Impact of vaping on respiratory health

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Abstract

Widespread uptake of vaping has signaled a sea change in the future of nicotine consumption. Vaping has grown in popularity over the past decade, in part propelled by innovations in vape pen design and nicotine flavoring. Teens and young adults have seen the biggest uptake in use of vape pens, which have superseded conventional cigarettes as the preferred modality of nicotine consumption. Relatively little is known, however, about the potential effects of chronic vaping on the respiratory system. Further, the role of vaping as a tool of smoking cessation and tobacco harm reduction remains controversial. The 2019 E-cigarette or Vaping Use-Associated Lung Injury (EVALI) outbreak highlighted the potential harms of vaping, and the consequences of long term use remain unknown. Here, we review the growing body of literature investigating the impacts of vaping on respiratory health. We review the clinical manifestations of vaping related lung injury, including the EVALI outbreak, as well as the effects of chronic vaping on respiratory health and covid-19 outcomes. We conclude that vaping is not without risk, and that further investigation is required to establish clear public policy guidance and regulation.

Introduction

The introduction of vape pens to international markets in the mid 2000s signaled a sea change in the future of nicotine consumption. Long the mainstay of nicotine use, conventional cigarette smoking was on the decline for decades in the US,[1 2] largely owing to generational shifts in attitudes toward smoking.[3] With the advent of vape pens, trends in nicotine use have reversed, and the past two decades have seen a steady uptake of vaping among young, never smokers.[4-6] Vaping is now the preferred modality of nicotine consumption among young people,[7] and 2020 surveys indicate that one in five US high school students currently vape.[8] These trends are reflected internationally, where the prevalence of vape products has grown in both China and the UK.[9] Relatively little is known, however, regarding the health consequences of chronic vape pen use.[10 11] Although vaping was initially heralded as a safer alternative to cigarette smoking,[12 13] the toxic substances found in vape aerosols have raised new questions about the long term safety of vaping.[14-17] The 2019 E-cigarette or Vaping product Use-Associated Lung Injury (EVALI) outbreak, ultimately linked to vitamin E acetate in THC vapes, raised further concerns about the health effects of vaping,[18-20] and has led to increased scientific interest in the health consequences of chronic vaping. This review summarizes the history and epidemiology of vaping, and the clinical manifestations and proposed pathophysiology of lung injury caused by vaping. The public health consequences of widespread vaping remain to be seen and are compounded by young users of vape pens later transitioning to combustible cigarettes.[4 21 22] Deepened scientific understanding and public awareness of the potential harms of vaping are imperative to confront the challenges posed by a new generation of nicotine users.

ABBREVIATIONS

- BAL bronchoalveolar lavage
- CBD cannabidiol
- CDC Centers for Disease Control and Prevention
- DLCO diffusing capacity of the lung for carbon monoxide
- EMR electronic medical record
- END electronic nicotine delivery systems
- EVALI E-cigarette or Vaping product Use-Associated Lung Injury
- LLM lipid laden macrophages
- THC tetrahydrocannabinol
- V/Q ventilation perfusion

Sources and selection criteria

We searched PubMed and Ovid Medline databases for the terms “vape”, “vaping”, “e-cigarette”, “electronic cigarette”, “electronic nicotine delivery”, “electronic nicotine device”, “END”, “EVALI”, “lung injury, diagnosis, management, and treatment” to find articles published between January 2000 and December 2021. We also identified references from the Centers for Disease Control and Prevention (CDC) website, as well as relevant review articles and public policy resources. Prioritization was

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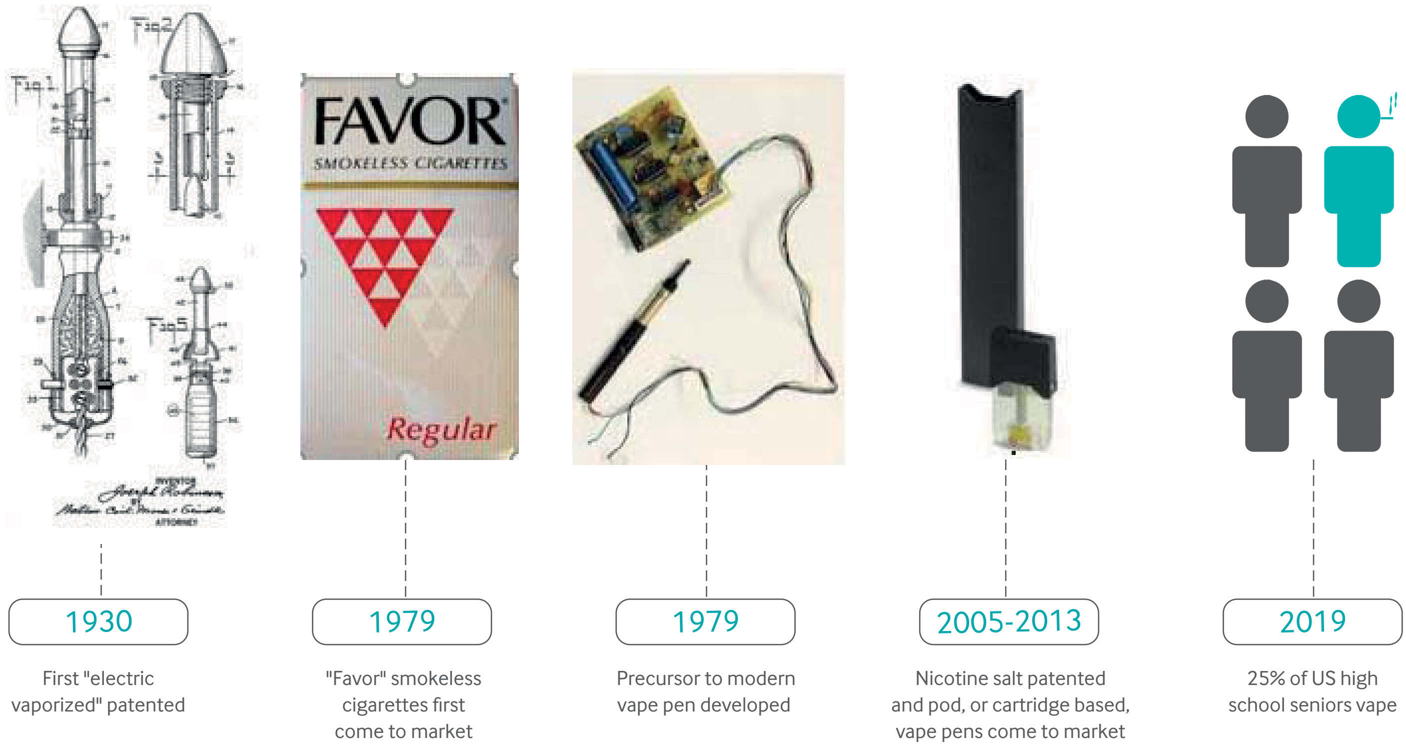

Fig 1 | Timeline of vape pen invention to widespread use (1970s-2020)

given to peer reviewed articles written in English in moderate-to-high impact journals, consensus statements, guidelines, and included randomized controlled trials, systematic reviews, meta-analyses, and case series. We excluded publications that had a qualitative research design, or for which a conflict of interest in funding could be identified, as defined by any funding source or consulting fee from nicotine manufacturers or distributors. Search terms were chosen to generate a broad selection of literature that reflected historic and current understanding of the effects of vaping on respiratory health.

The origins of vaping

Vaping achieved widespread popularity over the past decade, but its origins date back almost a century and are summarized in figure 1. The first known patent for an “electric vaporizer” was granted in 1930, intended for aerosolizing medicinal compounds.[23] Subsequent patents and prototypes never made it to market,[24] and it wasn’t until 1979 that the first vape pen was commercialized. Dubbed the “Favor” cigarette, the device was heralded as a smokeless alternative to cigarettes and led to the term “vaping” being coined to differentiate the “new age” method of nicotine consumption from conventional, combustible cigarettes.[25] “Favor” cigarettes did not achieve widespread appeal, in part because of the bitter taste of the aerosolized freebase nicotine; however, the term vaping persisted and would go on to be used by the myriad products that have since been developed.

The forerunner of the modern vape pen was developed in Beijing in 2003 and later introduced to US markets around 2006.[26 27] Around this time, the future Juul Laboratories founders developed the precursor of the current Juul vape pen while they were students at the Stanford Byers-Center for Biodesign.[28] Their model included disposable cartridges of flavored nicotine solution (pods) that could be inserted into the vape pen, which itself resembled a USB flash drive. Key to their work was the chemical alteration of freebase nicotine to a benzoate nicotine salt.[29] The lower pH of the nicotine salt resulted in an aerosolized nicotine product that lacked a bitter taste,[30] and enabled manufacturers to expand the range of flavored vape products.[31] Juul Laboratories was founded a decade later and quickly rose to dominate the US market,[32] accounting for an estimated 13-59% of the vape products used among teens by 2020.[68] Part of the Juul vape pen’s appeal stems from its discreet design, as well as its ability to deliver nicotine with an efficiency matching that of conventional cigarettes.[33 34] Subsequent generations of vape pens have included innovations such as the tank system, which allowed users to select from the wide range of different vape solutions on the market, rather than the relatively limited selection available in traditional pod based systems. Further customizations include the ability to select different vape pen components such as atomizers, heating coils, and fluid wicks, allowing users to calibrate the way in which the vape aerosol is produced. Tobacco companies have taken note of the shifting

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Box 1: CDC criteria for establishing EVALI diagnosis

CDC Lung Injury Surveillance

Primary case definitions
Confirmed case

- Vape use* in 90 days prior to symptom onset; and
- Pulmonary infiltrate on chest radiograph or ground glass opacities on chest computed tomography (CT) scan; and
- Absence of pulmonary infection on initial investigation†; and
- Absence of alternative plausible diagnosis (eg, cardiac, rheumatological, or neoplastic process).

Probable case

- Vape use* in 90 days prior to symptom onset; and
- Pulmonary infiltrate on chest radiograph or ground glass opacities on chest CT; and
- Infection has been identified; however is not thought to represent the sole cause of lung injury OR minimum criteria** to exclude infection have not been performed but infection is not thought to be the sole cause of lung injury
- Absence of alternative plausible diagnosis (eg, cardiac, rheumatological, or neoplastic process).

*Use of e-cigarette, vape pen, or dabbing.
†Minimum criteria for absence of pulmonary infection: negative respiratory viral panel, negative influenza testing (if supported by local epidemiological data), and all other clinically indicated infectious respiratory disease testing is negative.

demographics of nicotine users, as evidenced in 2018 by Altria's $12.8bn investment in Juul Laboratories.[35]

Vaping terminology

At present, vaping serves as an umbrella term that describes multiple modalities of aerosolized nicotine consumption. Vape pens are alternatively called e-cigarettes, electronic nicotine delivery systems (END), e-cigars, and e-hookahs. Additional vernacular terms have emerged to describe both the various vape pen devices (eg, tank, mod, dab pen), vape solution (eg, e-liquid, vape juice), as well as the act of vaping (eg, ripping, juuling, puffing, hitting).[36] A conventional vape pen is a battery operated handheld device that contains a storage chamber for the vape solution and an internal element for generating the characteristic vape aerosol. Multiple generations of vape pens have entered the market, including single use, disposable varieties, as well as reusable models that have either a refillable fluid reservoir or a disposable cartridge for the vape solution. Aerosol generation entails a heating coil that atomizes the vape solution, and it is increasingly popular for devices to include advanced settings that allow users to adjust features of the aerosolized nicotine delivery.[37 38] Various devices allow for coil temperatures ranging from 110 °C to over 1000 °C, creating a wide range of conditions for thermal degradation of the vape solution itself.[39 40]

The sheer number of vape solutions on the market poses a challenge in understanding the impact of vaping on respiratory health. The spectrum of vape solutions available encompasses thousands of varieties of flavors, additives, and nicotine concentrations.[41] Most vape solutions contain an active ingredient, commonly nicotine[42]; however, alternative agents include tetrahydrocannabinol (THC) or cannabidiol (CBD). Vape solutions are typically composed of a combination of a flavorant, nicotine, and a carrier, commonly propylene glycol or vegetable glycerin, that generates the characteristic smoke appearance of vape aerosols. Some 450 brands of vape now offer more than 8000 flavors,[41] a figure that nearly doubled over a three year period.[43] Such tremendous variety does not account for third party sellers who offer users the option to customize a vape solution blend. Addition of marijuana based products such as THC or CBD requires the use of an oil based vape solution carrier to allow for extraction of the psychoactive elements. Despite THC vaping use in nearly 9% of high schoolers,[44] THC vape solutions are subject to minimal market regulation. Finally, a related modality of THC consumption is termed dabbing, and describes the process of inhaling aerosolized THC wax concentrate.

Epidemiology of vaping

Since the early 2000s, vaping has grown in popularity in the US and elsewhere.[8 45] Most of the 68 million vape pen users are concentrated in China, the US, and Europe.[46] Uptake among young people has been particularly pronounced, and in the US vaping has overtaken cigarettes as the most common modality of nicotine consumption among adolescents and young adults.[47] Studies estimate that 20% of US high school students are regular vape pen users,[6 48] in contrast to the 5% of adults who use vape products.[2] Teen uptake of vaping has been driven in part by a perception of vaping as a safer alternative to cigarettes,[49 50] as well as marketing strategies that target adolescents.[33] Teen use of vape pens is further driven by the low financial cost of initiation, with "starter kits" costing less than $25,[51] as well as easy access through peer sales and inconsistent age verification at in-person and online retailers.[52] After sustained growth in use over the 2010s, recent survey data from 2020 suggest that the number of vape pen users has leveled off among teens, perhaps in part owing to increased perceived risk of vaping after the EVALI outbreak.[8 53] The public health implications of teen vaping are compounded by the prevalence of vaping among never smokers (defined as having smoked fewer than 100 lifetime cigarettes),[54] and subsequent uptake of cigarette smoking among vaping teens.[4 55] Similarly, half of adults who currently vape have never used cigarettes,[2] and concern remains that vaping serves as a gateway to conventional cigarette use,[56 57] although these results have been disputed.[58 59] Despite regulation limiting the sale of flavored vape products,[60] a 2020 survey found that high school students were still predominantly using fruit, mint, menthol, and dessert flavored vape solutions.[48] While most data available surround the use of nicotine-containing vape products, a recent meta-analysis showed growing prevalence of adolescents using cannabis-containing products as well.[61]

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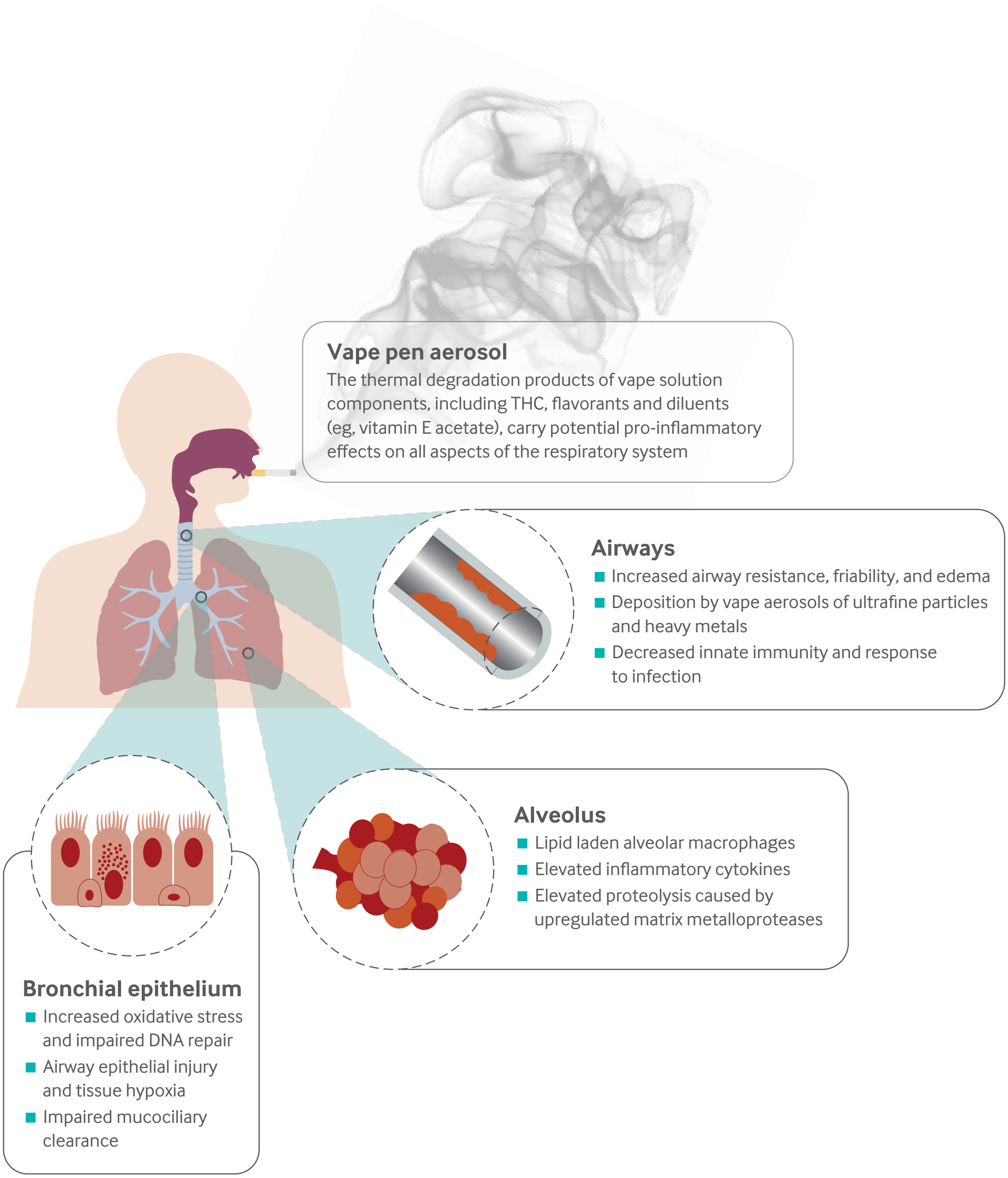

Fig 2 | Schematic illustrating pathophysiology of vaping lung injury

Vaping as harm reduction

Despite facing ongoing questions about safety, vaping has emerged as a potential tool for harm reduction among cigarette smokers.[12 27] An NHS report determined that vaping nicotine is "around 95% less harmful than cigarettes,"[62] leading to the development of programs that promote vaping as a tool of risk reduction among current smokers. A 2020 Cochrane review found that vaping nicotine assisted with smoking cessation over placebo[63] and recent work found increased rates of cigarette abstinence (18% *v* 9.9%) among those switching to vaping compared with conventional nicotine replacement (eg, gum, patch, lozenge).[64] US CDC guidance suggests that vaping nicotine may benefit current adult smokers who are able to achieve complete cigarette cessation by switching to vaping.[65 66]

The public health benefit of vaping for smoking cessation is counterbalanced by vaping uptake among never smokers,[2 54] and questions surrounding the safety of chronic vaping.[10 11] Controversy surrounding the NHS claim of vaping as 95% safer than cigarettes has emerged,[67 68] and multiple leading health organizations have concluded that vaping is harmful.[42 69] Studies have demonstrated airborne particulate matter in the proximity of active vapers,[70] and concern remains that secondhand exposure to vaped aerosols may cause adverse

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effects, complicating the notion of vaping as a net gain for public health.[71 72] Uncertainty about the potential chronic consequences of vaping combined with vaping uptake among never smokers has complicated attempts to generate clear policy guidance.[73 74] Further, many smokers may exhibit "dual use" of conventional cigarettes and vape pens simultaneously, further complicating efforts to understand the impact of vape exposure on respiratory health, and the role vape use may play in smoking cessation.[12] We are unable to know with certainty the extent of nicotine uptake among young people that would have been seen in the absence of vaping availability, and it remains possible that some young vape pen users may have started on conventional cigarettes regardless. That said, declining nicotine use over the past several decades would argue that many young vape pen users would have never had nicotine uptake had vape pens not been introduced.[12] It remains an open question whether public health measures encouraging vaping for nicotine cessation will benefit current smokers enough to offset the impact of vaping uptake among young, never smokers.[75]

Vaping lung injury—clinical presentations

Vaping related lung injury: 2012-19

The potential health effects of vape pen use are varied and centered on injury to the airways and lung parenchyma. Before the 2019 EVALI outbreak, the medical literature detailed case reports of sporadic vaping related acute lung injury. The first known case was reported in 2012, when a patient presented with cough, diffuse ground glass opacities, and lipid laden macrophages (LLM) on bronchoalveolar lavage (BAL) return in the context of vape pen use.[76] Over the following seven years, an additional 15 cases of vaping related acute lung injury were reported in the literature. These cases included a wide range of diffuse parenchymal lung disease without any clear unifying features, and included cases of eosinophilic pneumonia,[77-79] hypersensitivity pneumonitis,[80] organizing pneumonia,[81 82] diffuse alveolar hemorrhage,[83 84] and giant cell foreign body reaction.[85] Although parenchymal lung injury predominated the cases reported, additional cases detailed episodes of status asthmaticus[86] and pneumothoraces[87] attributed to vaping. Non-respiratory vape pen injury has also been described, including cases of nicotine toxicity from vape solution ingestion,[88 89] and injuries sustained owing to vape pen device explosions.[90]

The 2019 EVALI outbreak

In the summer of 2019 the EVALI outbreak led to 2807 cases of idiopathic acute lung injury in predominantly young, healthy individuals, which resulted in 68 deaths.[19 91] Epidemiological work to uncover the cause of the outbreak identified an association with vaping, particularly the use of THC-containing products, among affected individuals. CDC criteria for EVALI (box 1) included individuals presenting with respiratory symptoms who had pulmonary infiltrates on imaging in the context of having vaped or dabbed within 90 days of symptom onset, without an alternative identifiable cause.[92 93] After peaking in September 2019, EVALI case numbers steadily declined,[91] likely owing to identification of a link with vaping, and subsequent removal of offending agents from circulation. Regardless, sporadic cases continue to be reported, and a high index of suspicion is required to differentiate EVALI from covid-19 pneumonia.[94 95] A strong association emerged between EVALI cases and the presence of vitamin E acetate in the BAL return of affected individuals[96]; however, no definitive causal link has been established. Interestingly, the EVALI outbreak was nearly entirely contained within the US with the exception of several dozen cases, at least one of which was caused by an imported US product.[97-99] The pattern of cases and lung injury is most suggestive of a vape solution contaminant that was introduced into the distribution pipeline in US markets, leading to a geographically contained pattern of lung injury among users. CDC case criteria for EVALI may have obscured a potential link between viral pneumonia and EVALI, and cases may have been under-recognized following the onset of the covid-19 pandemic.

EVALI—clinical, radiographic, and pathologic features

In the right clinical context, diagnosis of EVALI includes identification of characteristic radiographic and pathologic features. EVALI patients largely fit a pattern of diffuse, acute lung injury in the context of vape pen exposure. A systematic review of 200 reported cases of EVALI showed that those affected were predominantly men in their teens to early 30s, and most (80%) had been using THC-containing products.[100] Presentations included predominantly respiratory (95%), constitutional (87%), and gastrointestinal symptoms (73%). Radiological studies mostly featured diffuse ground glass opacities bilaterally. Of 92 cases that underwent BAL, alveolar fluid samples were most commonly neutrophil predominant, and 81% were additionally positive for LLM on Oil Red O staining. Lung biopsy was not required to achieve the diagnosis; however, of 33 cases that underwent tissue biopsy, common features included organizing pneumonia, inflammation, foamy macrophages, and fibrinous exudates.

EVALI—outcomes

Most patients with EVALI recovered, and prognosis was generally favorable. A systematic review of identified cases found that most patients with confirmed disease required admission to hospital (94%), and a quarter were intubated.[100] Mortality among EVALI patients was low, with estimates around 2-3% across multiple studies.[101-103] Mortality was associated with age over 35 and underlying asthma, cardiac disease, or mental health conditions.[103] Notably, the cohorts studied only included patients

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who presented for medical care, and the samples are likely biased toward a more symptomatic population. It is likely that many individuals experiencing mild symptoms of EVALI did not present for medical care, and would have self-discontinued vaping following extensive media coverage of the outbreak at that time. Although most EVALI survivors recovered well, case series of some individuals show persistent radiographic abnormalities[101] and sustained reductions in DLCO.[104 105] Pulmonary function evaluation of EVALI survivors showed normalization in FEV_1/FVC on spirometry in some,[106] while others had more variable outcomes.[105 107 108]

Vaping induced lung injury—pathophysiology

The causes underlying vaping related acute lung injury remain interesting to clinicians, scientists, and public health officials; multiple mechanisms of injury have been proposed and are summarized in figure 2.[31 109 110] Despite increased scientific interest in vaping related lung injury following the EVALI outbreak, the pool of data from which to draw meaningful conclusions is limited because of small scale human studies and ongoing conflicts due to tobacco industry funding.[111] Further, insufficient time has elapsed since widespread vaping uptake, and available studies reflect the effects of vaping on lung health over a maximum 10-15 year timespan. The longitudinal effects of vaping may take decades to fully manifest and ongoing prospective work is required to better understand the impacts of vaping on respiratory health.

Pro-inflammatory vape aerosol effects

While multiple pathophysiological pathways have been proposed for vaping related lung injury, they all center on the vape aerosol itself as the conduit of lung inflammation. Vape aerosols have been found to harbor a number of toxic substances, including thermal degradation products of the various vape solution components.[112] Mass spectrometry analysis of vape aerosols has identified a variety of oxidative and pro-inflammatory substances including benzene, acrolein, volatile organic compounds, and propylene oxide.[16 17] Vaping additionally leads to airway deposition of ultrafine particles,[14 113] as well as the heavy metals manganese and zinc which are emitted from the vaping coils.[15 114] Fourth generation vape pens allow for high wattage aerosol generation, which can cause airway epithelial injury and tissue hypoxia,[115 116] as well as formaldehyde exposure similar to that of cigarette smoke.[117] Common carrier solutions such as propylene glycol have been associated with increased airway hyper-reactivity among vape pen users,[31 118 119] and have been associated with chronic respiratory conditions among theater workers exposed to aerosolized propylene glycol used in the generation of artificial fog.[120] Nicotine salts used in pod based vape pen solutions, including Juul, have been found to penetrate the cell membrane and have cytotoxic effects.[121]

The myriad available vape pen flavors correlate with an expansive list of chemical compounds with potential adverse respiratory effects. Flavorants have come under increased scrutiny in recent years and have been found to contribute to the majority of aldehyde production during vape aerosol production.[122] Compounds such as cinnamaldehyde,[123 124] 2,5-dimethylpyrazine (chocolate flavoring),[125] and 2,3-pentanedione[126] are common flavor additives and have been found to contribute to airway inflammation and altered immunological responses. The flavorant diacetyl garnered particular attention after it was identified on mass spectrometry in most vape solutions tested.[127] Diacetyl is most widely associated with an outbreak of diacetyl associated bronchiolitis obliterans ("popcorn lung") among workers at a microwave popcorn plant in 2002.[128] Identification of diacetyl in vape solutions raises the possibility of development of a similar pattern of bronchiolitis obliterans among individuals who have chronic vape aerosol exposure to diacetyl-containing vape solutions.[129]

Studies of vape aerosols have suggested multiple pro-inflammatory effects on the respiratory system. This includes increased airway resistance,[130] impaired response to infection,[131] and impaired mucociliary clearance.[132] Vape aerosols have further been found to induce oxidative stress in lung epithelial cells,[133] and to both induce DNA damage and impair DNA repair, consistent with a potential carcinogenic effect.[134] Mice chronically exposed to vape aerosols developed increased airway hyper-reactivity and parenchymal changes consistent with chronic obstructive pulmonary disease.[135] Human studies have been more limited, but reveal increased airway edema and friability among vape pen users, as well as altered gene transcription and decreased innate immunity.[136-138] Upregulation of neutrophil elastase and matrix metalloproteases among vape users suggests increased proteolysis, potentially putting those patients at risk of chronic respiratory conditions.[139]

THC-containing products

Of particular interest during the 2019 EVALI outbreak was the high prevalence of THC use among EVALI cases,[19] raising questions about a novel mechanism of lung injury specific to THC-containing vape solutions. These solutions differ from conventional nicotine based products because of the need for a carrier capable of emulsifying the lipid based THC component. In this context, additional vape solution ingredients rose to attention as potential culprits—namely, THC itself, which has been found to degrade to methacrolein and benzene,[140] as well as vitamin E acetate which was found to be a common oil based diluent.[141]

Vitamin E acetate has garnered increasing attention as a potential culprit in the pathophysiology of the EVALI outbreak. Vitamin E acetate was found in 94% of BAL samples collected from EVALI patients, compared with none identified in unaffected

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vape pen users.[96] Thermal degradation of vitamin E acetate under conditions similar to those in THC vape pens has shown production of ketene, alkene, and benzene, which may mediate epithelial lung injury when inhaled.[39] Previous work had found that vitamin E acetate impairs pulmonary surfactant function,[142] and subsequent studies have shown a dose dependent adverse effect on lung parenchyma by vitamin E acetate, including toxicity to type II pneumocytes, and increased inflammatory cytokines.[143] Mice exposed to aerosols containing vitamin E acetate developed LLM and increased alveolar protein content, suggesting epithelial injury.[140 143]

The pathophysiological insult underlying vaping related lung injury may be multitudinous, including potentially compound effects from multiple ingredients comprising a vape aerosol. The heterogeneity of available vape solutions on the market further complicates efforts to pinpoint particular elements of the vape aerosol that may be pathogenic, as no two users are likely to be exposed to the same combination of vape solution products. Further, vape users may be exposed to vape solutions containing terpenes, medium chain triglycerides, or coconut oil, the effects of which on respiratory epithelium remain under investigation.[144]

Lipid laden macrophages

Lipid laden alveolar macrophages have risen to prominence as potential markers of vaping related lung injury. Alveolar macrophages describe a scavenger white blood cell responsible for clearing alveolar spaces of particulate matter and modulating the inflammatory response in the lung parenchyma.[145] LLM describe alveolar macrophages that have phagocytosed fat containing deposits, as seen on Oil Red O staining, and have been described in a wide variety of pulmonary conditions, including aspiration, lipoid pneumonia, organizing pneumonia, and medication induced pneumonitis.[146 147] During the EVALI outbreak, LLM were identified in the alveolar spaces of affected patients, both in the BAL fluid and on both transbronchial and surgical lung biopsies.[148 149] Of 52 EVALI cases reported in the literature who underwent BAL, LLM were identified in over 80%.[19 100 101 148-153] Accordingly, attention turned to LLM as not only a potential marker of lung injury in EVALI, but as a possible contributor to lung inflammation itself. This concern was compounded by the frequent reported use of oil based THC vape products among EVALI patients, raising the possibility of lipid deposits in the alveolus resulting from inhalation of THC-containing vape aerosols.[154] The combination of LLM, acute lung injury, and inhalational exposure to an oil based substance raised the concern for exogenous lipoid pneumonia.[152 153] However, further evaluation of the radiographic and histopathologic findings failed to identify cardinal features that would support a diagnosis of exogenous lipoid pneumonia—namely, low attenuation areas on CT imaging and foreign body giant cells on histopathology.[155 156] However, differences in the particle size and distribution between vape aerosol exposure and traditional causes of lipoid pneumonia (ie, aspiration of a large volume of an oil-containing substance), could reasonably lead to differences in radiographic appearance, although this would not account for the lack of characteristic histopathologic features on biopsy that would support a diagnosis of lipoid pneumonia.

Recent work suggests that LLM reflect a non-specific marker of vaping, rather than a marker of lung injury. One study found that LLM were not unique to EVALI and could be identified in healthy vape pen users, as well as conventional cigarette smokers, but not in never smokers.[157] Interestingly, this work showed increased cytokines IL-4 and IL-10 among healthy vape users, suggesting that cigarette and vape pen use are associated with a pro-inflammatory state in the lung.[157] An alternative theory supports LLM presence reflecting macrophage clearance of intra-alveolar cell debris rather than exogenous lipid exposure.[149 150] Such a pattern would be in keeping with the role of alveolar macrophages as modulating the inflammatory response in the lung parenchyma.[158] Taken together, available data would support LLM serving as a non-specific marker of vape product use, rather than playing a direct role in vaping related lung injury pathogenesis.[102]

Clinical aspects

Diagnosis

A high index of suspicion is required in establishing a diagnosis of vaping related lung injury, and a general approach is summarized in figure 3. Clinicians may consider the diagnosis when faced with a patient with new respiratory symptoms in the context of vape pen use, without an alternative cause to account for their symptoms. Suspicion should be especially high if respiratory complaints are coupled with constitutional and gastrointestinal symptoms. Patients may present with non-specific markers indicative of an ongoing inflammatory process: fevers, leukocytosis, elevated C reactive protein, or elevated erythrocyte sedimentation rate.[19]

Vaping related lung injury is a diagnosis of exclusion. Chest imaging via radiograph or CT may identify a variety of patterns, although diffuse ground glass opacities remain the most common radiographic finding. Generally, patients with an abnormal chest radiograph should undergo a chest CT for further evaluation of possible vaping related lung injury.

Exclusion of infectious causes is recommended. Testing should include evaluation for bacterial and viral causes of pneumonia, as deemed appropriate by clinical judgment and epidemiological data. Exclusion of common viral causes of pneumonia is imperative, particularly influenza and SARS-CoV-2. Bronchoscopy with BAL should be considered on a case-by-case basis for those with more severe disease and may be helpful to identify patients with vaping mediated eosinophilic lung injury. Further,

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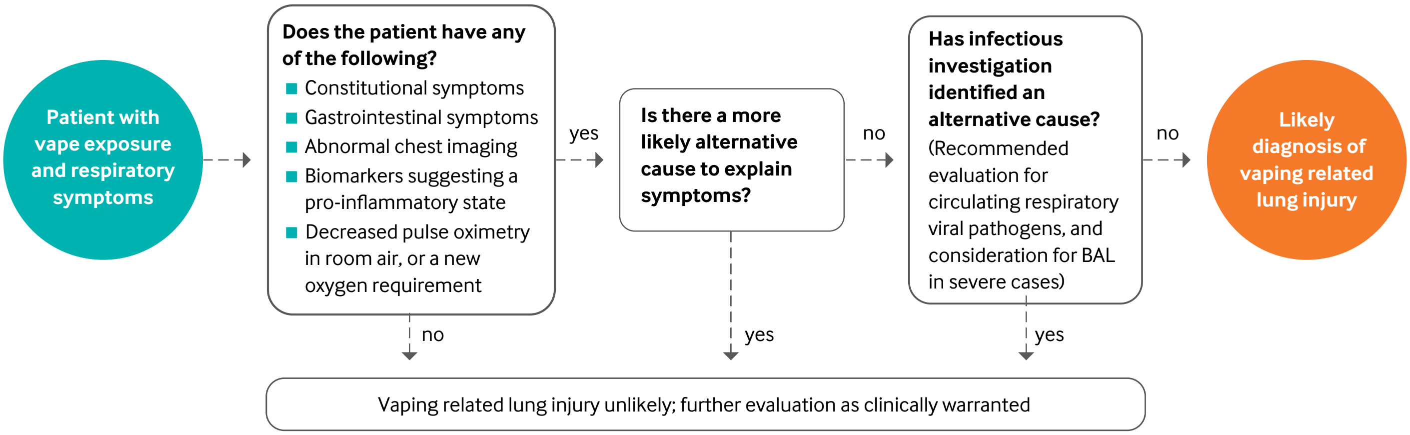

Fig 3 | Flowchart outlining the procedure for diagnosing a vaping related lung injury

lung biopsy may be beneficial to exclude alternative causes of lung injury in severe cases.[92]

Treatment

No definitive therapy has been identified for the treatment of vaping related lung injury, and data are limited to case reports and public health guidance on the topic. Management includes supportive care and strong consideration for systemic corticosteroids for severe cases of vaping related lung injury. CDC guidance encourages consideration of systemic corticosteroids for patients requiring admission to hospital, or those with higher risk factors for adverse outcomes, including age over 50, immunosuppressed status, or underlying cardiopulmonary disease.[100] Further, given case reports of vaping mediated acute eosinophilic pneumonia, steroids should be implemented in those patients who have undergone a confirmatory BAL.[77 79]

Additional therapeutic options include empiric antibiotics and/or antivirals, depending on the clinical scenario. For patients requiring admission to hospital, prompt subspecialty consultation with a pulmonologist can help guide management. Outpatient follow-up with chest imaging and spirometry is recommended, as well as referral to a pulmonologist. Counseling regarding vaping cessation is also a core component in the post-discharge care for this patient population. Interventions specific to vaping cessation remain under investigation; however, literature supports the use of behavioral counseling and/or pharmacotherapy to support nicotine cessation efforts.[66]

Health outcomes among vape pen users

Health outcomes among chronic vape pen users remains an open question. To date, no large scale prospective cohort studies exist that can establish a causal link between vape use and adverse respiratory outcomes. One small scale prospective cohort study did not identify any spirometric or radiographic changes among vape pen users over a 3.5 year period.[159] Given that vaping remains a relatively novel phenomenon, many users will have a less than 10 "pack year" history of vape pen use, arguably too brief an exposure period to reflect the potential harmful nature of chronic vaping. Studies encompassing a longer period of observation of vape pen users have not yet taken place, although advances in electronic medical record (EMR) data collection on vaping habits make such work within reach.

Current understanding of the health effects of vaping is largely limited to case reports of acute lung injury, and health surveys drawing associations between vaping exposure and patient reported outcomes. Within these limitations, however, early work suggests a correlation between vape pen use and poorer cardiopulmonary outcomes. Survey studies of teens who regularly vape found increased frequencies of respiratory symptoms, including productive cough, that were independent of smoking status.[160 161] These findings were corroborated in a survey series identifying more severe asthma symptoms and more days of school missed owing to asthma among vape pen users, regardless of cigarette smoking status.[162-164] Studies among adults have shown a similar pattern, with increased prevalence of chronic respiratory conditions (ie, asthma or chronic obstructive pulmonary disease) among vape pen users,[165 166] and higher risk of myocardial infarction and stroke, but lower risk of diabetes.[167]

The effects of vaping on lung function as determined by spirometric studies are more varied. Reported studies have assessed lung function after a brief exposure to vape aerosols, varying from 5-60 minutes in duration, and no longer term observational cohort studies exist. While some studies have shown increased airway resistance after vaping exposure,[130 168 169] others have shown no change in lung function.[137 170 171] The cumulative exposure of habitual vape pen users to vape aerosols is much longer than the period evaluated in these studies, and the impact of vaping on longer term respiratory heath remains to be seen. Recent work evaluating ventilation-perfusion matching among chronic vapers compared with healthy controls found increased ventilation-perfusion mismatch, despite normal spirometry in both groups.[172] Such work

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reinforces the notion that changes in spirometry are a feature of more advanced airways disease, and early studies, although inconsistent, may foreshadow future respiratory impairment in chronic vapers.

Covid-19 and vaping

The covid-19 pandemic brought renewed attention to the potential health impacts of vaping. Studies investigating the role of vaping in covid-19 prevalence and outcomes have been limited by the small size of the populations studied and results have been inconsistent. Early work noted a geographic association in the US between vaping prevalence and covid-19 cases,[173] and a subsequent survey study found that a covid-19 diagnosis was five times more likely among teens who had ever vaped.[174] In contrast, a UK survey study found no association between vaping status and covid-19 infection rates, although captured a much smaller population of vape pen users.[175] Reports of nicotine use upregulating the angiotensin converting enzyme 2 (ACE-2) receptor,[176] which serves as the binding site for SARS-CoV-2 entry, raised the possibility of increased susceptibility to covid-19 among chronic nicotine vape pen users.[177 178] Further, vape use associated with sharing devices and frequent touching of the mouth and face were posited as potential confounders contributing to increased prevalence of covid-19 in this population.[179]

Covid-19 outcomes among chronic vape pen users remain an open question. While smoking has been associated with progression to more severe infections,[180 181] no investigation has been performed to date among vaping cohorts. The young average age of chronic vape pen users may prove a protective factor, as risk of severe covid-19 infection has been shown to increase with age.[182] Regardless, a prudent recommendation remains to abstain from vaping to mitigate risk of progression to severe covid-19 infection.[183]

Increased awareness of respiratory health brought about by covid-19 and EVALI is galvanizing the changing patterns in vape pen use.[184] Survey studies have consistently shown trends toward decreasing use among adolescents and young adults.[174 185 186] In one study, up to two thirds of participants endorsed decreasing or quitting vaping owing to a combination of factors including difficulty purchasing vape products during the pandemic, concerns about vaping effects on lung health, and difficulty concealing vape use while living with family.[174] Such results are reflected in nationwide trends that show halting growth in vaping use among high school students.[8] These trends are encouraging in that public health interventions countering nicotine use among teens may be meeting some measure of success.

Clinical impact—collecting and recording a vaping history

Vaping history in electronic medical records

Efforts to prevent, diagnose, and treat vaping related lung injury begin with the ability of our healthcare system to identify vape users. Since vaping related lung injury remains a diagnosis of exclusion, clinicians must have a high index of suspicion when confronted with idiopathic lung injury in a patient with vaping exposure. Unlike cigarette use, vape pen use is not built into most EMR systems, and is not included in meaningful use criteria for EMRs.[187] Retrospective analysis of outpatient visits showed that a vaping history was collected in less than 0.1% of patients in 2015,[188] although this number has been increasing.[189 190] In part augmented by EMR frameworks that prompt collection of data on vaping history, more recent estimates indicate that a vaping history is being collected in up to 6% of patients.[191] Compared with the widespread use of vaping, particularly among adolescent and young adult populations, this number remains low. Considering generational trends in nicotine use, vaping will likely eventually overcome cigarettes as the most common mode of nicotine use, raising the importance of collecting a vaping related history. Further, EMR integration of vaping history is imperative to allow for retrospective, large scale analyses of vape exposure on longitudinal health outcomes at a population level.

Practical considerations—gathering a vaping history

As vaping becomes more common, the clinician's ability to accurately collect a vaping history and identify patients who may benefit from nicotine cessation programs becomes more important. Reassuringly, gathering a vaping history is not dissimilar to asking about smoking and use of other tobacco products, and is summarized in box 2 . Collecting a vaping history is of particular importance for providers caring for adolescents and young adults who are among the highest risk demographics for vape pen use. Adolescents and young adults may be reluctant to share their vaping history, particularly if they are using THC-containing or CBD-containing vape solutions. Familiarity with vernacular terms to describe vaping, assuming a non-judgmental approach, and asking parents or guardians to step away during history taking will help to break down these barriers.[192]

The following provides a practical guide on considerations when collecting a vaping history. Of note, collecting a partial history is preferable to no history at all, and simply recording whether a patient is vaping or not adds valuable information to the medical record.

Vape use—age at time of vaping onset and frequency of vape pen use. Vape pen use >5 times a day would be considered frequent. Alternatively, clinicians may inquire how long it takes to deplete a vape solution pod (use of one or more pods a day would be considered heavy use), or how frequently users are refilling their vape pens for refillable models.

Vape products—given significant variation in vape solutions available on the market, and

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Box 2: Practical guide to collecting a vaping history

Ask with empathy

Young adults may be reluctant to share history of vaping use. Familiarity with vaping terminology, asking in a non-judgmental manner, and asking in a confidential space may help.

Ask what they are vaping

Vape products—vape pens commonly contain nicotine or an alternative active ingredient, such as THC or CBD. Providers may also inquire about flavorants, or other vape solution additives, that their patient is consuming, particularly if vaping related lung injury is suspected.

Source—ask where they source their product from. Sources may include commercially available products, third party distributors, or friends or local contacts.

Ask how they are vaping

Device—What style of device are they using?

Frequency—How many times a day do they use their vape pen (with frequent use considered >5 times a day)? Alternatively, providers may inquire how long it takes to deplete a vape solution cartridge (with use of one or more pods a day considered heavy use).

Nicotine concentration—For individuals consuming nicotine-containing products, clinicians may inquire about concentration and frequency of use, as this may allow for development of a nicotine replacement therapy plan.

Ask about other inhaled products

Clinicians should ask patients who vape about use of other inhaled products, particularly cigarettes. Further, clinicians may ask about use of water pipes, heat-not-burn devices, THC-containing products, or dabbing.

variable risk profiles of the multitude of additives, inquiring as to which products a patient is using may add useful information. Further, clinicians may inquire about use of nicotine versus THC-containing vape solutions, and whether said products are commercially available or are customized by third party sellers.

Concurrent smoking—simultaneous use of multiple inhaled products is common among vape users, including concurrent use of conventional cigarettes, water pipes, heat-not-burn devices, and THC-containing or CBD-containing products. Among those using marijuana products, gathering a history regarding the type of product use, the device, and the modality of aerosol generation may be warranted. Gathering such detailed information may be challenging in the face of rapidly evolving product availability and changing popular terminology. Lastly, clinicians may wish to inquire about "dabbing"—the practice of inhaling heated butane hash oil, a concentrated THC wax—which may also be associated with lung injury.[193]

Future directions

Our understanding of the effects of vaping on respiratory health is in its early stages and multiple trials are under way. Future work requires enhanced understanding of the effects of vape aerosols on lung biology, such as ongoing investigations into biomarkers of oxidative stress and inflammation among vape users (clinicaltrials.gov NCT03823885). Additional studies seek to elucidate the relation between vape aerosol exposure and cardiopulmonary outcomes among vape pen users (NCT03863509, NCT05199480), while an ongoing prospective cohort study will allow for longitudinal assessment of airway reactivity and spirometric changes among chronic vape pen users (NCT04395274).

Public health and policy interventions are vital in supporting both our understanding of vaping on respiratory health and curbing the vaping epidemic among teens. Ongoing, large scale randomized controlled studies seek to assess the impact of the FDA's "The Real Cost" advertisement campaign for vaping prevention (NCT04836455) and another trial is assessing the impact of a vaping prevention curriculum among adolescents (NCT04843501). Current trials are seeking to understand the potential for various therapies as tools for vaping cessation, including nicotine patches (NCT04974580), varenicline (NCT04602494), and text message intervention (NCT04919590).

Table 1 | Summary of clinical guidelines

Source	Reference	Date Published	Imaging	Infectious investigation	Further diagnostic investigation	Empiric antibiotics	Steroid administration	Follow-up testing
J Thorac Oncol	Rice, 2020	November 2020	Outpatients: chest radiograph Inpatients: chest radiograph or CT scan	Outpatients: influenza testing Inpatients: infectious testing including covid-19	BAL or lung biopsy for admitted patients	Empiric antibiotics for inpatients "as the condition warrants"	Systemic steroids "as the condition warrants"	No recommendation
J Thorac Dis	Hage, 2020	July 2020	Chest CT preferable. Any patient with an abnormal chest radiograph should undergo chest CT	Blood cultures, sputum culture, and Gram staining, urine *Legionella* and *Pneumococcus* antigen, respiratory viral panel	BAL for patients with abnormal radiology; consider staining for lipids. Arterial blood gas, urine toxicology, spirometry	Antibiotic and/or antiviral therapy should be considered	High dose systemic corticosteroids associated with improvement	Pulse oximetry, chest radiograph, spirometry with CO diffusion
CDC	MMWR 68;919-927	October 2019	Chest radiograph on all patients. Consider Chest CT on a case-by-case basis	Respiratory viral panel, additional testing per guidelines for evaluation of community acquired pneumonia	BAL on a case-by-case basis, including staining for lipids	Outpatients: consider empiric antibiotics or antivirals Inpatients: strongly consider empiric antibiotics and/or antivirals for severe illness	Systemic corticosteroids might be helpful; empiric trial warranted in severe illness	Pulse oximetry, chest radiograph, spirometry with CO diffusion

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Finally, evaluation of vaping as a potential tool for harm reduction among current cigarette smokers is undergoing further evaluation (NCT03235505), which will add to the body of work and eventually lead to clear policy guidance.

Guidelines

Several guidelines on the management of vaping related lung injury have been published and are summarized in table 1.[194-196] Given the relatively small number of cases, the fact that vaping related lung injury remains a newer clinical entity, and the lack of clinical trials on the topic, guideline recommendations reflect best practices and expert opinion. Further, published guidelines focus on the diagnosis and management of EVALI, and no guidelines exist to date for the management of vaping related lung injury more generally.

Conclusions

Vaping has grown in popularity internationally over the past decade, in part propelled by innovations in vape pen design and nicotine flavoring. Teens and young adults have seen the biggest uptake in use of vape pens, which have superseded conventional cigarettes as the preferred modality of nicotine consumption. Despite their widespread popularity, relatively little is known about the potential effects of chronic vaping on the respiratory system, and a growing body of literature supports the notion that vaping is not without risk. The 2019 EVALI outbreak highlighted the potential harms of vaping, and the consequences of long term use remain unknown.

Discussions regarding the potential harms of vaping are reminiscent of scientific debates about the health effects of cigarette use in the 1940s. Interesting parallels persist, including the fact that only a minority of conventional cigarette users develop acute lung injury, yet the health impact of sustained, longitudinal cigarette use is unquestioned. The true impact of vaping on respiratory health will manifest over the coming decades, but in the interval a prudent and time tested recommendation remains to abstain from consumption of inhaled nicotine and other products.

QUESTIONS FOR FUTURE RESEARCH

- How does chronic vape aerosol exposure affect respiratory health?
- Does use of vape pens affect respiratory physiology (airway resistance, V/Q matching, etc) in those with underlying lung disease?
- What is the role for vape pen use in promoting smoking cessation?
- What is the significance of pulmonary alveolar macrophages in the pathophysiology of vaping related lung injury?
- Are particular populations more susceptible to vaping related lung injury (ie, by sex, demographic, underlying comorbidity, or age)?

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