidence of myocardial infarction (90), They found that after adjusting for cigarette smoking, demographic variables, and clinical variables, the everyday use (adjusted odds ratio, 2.25; 95% confidence interval: 1.23, 4.11) and someday use (adjusted odds ratio, 1.99; 95% confidence interval: 1.11, 3.58) of e-cigarettes were both independently associated with increased odds of having had a myocardial infarction (90). They also found a significant dose response for this relationship for this effect ($P < .0005$) (eg, more e-cigarette use was associated with even higher rates of myocardial infarction) (90). The odds ratio for myocardial infarction in those with a history of daily dual use of both products (cigarettes and e-cigarettes) was much

higher (odds ratio, 6.64) than in those individuals who never used e-cigarettes (90). The authors make an important conclusion to their publication: "(The) effect(s) of e-cigarettes are similar (to) conventional cigarette(s) and (the) dual use of e-cigarettes and conventional cigarettes … is risker (for myocardial infarction) than using either product alone" (90).

In addition, in a second population study, e-cigarette use was associated with an increased risk of myocardial infarction and stroke compared with nonsmokers (91). These early longitudinal data strongly suggest that vaping is not necessarily a safer alternative to cigarette smoking.

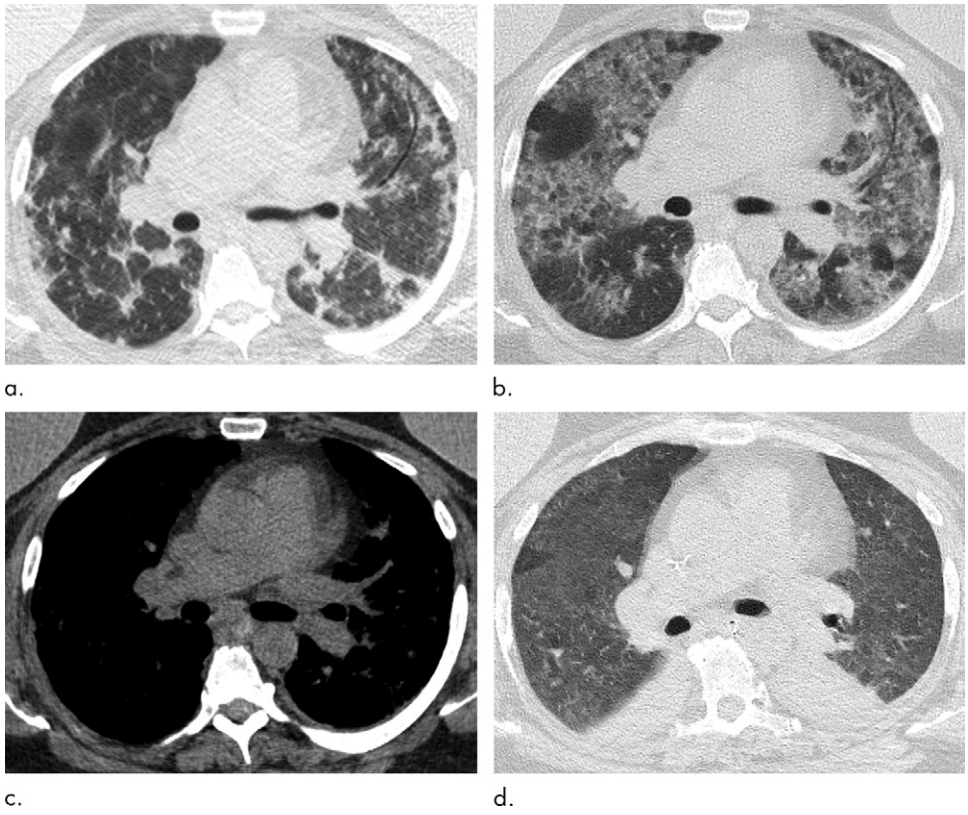


Figure 12: Images show multiple episodes of electronic cigarette or vaping product use–associated lung injury due to repeated vaping of nicotine with mint flavoring in a 51-year-old woman. Bronchoalveolar lavage (BAL) fluid showed numerous foamy lipid-laden macrophages with positive Oil-Red-O lipid staining. **(a)** CT in September shows organizing pneumonia pattern with scattered areas of ground-glass opacity with subpleural sparing. Work-up for infection was negative, and patient was started on steroids and improved. **(b)** Two months later, patient returned to emergency department with dyspnea and fever. CT image shows more extensive ground-glass opacity with areas of lobular and subpleural sparing. Interlobular and intralobular septal thickening is present, creating "crazy paving" pattern. **(c)** Although patient's BAL fluid showed many lipid-laden macrophages, soft-tissue image shows no evidence of intraparenchymal fat attenuation, a common finding in lipoid pneumonia. Patient's condition deteriorated, and she was intubated and started on steroids. **(d)** Ten days after initiation of steroids, ground-glass opacity has improved but persists. Patient's condition was complicated by aspiration pneumonia and bilateral lower-lobe collapse.

Future Discoveries

The current data about EVALI are preliminary. At this juncture, what we do not know far exceeds what we do know, and numerous questions remain unanswered (Table 2). We can, however, begin to develop a strategy for scientifically learning about the effects of vaping using methods derived from inhalational toxicology and experimental pathology, and additional observations in human patients. As the deleterious effects of vaping become better understood, legal and legislative remedies may be necessary, which are beyond the scope of this article (92). It is also unknown if vaping will be associated with the same inflammatory and fibrotic lung diseases typically caused by smoking. For instance, no cases of respiratory bronchiolitis, desquamative interstitial pneumonia, or pulmonary Langerhans cell histiocytosis have been described in people who only use e-cigarettes. Although one case of pathologically proven giant cell interstitial pneumonia has been described (60), it is unclear if vaping will be associated with idiopathic pulmonary fibrosis, where the majority of patients have a history of smoking.

The long-term effects of vaping on the body are even less clear. Chronic obstructive pulmonary disease, fibrosis, cancer, cardiovascular disease, and the numerous other causes of morbidity and mortality secondary to cigarette smoking often take decades to develop; it is unclear if they will develop in e-cigarette users, and if so, to what degree.

Conclusion

Electronic cigarettes, often touted as a safer alternative to traditional cigarettes, have proven to have unexpected deleterious health consequences. Electronic cigarette or vaping product use–associated lung injury (EVALI), characterized primarily by acute lung injury consisting of histopathologic and imaging patterns of organizing pneumonia, diffuse alveolar damage, or both, has emerged as a serious and sometimes fatal complication of vaping. Despite ongoing investigations by local, state, and federal public health officials, the exact cause(s) and mechanism(s) of EVALI remain unclear. What is currently known is that most patients are young adult and adolescent males and more than 80% report vaping tetrahydrocannabinol (THC) or compounds containing cannabidiol. Given the almost infinite combinations of devices, unknown or loosely regulated compounds in vaping liquids, and alterations to delivery systems, pinpointing the exact cause(s) of EVALI has been challenging.

Beyond these potential acute effects of vaping, long-term health effects are also a concern. Nicotine and THC addiction, cardiovascular disease, and chronic pulmonary injury are all potential sequelae of electronic cigarette use and are of particular concern in the predominantly younger population that engages in the practice of vaping. Studies with long-term follow-up will be needed to evaluate for these conditions and others, including malignancies, that may require longer-term vaping exposure to develop.

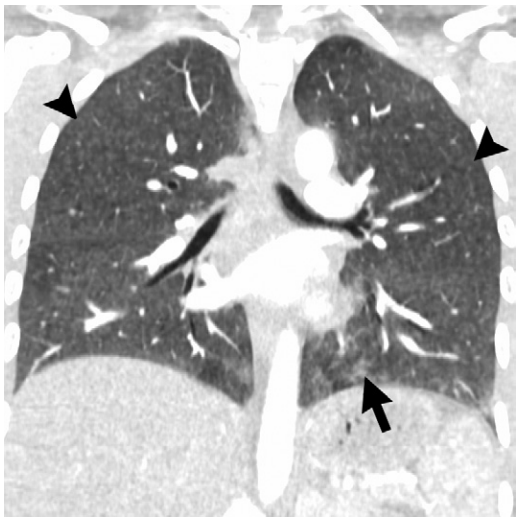


Figure 13: Coronal image shows hypersensitivity pneumonitis (HP) pattern in a 35-year-old man who vaped tetrahydrocannabinol products. Extensive hazy centrilobular nodularity (arrowheads) is most pronounced in midlung and upper lung zones consistent with inhalational injury. Mild ground-glass opacity is present as bases (arrow). This imaging pattern is commonly seen in HP. Patient's condition rapidly improved after steroid administration and no biopsy was obtained. Although authors have seen a few cases with HP pattern, there are no cases in literature with pathologic confirmation. Other possible etiologies for diffuse pattern of centrilobular nodules in electronic cigarette or vaping product use–associated lung injury includes airway-centered foci of organizing pneumonia.

Radiologists must be aware of the clinical manifestations and imaging findings of electronic cigarette or vaping product use–associated lung injury (EVALI) and should consider these when interpreting and reporting imaging studies of patients who present with acute respiratory illnesses or distress. Although the imaging findings of EVALI overlap with other causes for similar patterns of acute lung injury, in the correct clinical context, radiologists can strongly suggest EVALI as a consideration. Therefore, when imaging findings suspicious for EVALI are found, direct communication with treating physicians is recommended to ensure that EVALI is considered as a potential diagnosis; this will help to ensure rapid diagnosis and the prompt institution of appropriate therapy.

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References

1. Geller M. E-cigs a 'consumer-driven' revolution born from a bad dream. https://www.reuters.com/article/us-ecigarettes-inventor/e-cigs-a-consumer-driven-revolution-born-from-a-bad-dream-idUSKBN0OP1YV20150609. Published 2015. Accessed November 1, 2019.

Table 2: Some Unanswered Questions regarding How Vaping and Host-related Factors May Affect Electronic Cigarette or Vaping–associated Lung Injury

Vaping-related Factors	Host-related Factors
Understanding the chemical composition of current commercial vaping liquids and how the composition changes with thermal excitation, subsequent inhalation, and reaction with pulmonary tissue	Overall lung health and cardiopulmonary reserve
Maximum and minimum temperature of the heating filament and how this changes with varying inspiration by the user	Immune response to the vaping gas
Nature of black-market and bootleg vaping liquids	Activity level of host macrophages for cleaning up damaged respiratory epithelium
Effect of mixed use of nicotine and marijuana vaping liquids	Intrinsic bronchial pathology (eg, asthma, cystic fibrosis, and mycobacterial infection)
Effects of variable but often high nicotine concentrations in vaping fluid	How long-term use will affect lung function and to what degree permanent lung destruction will occur
Stability and integrity of the vaping filament over time (ie, will metal particles break off into the inhaled vaping gas)	Level of addiction, frequency of use, and depth of inspiration
Effect of vaping liquid on lung repair	How to evaluate usage comparable to pack-years used for cigarette smoking
Particle size is affected by vaping filament temperaPtures	Vasoactive smaller particles may gain direct entry to the bloodstream at the alveolus and are not filtered out by mucociliary clearance

2. Cummings KM, Dresler CM, Field JK, et al. E-cigarettes and cancer patients. J Thorac Oncol 2014;9(4):438–441.
3. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation 2014;129(19):1972–1986.
4. Jones L. Vaping: How popular are e-cigarettes? https://www.bbc.com/news/business-44295336. Published 2019.
5. Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the Field: Use of Electronic Cigarettes and Any Tobacco Product Among Middle and High School Students - United States, 2011-2018. MMWR Morb Mortal Wkly Rep 2018;67(45):1276–1277.
6. Miech R, Johnston L, O'Malley PM, Bachman JG, Patrick ME. Adolescent Vaping and Nicotine Use in 2017-2018 - U.S. National Estimates. N Engl J Med 2019;380(2):192–193.
7. United States. Public Health Service. Office of the Surgeon General, National Center for Chronic Disease Prevention and Health Promotion (U.S.). Office on Smoking and Health. E-cigarette use among youth and young adults: a report of the Surgeon General. Rockville, MD, Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General; U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. http://www.ncbi.nlm.nih.gov/books/NBK538680/. https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_508.pdf. Published 2016. Accessed November 3, 2019.
8. Floyd EL, Queimado L, Wang J, Regens JL, Johnson DL. Electronic cigarette power affects count concentration and particle size distribution of vaping aerosol. PLoS One 2018;13(12):e0210147.
9. Olmedo P, Goessler W, Tanda S, et al. Metal Concentrations in e-Cigarette Liquid and Aerosol Samples: The Contribution of Metallic Coils. Environ Health Perspect 2018;126(2):027010.
10. Robinson RJ, Hensel EC, Morabito PN, Roundtree KA. Electronic Cigarette Topography in the Natural Environment. PLoS One 2015;10(6):e0129296.
11. Landry RL, Groom AL, Vu TT, et al. The role of flavors in vaping initiation and satisfaction among U.S. adults. Addict Behav 2019;99:106077.
12. Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. Prev Med Rep 2016;5:33–40.
13. Hsu G, Sun JY, Zhu SH. Evolution of Electronic Cigarette Brands From 2013-2014 to 2016-2017: Analysis of Brand Websites. J Med Internet Res 2018;20(3):e80.
14. Ghinai I, Pray IW, Navon L, et al. E-cigarette Product Use, or Vaping, Among Persons with Associated Lung Injury - Illinois and Wisconsin, April-September 2019. MMWR Morb Mortal Wkly Rep 2019;68(39):865–869.
15. Dai H, Catley D, Richter KP, Goggin K, Ellerbeck EF. Electronic Cigarettes and Future Marijuana Use: A Longitudinal Study. Pediatrics 2018;141(5):e20173787.
16. Chadi N, Schroeder R, Jensen JW, Levy S. Association Between Electronic Cigarette Use and Marijuana Use Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Pediatr 2019;173(10):e192574.
17. Borodovsky JT, Crosier BS, Lee DC, Sargent JD, Budney AJ. Smoking, vaping, eating: Is legalization impacting the way people use cannabis? Int J Drug Policy 2016;36:141–147.
18. Jones CB, Hill ML, Pardini DA, Meier MH. Prevalence and correlates of vaping cannabis in a sample of young adults. Psychol Addict Behav 2016;30(8):915–921.
19. Lee DC, Crosier BS, Borodovsky JT, Sargent JD, Budney AJ. Online survey characterizing vaporizer use among cannabis users. Drug Alcohol Depend 2016;159:227–233.
20. Fuoco FC, Buonanno G, Stabile L, Vigo P. Influential parameters on particle concentration and size distribution in the mainstream of e-cigarettes. Environ Pollut 2014;184:523–529.
21. Geiss O, Bianchi I, Barahona F, Barrero-Moreno J. Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes. Int J Hyg Environ Health 2015;218(1):169–180.
22. Goel R, Durand E, Trushin N, et al. Highly reactive free radicals in electronic cigarette aerosols. Chem Res Toxicol 2015;28(9):1675–1677.
23. Sussan TE, Gajghate S, Thimmulappa RK, et al. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. PLoS One 2015;10(2):e0116861.
24. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87(10):840–844.
25. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340(8828):1111–1115.
26. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27(21):2588–2605.
27. Gepner AD, Keevil JG, Wyman RA, et al. Use of carotid intima-media thickness and vascular age to modify cardiovascular risk prediction. J Am Soc Echocardiogr 2006;19(9):1170–1174.
28. Langham MC, Zhou Y, Chirico EN, et al. Effects of age and smoking on endothelial function assessed by quantitative cardiovascular magnetic resonance in the peripheral and central vasculature. J Cardiovasc Magn Reson 2015;17(1):19.
29. Carnevale R, Sciarretta S, Violi F, et al. Acute Impact of Tobacco vs Electronic Cigarette Smoking on Oxidative Stress and Vascular Function. Chest 2016;150(3):606–612.
30. Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, et al. Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers. J Am Coll Cardiol 2016;67(23):2802–2803.
31. Caporale A, Langham MC, Guo W, Johncola A, Chatterjee S, Wehrli FW. Acute Effects of Electronic Cigarette Aerosol Inhalation on Vascular Function Detected at Quantitative MRI. Radiology 2019;293(1):97–106.
32. Chatterjee S, Tao JQ, Johncola A, et al. Acute exposure to e-cigarettes causes inflammation and pulmonary endothelial oxidative stress in nonsmoking, healthy young subjects. Am J Physiol Lung Cell Mol Physiol 2019;317(2):L155–L166.
33. Perrine CG, Pickens CM, Boehmer TK, et al. Characteristics of a Multistate Outbreak of Lung Injury Associated with E-cigarette Use, or Vaping - United States, 2019. MMWR Morb Mortal Wkly Rep 2019;68(39):860–864.
34. George J, Hussain M, Vadiveloo T, et al. Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. J Am Coll Cardiol 2019;74(25):3112–3120.
35. Benowitz NL. Nicotine addiction. N Engl J Med 2010;362(24):2295–2303.
36. Nestler EJ. Is there a common molecular pathway for addiction? Nat Neurosci 2005;8(11):1445–1449.
37. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry 1986;43(3):289–294.
38. Zehra A, Burns J, Liu CK, et al. Cannabis Addiction and the Brain: a Review. J Neuroimmune Pharmacol 2018;13(4):438–452.
39. Kandel D, Schaffran C, Griesler P, Samuolis J, Davies M, Galanti R. On the measurement of nicotine dependence in adolescence: comparisons of the mFTQ and a DSM-IV-based scale. J Pediatr Psychol 2005;30(4):319–332.
40. National Institute on Drug Abuse. University of Michigan. Institute for Social Research. Monitoring the future, national survey results on drug use. NIH publication. Bethesda, Md: National Institute on Drug Abuse, U.S. Dept. of Health and Human Services, National Institutes of Health, 2000.
41. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370(23):2219–2227.
42. Prochaska JJ. The public health consequences of e-cigarettes: a review by the National Academies of Sciences. A call for more research, a need for regulatory action. Addiction 2019;114(4):587–589.
43. Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults. JAMA Pediatr 2015;169(11):1018–1023.
44. Miech R, Patrick ME, O'Malley PM, Johnston LD. E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students. Tob Control 2017;26(e2):e106–e111.
45. Schier JG, Meiman JG, Layden J, et al. Severe Pulmonary Disease Associated with Electronic-Cigarette-Product Use - Interim Guidance. MMWR Morb Mortal Wkly Rep 2019;68(36):787–790.
46. Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Preliminary Report. N Engl J Med 2019 Sep 6 [Epub ahead of print] https://doi.org/10.1056/NEJMoa1911614.
47. Siegel DA, Jatlaoui TC, Koumans EH, et al. Update: Interim Guidance for Health Care Providers Evaluating and Caring for Patients with Suspected E-cigarette, or Vaping, Product Use Associated Lung Injury - United States, October 2019. MMWR Morb Mortal Wkly Rep 2019;68(41):919–927.
48. (U.S.) CfDC. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Published 2019. Accessed November 17, 2019.
49. Moritz ED, Zapata LB, Lekiachvili A, et al. Update: Characteristics of Patients in a National Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injuries - United States, October 2019. MMWR Morb Mortal Wkly Rep 2019;68(43):985–989.
50. Grady, Denise. Teenager with Vaping Injury Gets Double Lung Transplant. https://www.nytimes.com/2019/11/12/health/vaping-double-lung-transplant.html. Published 2019. Accessed January 13, 2020.
51. Blount BC, Karwowski MP, Morel-Espinosa M, et al. Evaluation of Bronchoalveolar Lavage Fluid from Patients in an Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury - 10 States, August-October 2019. MMWR Morb Mortal Wkly Rep 2019;68(45):1040–1041.

52. He T, Oks M, Esposito M, Steinberg H, Makaryus M. "Tree-in-Bloom": Severe Acute Lung Injury Induced by Vaping Cannabis Oil. Ann Am Thorac Soc 2017;14(3):468–470.
53. Khan MS, Khateeb F, Akhtar J, et al. Organizing pneumonia related to electronic cigarette use: A case report and review of literature. Clin Respir J 2018;12(3):1295–1299.
54. Agustin M, Yamamoto M, Cabrera F, Eusebio R. Diffuse Alveolar Hemorrhage Induced by Vaping. Case Rep Pulmonol 2018;2018:9724530.
55. Viswam D, Trotter S, Burge PS, Walters GI. Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. BMJ Case Rep 2018;2018:bcr-2018-224350.
56. Flower M, Nandakumar L, Singh M, Wyld D, Windsor M, Fielding D. Respiratory bronchiolitis-associated interstitial lung disease secondary to electronic nicotine delivery system use confirmed with open lung biopsy. Respirol Case Rep 2017;5(3):e00230 https://doi.org/10.1002/rcr2.230.
57. Arter ZL, Wiggins A, Hudspath C, Kisling A, Hostler DC, Hostler JM. Acute eosinophilic pneumonia following electronic cigarette use. Respir Med Case Rep 2019;27:100825 https://doi.org/10.1016/j.rmcr.2019.100825.
58. Sommerfeld CG, Weiner DJ, Nowalk A, Larkin A. Hypersensitivity Pneumonitis and Acute Respiratory Distress Syndrome From E-Cigarette Use. Pediatrics 2018;141(6):e20163927.
59. Henry TS, Kanne JP, Kligerman SJ. Imaging of Vaping-Associated Lung Disease. N Engl J Med 2019;381(15):1486–1487.
60. Henry TS, Kligerman SJ, Raptis CA, Mann H, Sechrist JW, Kanne JP. Imaging Findings of Vaping-Associated Lung Injury. AJR Am J Roentgenol 2019 Oct 8:1–8 [Epub ahead of print] https://doi.org/10.2214/AJR.19.22251.
61. Butt YM, Smith ML, Tazelaar HD, et al. Pathology of Vaping-Associated Lung Injury. N Engl J Med 2019;381(18):1780–1781.
62. Mukhopadhyay S, Mehrad M, Dammert P, et al. Lung Biopsy Findings in Severe Pulmonary Illness Associated With E-Cigarette Use (Vaping). Am J Clin Pathol 2020;153(1):30–39.
63. Kligerman SJ, Franks TJ, Galvin JR. From the radiologic pathology archives: organization and fibrosis as a response to lung injury in diffuse alveolar damage, organizing pneumonia, and acute fibrinous and organizing pneumonia. RadioGraphics 2013;33(7):1951–1975.
64. Rossi SE, Erasmus JJ, Volpacchio M, Franquet T, Castiglioni T, McAdams HP. "Crazy-paving" pattern at thin-section CT of the lungs: radiologic-pathologic overview. RadioGraphics 2003;23(6):1509–1519.
65. Devakonda A, Raoof S, Sung A, Travis WD, Naidich D. Bronchiolar disorders: a clinical-radiological diagnostic algorithm. Chest 2010;137(4):938–951.
66. Berkowitz EA, Henry TS, Veeraraghavan S, Staton GW Jr, Gal AA. Pulmonary effects of synthetic marijuana: chest radiography and CT findings. AJR Am J Roentgenol 2015;204(4):750–757.
67. Mohr H. Some CBD vapes contain street drug instead of the real thing. https://apnews.com/7b452f4af90b4620ab0ff0eb2cca62cc. Published 2019. Accessed December 6, 2019.
68. Nguyen VT, Chan ES, Chou SH, et al. Pulmonary effects of i.v. injection of crushed oral tablets: "excipient lung disease". AJR Am J Roentgenol 2014;203(5):W506–W515.
69. Madison MC, Landers CT, Gu BH, et al. Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. J Clin Invest 2019;129(10):4290–4304.
70. Tazelaar HD, Linz LJ, Colby TV, Myers JL, Limper AH. Acute eosinophilic pneumonia: histopathologic findings in nine patients. Am J Respir Crit Care Med 1997;155(1):296–302.
71. King MA, Pope-Harman AL, Allen JN, Christoforidis GA, Christoforidis AJ. Acute eosinophilic pneumonia: radiologic and clinical features. Radiology 1997;203(3):715–719.
72. Shorr AF, Scoville SL, Cersovsky SB, et al. Acute eosinophilic pneumonia among US Military personnel deployed in or near Iraq. JAMA 2004;292(24):2997–3005.
73. Uchiyama H, Suda T, Nakamura Y, et al. Alterations in smoking habits are associated with acute eosinophilic pneumonia. Chest 2008;133(5):1174–1180.
74. Betancourt SL, Martinez-Jimenez S, Rossi SE, Truong MT, Carrillo J, Erasmus JJ. Lipoid pneumonia: spectrum of clinical and radiologic manifestations. AJR Am J Roentgenol 2010;194(1):103–109.
75. Baron SE, Haramati LB, Rivera VT. Radiological and clinical findings in acute and chronic exogenous lipoid pneumonia. J Thorac Imaging 2003;18(4):217–224.
76. Maddock SD, Cirulis MM, Callahan SJ, et al. Pulmonary Lipid-Laden Macrophages and Vaping. N Engl J Med 2019;381(15):1488–1489.
77. Davidson K, Brancato A, Heetderks P, et al. Outbreak of Electronic-Cigarette-Associated Acute Lipoid Pneumonia - North Carolina, July-August 2019. MMWR Morb Mortal Wkly Rep 2019;68(36):784–786.
78. Corwin RW, Irwin RS. The lipid-laden alveolar macrophage as a marker of aspiration in parenchymal lung disease. Am Rev Respir Dis 1985;132(3):576–581.
79. Basset-Léobon C, Lacoste-Collin L, Aziza J, Bes JC, Jozan S, Courtade-Saïdi M. Cut-off values and significance of Oil Red O-positive cells in bronchoalveolar lavage fluid. Cytopathology 2010;21(4):245–250.
80. Miller R, Allen TC, Barrios RJ, et al. Hypersensitivity Pneumonitis A Perspective From Members of the Pulmonary Pathology Society. Arch Pathol Lab Med 2018;142(1):120–126.
81. Hariri LP, Mino-Kenudson M, Shea B, et al. Distinct histopathology of acute onset or abrupt exacerbation of hypersensitivity pneumonitis. Hum Pathol 2012;43(5):660–668.
82. Patel RA, Sellami D, Gotway MB, Golden JA, Webb WR. Hypersensitivity pneumonitis: patterns on high-resolution CT. J Comput Assist Tomogr 2000;24(6):965–970.
83. Bernardo J, Hunninghake GW, Gadek JE, Ferrans VJ, Crystal RG. Acute hypersensitivity pneumonitis: serial changes in lung lymphocyte subopulations after exposure to antigen. Am Rev Respir Dis 1979;120(5):985–994.
84. Salisbury ML, Gu T, Murray S, et al. Hypersensitivity Pneumonitis: Radiologic Phenotypes Are Associated With Distinct Survival Time and Pulmonary Function Trajectory. Chest 2019;155(4):699–711.
85. Erythropel HC, Jabba SV, DeWinter TM, et al. Formation of flavorant-propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids. Nicotine Tob Res 2019;21(9):1248–1258.
86. Clapp PW, Jaspers I. Electronic Cigarettes: Their Constituents and Potential Links to Asthma. Curr Allergy Asthma Rep 2017;17(11):79.
87. Song MA, Reisinger SA, Freudenheim JL, et al. Effects of Electronic Cigarette Constituents on the Human Lung: A Pilot Clinical Trial. Cancer Prev Res (Phila) 2019 Oct 16 [Epub ahead of print] https://doi.org/10.1158/1940-6207.CAPR-19-0400.
88. Study: E-Cigarettes May Be More Harmful to Heart Health Than Tobacco. https://www.cedars-sinai.org/newsroom/study-e-cigarettes-may-be-more-harmful-to-heart-health-than-tobacco/. Published 2019. Accessed November 2, 2019.
89. Bhatta DN, Glantz SA. Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. Am J Prev Med 2019 Dec 11 [Epub ahead of print].
90. Bhatta DN, Glantz SA. Electronic Cigarette Use and Myocardial Infarction Among Adults in the US Population Assessment of Tobacco and Health. J Am Heart Assoc 2019;8(12):e012317.
91. Vindhyal MR, Ndunda P, Munguti C, Vindhyal S, Okut H. IMPACT ON CARDIOVASCULAR OUTCOMES AMONG E-CIGARETTE USERS: A REVIEW FROM NATIONAL HEALTH INTERVIEW SURVEYS. J Am Coll Cardiol 2019;73(9 Supplement 2):11.
92. Balmes JR. Vaping-induced Acute Lung Injury: An Epidemic That Could Have Been Prevented. Am J Respir Crit Care Med 2019;200(11):1342–1344.