# E-cigarette or vaping product use-associated lung injury


## Abstract

E-cigarette or vaping product use-associated lung injury is a recently recognised, acute pulmonary syndrome which has been reported (particularly from June to October 2019) throughout the USA, but not in Europe (although one probable case, in the UK, has been reported; Medicines and Healthcare products Regulatory Agency, 2020). It presents acutely, most often in young men, as severe pulmonary consolidation, usually with respiratory failure. The mortality is around 2%. The cause(s) are unknown, but it is associated with vaping, particularly using unlicensed cannabis-containing products with tetrahydrocannabinol. Vitamin E acetate, often present in tetrahydrocannabinol-containing vape products as a solvent, has been implicated, as it has been identified in the bronchoalveolar lavage fluid of patients with e-cigarette or vaping product use-associated lung injury. This article reviews the recent literature, including clinical features, presentation and investigations, and possible mechanisms, in the context of vaping practices in the USA and the UK.



**Key words:** Acute lung injury; E-cigarette; EVALI; Vaping

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## Introduction

Electronic cigarettes (e-cigarettes) were introduced about 15 years ago as an alternative to conventional cigarette smoking. The safety aspects have always been controversial, as they were marketed without extensive toxicological studies and there are no long-term data in humans. Vaping has become a multibillion dollar industry, largely controlled by the tobacco companies (U.S. Department of Health and Human Services, 2016; The Business Research Company, 2020).

E-cigarette or vaping product use-associated lung injury is a recently recognised (particularly between June and October 2019) acute pulmonary syndrome (Layden et al, 2019; Lewis et al, 2019; Siegel et al, 2019; Dicpinigaitis et al, 2020), occurring throughout the USA. The cause(s) are unknown, but it is associated with vaping and particularly using unlicensed, cannabis-containing products with tetrahydrocannabinol (Table 1).

Vaping refers to using one of various electronic nicotine delivery systems – e-cigarettes, vaporisers, vape or vape pens – to inhale substances such as nicotine, marijuana, tetrahydrocannabinol, cannabidiol or synthetic cannabinoids. 'Dabbing' is a term used to refer to the vaporising of cannabis oils.

## E-cigarette safety and regulation

In both the USA and the UK, e-cigarettes and e-liquids only came under tobacco legislation in 2016. An estimated 41 000 different vaping products are available in the UK; 90% relating to containers and refills and 10% to e-cigarette devices and components (including approximately 7000 flavourings). Sales to under 18-year-olds are banned in the UK (McNeill et al, 2018). While vaping is restricted in various situations in the UK, it is banned completely in various cities, counties and six states in the USA.

Major controversy about the safety of e-cigarettes continues (reviewed by Gotts et al, 2019), although it is likely that they are safer than conventional tobacco smoking and beneficial in smoking cessation. A number of cross-sectional studies has found increased


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**Table 1. Clinical characteristics of e-cigarette or vaping product use-associated lung injury: prevalence (%) in three published series**

| Feature | | Layden et al (2019) | Lewis et al (2019) | Siegel et al (2019) |
|---|---|---|---|---|
| *n* | | 53: 28 from Wisconsin, 25 from Illinois | 83 from Utah* | 1299 (national surveillance) |
| Median age (range) y | | 19 (16–53) | 26 (14–66) | 24 (13–75) (*n*=1043) |
| Male (%) | | 83 | 69 | 70 (*n*=1043) |
| Symptoms | Mean duration (days) | 6 | – | – |
| | Respiratory (%) | 98 | – | 95 (*n*=339) |
| | Gastrointestinal (%) | 81 | – | 77 (*n*=339) |
| | Constitutional (%) | 100 | – | 85 (*n*=339) |
| History | Asthma (%) | 30 | 20 | – |
| | Anxiety (%) | 34 | 34 | – |
| | Vaping tetrahydrocannabinol (%)† | 84 | 92 | 76 (*n*=573) |
| | Nicotine alone (%)‡ | 17 | 6 | 13 (*n*=573) |
| At presentation | Fever (%) | 29 | – | – |
| | Heart rate>100/min (%) | 64 | – | 57 (*n*=310) |
| | Respiratory rate>20/min (%) | 43 | – | 45 (*n*=172) |
| | Oxygen saturation ($SaO_2$) <95% (%) | 69 | – | 57 (*n*=253) |
| | White cell count >11 000/microlitre (%) | 87 | – | – |
| | Neutrophils >80% (%) | 94 | – | – |
| | Erythrocyte sedimentation rate >30 (%) | 93 | – | – |
| | Abnormal chest X-ray¶ (%) | 91 | – | – |
| | Hospitalised (%) | 94 | 89 | 96 (*n*=1002) |
| | Mean stay (days) | 6 | 4 | 6.7 |
| | Intensive therapy unit (%) | 58 | 44 | 47 (*n*=342) |
| | Intubated (%) | 32 | 11 | 22 (*n*=342) |
| | Deaths (%) | 2 | 0 | 2 |
| Treatment | Added oxygen (%) | 87 | | – |
| | Antibiotics (%) | 90 | – | |
| | Steroids (%) | 92 | 75 | 88 (*n*=287) |

**Centers for Disease Control report up to 8 October 2019, with different n values for different measures;†some component of tetrahydrocannabinol +/– nicotine; ‡vaping of nicotine alone recorded; ¶ abnormal computed tomography scan in 100% (by definition).*

respiratory symptoms and possible asthma in adolescents. Vaping in the previous month was associated with increased reporting of cough or phlegm (odds ratio 2.1, 95% confidence interval 1.8–2.5) in a survey of 45 128 adolescents in Hong Kong (Wang et al, 2016). Previous and current use of e-cigarettes in 2086 high school students in southern California was associated with an almost twofold increase in the risk of chronic cough or phlegm (McConnell et al, 2017). A survey of 35 904 Korean high school students found a physician diagnosis of asthma in the previous year was reported more frequently in current e-cigarette users than never users (odds ratio 2.7, confidence interval 1.3–5.8) (Cho and Paik, 2016). In 36 085 high school students who participated in the 2012 Florida Youth Tobacco Survey,

prevalence of ever and past-30-day use of e-cigarettes among students who reported having asthma were 10.4% and 5.3% respectively, which was higher than their counterparts who had never been diagnosed with asthma (ever use=7.2% and past 30-day use=2.5%; $P<0.01$). Furthermore, among participants with asthma ($n=5865$) past-30-day e-cigarette use was associated with an asthma attack in the previous year ($P<0.01$) (Choi and Bernat, 2016). In a 2015 state-wide survey of 6089 adolescents in Florida schools, current e-cigarette use was associated with current asthma vs never having asthma (adjusted odds ratio 1.48, confidence interval 1.26–1.74) independent of cigarette smoking, marijuana use, ethnic origin and other covariates (Schweitzer et al, 2017).

In adults, a number of cross-sectional studies has reported an association of e-cigarette use with increased respiratory symptoms. A telephone survey in Hawaii ($n=8087$) reported associations between e-cigarette use and diagnoses of chronic obstructive pulmonary disease and asthma, which were more marked in non-smokers (Wills et al, 2019). In a population-based study in Sweden, associations of e-cigarette use with respiratory symptoms (chronic cough, sputum or wheeze) were strongest among dual users who also smoked cigarettes (Hedman et al, 2018). An analysis of 39 747 participants in the Health eHeart Study found that e-cigarette use (and dual use) was associated with higher self-ratings of dyspnoea, reports of chronic obstructive pulmonary disease and asthma, and worse general health (Wang et al, 2018).

More direct effects of e-cigarettes on airflow and airway calibre, as assessed by acute spirometric changes, are somewhat inconsistent. These effects, as well as those on small airways, assessed indirectly by various biomarkers, are summarised by Gotts et al (2019). They also include a discussion of the wide variety of in vitro, adverse cellular effects on pulmonary inflammation, oxidative stress, mucociliary function and innate immunity. These are often inconsistent, may be nicotine-dependent and independent, but are outside the scope of this review.

Not surprisingly, acute and more chronic e-cigarette exposure studies involving propylene glycol or vegetable glycerine, with or without nicotine, and various commercial e-liquids have been carried out in animals. A very wide spectrum of potentially adverse effects on pulmonary inflammatory cells, their products including mucins, cytokines, other proteins, oxidative stress, impaired autophagy, impaired bacterial clearance, airway remodelling, airway hyper-responsiveness, alveolar cell apoptosis and changes suggestive of emphysema have been reported in about 60 studies in rodents, particularly mice (reviewed by Gotts et al, 2019).

A possible mechanism for the presence of lipid-laden macrophages in the bronchoalveolar lavage fluid is suggested by a mouse study showing that exposure to e-cigarette vapour (60% propylene glycol and 40% vegetable glycerine) for 4 months, independent of nicotine, led to altered alveolar macrophage and epithelial cell lipid homeostasis with aberrant phospholipids and increased surfactant-associated phospholipids in the airway (Madison et al, 2019). Additionally, they reported evidence of downregulated innate immunity against viral pathogens in resident macrophages and poor response to viral challenge.

While animal studies of up to 6 months' duration have been published, there are no long-term human studies, which is of particular concern considering how long it took to determine, scientifically, the adverse pulmonary effects of chronic cigarette smoking, let alone the decades it took to defeat the tobacco companies and limit the harm they continue to cause.

## Usage in the USA and the UK

A behavioural risk factor analysis of 466 842 adults suggested that 4.5% of the American population (10.8 million adults) were current e-cigarette users (Mirbolouk et al, 2018). In the UK, Action on Smoking and Health YouGov annual surveys have shown an increase from around 700 000 adult e-cigarettes users in 2012 to around 3.6 million in 2019 (Action on Smoking and Health, 2019). Fruit-based flavours have increased in popularity since 2015. Pre-filled cartridges (pods) such as JUUL account for 40% of retail sales in the USA but much less in the UK market (Huang et al, 2019). There are considerable differences in usage and practice of vaping in the UK compared to the USA (**Table 2**) (Huang et al, 2019). It seems very likely that the discrepant reporting of e-cigarette or vaping product use-associated lung injury in the two countries may relate to one or more of these differences.

## Lung disease and e-cigarettes

Clusters of e-cigarette or vaping product use-associated lung injury cases (Layden et al, 2019; Lewis et al, 2019; Siegel et al, 2019; Dicpinigaitis et al, 2020) have been widely reported throughout the USA, but not in Europe. This has been the subject of a number of public health reports and recommendations in the USA (Blount et al, 2019; Lewis et al, 2019; Siegel et al, 2019).

A variety of other pulmonary conditions, apparently associated with e-cigarette use, has appeared, sporadically, in a small number of case reports (Table 3).

## Clinical features

The clinical features of e-cigarette or vaping product use-associated lung injury, described in three of the largest published series, are summarised in Table 1 (Layden et al, 2019; Lewis et al, 2019; Siegel et al, 2019). Typically, it is an acute illness characterised by respiratory and gastrointestinal symptoms, and systemic upset. Its onset has usually been ≤7 days (although there are reports of up to 3 months' delay). It has most often occurred in previously fit, mainly young, men (80% have been less than 35 years old), but has also been reported in older people. By definition, it is associated with use of vaping or dabbing within 90 days (mainly after much shorter intervals) and nearly always with

**Table 2. Differences between USA and UK experience with vaping**

| UK | USA |
|---|---|
| Widely used (7.1% adults) | Widely used (4.5% adults) |
| Used mainly as smoking cessation | Used mainly recreationally |
| Some bans in public spaces | Banned in some states |
| | Some flavourings banned |
| Mainly refillable tank devices | Pre-filled 'pods' more popular |
| Mainly used containing 1–12 mg/ml nicotine | Higher nicotine doses (up to 50 mg/ml) available |
| Cannabidiol e-liquids legal and available | Cannabidiol products widely available |
| All tetrahydrocannabinol banned (usage unknown) | Tetrahydrocannabinol use legal in 11 states |

*From Holden and Hines (2016), McNeill et al (2018), Action on Smoking and Health (2019)*

**Table 3. Pulmonary conditions which have been associated with vaping**

| Condition | References |
|---|---|
| Acute pulmonary syndrome | Moore et al (2015); Landman et al (2019); Dicpinigaitis et al (2020) |
| Lipoid pneumonia | Moore et al (2015), Viswam et al (2018), Butt et al (2019), Landman et al (2019), Layden et al (2019), Maddock et al (2019), Dicpinigaitis et al (2020) |
| Eosinophilic pneumonia | Arter et al (2019) |
| Hypersensitivity pneumonitis | Sommerfield et al (2018) |
| Organising pneumonia | Kahn et al (2018) |
| Diffuse alveolar haemorrhage | Augustin et al (2018) |
| Rare interstitial lung disease (eg giant cell interstitial lung disease) | Flower et al (2017) |
| Bronchiolitis | Landman et al (2019) |
| Pneumothorax | Bonilla et al (2019) |
| Pneumonia and pleural effusions | Moore et al (2015); Anderson et al (2019) |

tetrahydrocannabinol-containing products. On presentation, it is associated with signs of tachycardia, tachypnoea, hypoxia (oxygen saturation <95% and usually lower). Imaging is non-specific with bilateral pneumonic changes – usually on chest X-ray, but invariably on high resolution computed tomography (Henry et al, 2019) when there may also be ground glass shadowing, consolidation and nodules. Blood tests usually show a leucocytosis, an acute phase response (raised C-reactive protein level or erythrocyte sedimentation rate), and sometimes abnormal liver function.

A 'confirmed' case requires exclusion of infection as far as possible; this should include negative virology (particularly influenza, although cases have occurred well outside the flu season), and negative bacteriology (particularly Pneumococcus and Legionella, by urine testing) (Siegel et al, 2019).

Bronchoscopy and bronchoalveolar lavage have yielded variable results, with variable leucocytosis, no eosinophilia, and often 'foamy' or lipid-laden macrophages (positive O red or Sudan staining), which has led to the suggestion of 'lipoid pneumonia' changes (Viswam et al, 2018; Layden et al, 2019; Lewis et al, 2019; Maddock et al, 2019; Dicpinigaitis et al, 2020). However, the significance of this is controversial. Paradoxically, the limited histology available (a total of 17 transbronchial and open lung biopsies) did not support the diagnosis of lipoid pneumonia, rather suggesting a possible airway-centred chemical pneumonitis (Butt et al, 2019). Furthermore, the typical changes of lipoid pneumonia are not generally seen on computed tomography (Henry et al, 2019). E-cigarette or vaping product use-associated lung injury had proved fatal in 39 (2%) of a total of 2051 cases by November 2019 (Blount et al, 2019) and in 57 out of 2355 cases by December 2019 (Ellington et al, 2020). Cases, emergency room visits and hospitalisations have all declined from a peak in September 2019 (Hartnett et al, 2020; Krishnasamy et al, 2020).

## Potential causes

E-cigarettes are filled with 'e-liquid' consisting of a carrier solvent, usually a blend of propylene glycol and vegetable glycerine (both water soluble), combined with one or more flavouring compounds and nicotine. Typical use results in significantly lower exposure to potentially toxic substances than with combustible tobacco cigarettes, with the exception of nicotine (Eaton et al, 2018).

However, most e-cigarette products contain and emit numerous potentially toxic substances (Table 4), which will vary according to device, e-liquid and mode of use. These include polycyclic aromatic hydrocarbons, nitrosamines, volatile organic chemicals, and inorganic chemicals such as toxic metals. Some contaminants are probably related to the use of impure nicotine, propylene glycol or vegetable glycerine. Other constituents may be related to flavourings and others to the packaging or manufacture of the products. Thermal decomposition products (thought to originate from e-liquid components, primarily propylene glycol and vegetable glycerine), including formaldehyde, acetaldehyde and acrolein, have been identified in e-cigarette vapour (Klager et al, 2017).

**Table 4. Potential harmful constituents of e-cigarette products**

| Component | Examples |
|---|---|
| Heavy metals | Nickel, lead, chromium, zinc, manganese, cobalt |
| Solvents | Propylene glycol, vegetable glycerine |
| | Vitamin E acetate |
| Flavourings | Vanilla, cinnamon, damascenone, menthol, terpenes, benzyl alcohol, aldehydes, pyrazines |
| Miscellaneous | Polycyclic aromatic hydrocarbons, nitrosamines |
| | Volatile organic compounds, thermal decomposition products, formaldehyde, acrolein |
| Impurities | Mineral, vegetable oils, hash oils |

*From Klager et al (2017), Mishra et al (2017), Eaton et al (2018), McNeill et al (2018), Olmedo et al (2018), Blount et al (2020)*

Flavourings include aldehydes (eg vanillin (vanilla), benzaldehyde (berry or fruit), cinnamaldehyde (cinnamon), damascenone (tobacco)), benzyl alcohol, terpenes (eg linalool (flowery), farnesol (apple)), pyrazines (eg coffee, chocolate), menthol, menthone and other minty compounds), and sweet flavours including ethyl maltol. While food flavourings may be safe by the oral route, they have generally not been tested for sensitising, toxic or irritant potential by inhalation. Bronchiolitis obliterans induced by diacetyl and 2,3-pentanedione (buttery flavouring) has long been recognised (Holden and Hines, 2016). An increasing number of studies has also found toxic metals such as nickel, lead and chromium in e-cigarette emissions, most likely released from the metallic coil used to heat the e-liquid during aerosol generation (Mishra et al, 2017; Olmedo et al, 2018). While it is well established that metals can be toxic for multiple organs and systems through inhalation, no studies have looked at the specific health effects of metals in e-cigarettes.

One or more of these potential toxins may be responsible for causing e-cigarette or vaping product use-associated lung injury, which could well be heterogeneous. A tetrahydrocannabinol-related component is thought to be likely. In a paper expanding on a Centers for Disease Control and Prevention Update, vitamin E acetate was identified in bronchoalveolar lavage samples from 48 out of 51 e-cigarette or vaping product use-associated lung injury (26 confirmed and 25 probable) patients and in none of 99 healthy controls (Blount et al, 2020). In one patient, coconut oil was detected in bronchoalveolar lavage, in addition to vitamin E acetate. In another patient, limonene (a diluent terpene) was found in the absence of vitamin E acetate or tetrahydrocannabinol. All other patients were negative for other priority toxicants: plant oils, medium-chain triglyceride oil, coconut oil, petroleum distillates, and diluent terpenes. Tetrahydrocannabinol or its metabolites were detected in bronchoalveolar lavage from 40 of 47 patients (85%) with e-cigarette or vaping product use-associated lung injury, including nine out of 11 patients who reported no use of tetrahydrocannabinol-containing e-cigarette products beforehand. In total, tetrahydrocannabinol use was reported or identified in 47 of 50 (94%) e-cigarette or vaping product use-associated lung injury patients.

Vitamin E acetate was previously widely reported in tetrahydrocannabinol-containing products used by e-cigarette or vaping product use-associated lung injury patients from late 2018; it now seems that its addition to vaping fluids parallels the e-cigarette or vaping product use-associated lung injury outbreak (Blount et al, 2020). Furthermore, it is not difficult to imagine potential mechanisms of toxicity. It has a long aliphatic tail which may align it in parallel with phospholipids in surfactant; enhanced transition of phosphatidylcholines from a gel to a liquid crystalline phase could then disrupt surfactant. Decomposition of vitamin E acetate on heating may produce other toxic compounds such as ketene. Although vitamin E acetate has now been convincingly identified at the site of lung injury, this does not prove that it is the cause of e-cigarette or vaping product use-associated lung injury; damage could result from one or more other ingredients.

## Clinical management

Empirical treatment has generally, understandably, included broad spectrum antibiotics (which have often been stopped early) and high dose corticosteroids (often methylprednisolone) with the clinical impression of associated rapid benefit, as well as supplemental oxygen and supportive care (Layden et al, 2019; Lewis et al, 2019; Siegel et al, 2019; Dicpinigaitis et al, 2020).

Quite rapid deterioration can occur, requiring admission to the intensive therapy unit and intubation and ventilation in a substantial number of cases. Up to 2% of patients have died despite intensive therapy unit interventions (Blount et al, 2019; Layden et al, 2019; Lewis et al, 2019; Siegel et al, 2019; Dicpinigaitis et al, 2020).

E-cigarette or vaping product use-associated lung injury remains a diagnosis of exclusion; there are no specific diagnostic tests but criteria have been published (Siegel et al, 2019) for so-called ‘confirmed’ and ‘probable cases’ (which might be better named ‘probable’ and ‘possible’). Infection, but also cardiac, rheumatological and cancerous causes, must have been excluded.

## Key points

- E-cigarette or vaping product use-associated lung injury is an apparently novel, acute pulmonary syndrome, often occurring in previously young, healthy men exposed to vaping, which has been described throughout the USA, but not in the UK.
- It has usually presented dramatically, with about 50% of cases being admitted to an intensive therapy unit, 20% requiring intubation and ventilation, and a mortality of 2%.
- High-dose corticosteroid therapy may be beneficial.
- Other rare sporadic case reports of pulmonary conditions associated with vaping have been published in the last few years.
- E-cigarette or vaping product use-associated lung injury appears to be related to tetrahydrocannabinol-containing vape liquids and possibly to the solvent additive vitamin E acetate.
- E-cigarette or vaping product use-associated lung injury may well be heterogenous, as some cases have been associated with foamy macrophages and 'lipoid' pneumonia.
- Information is evolving rapidly and the syndrome may be declining in prevalence.

## Uncertainties regarding e-cigarette or vaping product use-associated lung injury

Unsurprisingly, given its recent description and rapid evolution, considerable uncertainties surround e-cigarette or vaping product use-associated lung injury. The epidemiology and natural history are not well defined; milder forms of acute syndrome may as yet be unrecognised, the effects of exposure to individual components of electronic nicotine delivery systems remain to be described, the prognosis if exposure is stopped, and the response to corticosteroids and any long-term sequelae are unclear. The suggestion from Centers for Disease Control and Prevention reports and recent surveillance (Hartnett et al, 2020) that the incidence may have decreased between September and December 2019 may be over-optimistic. Potential causative mechanism(s), particularly in patients who have not been exposed to tetrahydrocannabinol, require elucidation as does the significance of lipoid pneumonia in some of the cases.

## Conclusions

E-cigarette or vaping product use-associated lung injury is an apparently novel, acute pulmonary syndrome, often seen in young, healthy people. It usually presents dramatically, and has been described throughout the USA. It is noteworthy that, while other rare vaping-associated lung conditions have previously been recognised (including from the UK), clusters of cases of this syndrome have not been seen in Europe. About 80% of cases (probably an underestimate) have been associated with vaping of tetrahydrocannabinol-containing unregulated products. The prevalence of this outside the USA is unknown. Circumstantial evidence incriminates vitamin E acetate (Blount et al, 2019). Many uncertainties surround e-cigarette or vaping product use-associated lung injury, which may be heterogeneous. The situation is evolving rapidly. It is suggested that the prevalence may be reducing (from September to October 2019 and now to December) (Hartnett et al, 2020).

Clinicians need to remember the importance of taking a vaping history in patients with respiratory symptoms and diagnoses.

**Conflicts of interest**

The author declares no conflicts of interest.

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