Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study

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Summary

Background An ongoing outbreak of lung injury associated with e-cigarettes or vaping (also known as E-VALI or VALI) started in March, 2019, in the USA. The cause, diagnosis, treatment, and course of this disease remains unknown.

Methods In this multicentre, prospective, observational, cohort study, we collected data on all patients with lung injury associated with e-cigarettes or vaping seen in Intermountain Healthcare, an integrated health system based in Utah, USA, between June 27 and Oct 4, 2019. Telecritical care, based in Salt Lake City, UT, USA, was used as the central repository for case validation, public reporting, and system-wide dissemination of expertise, which included a proposed diagnosis and treatment guideline for lung injury associated with e-cigarettes or vaping. We extracted data on patient presentation, treatment, and short-term follow-up (2 weeks after discharge) from chart review and interviews with patients undertaken by the Utah Department of Health (Salt Lake City, UT, USA).

Findings 60 patients presented with lung injury associated with e-cigarettes or vaping at 13 hospitals or outpatient clinics in the integrated health system. 33 (55%) of 60 were admitted to an intensive care unit (ICU). 53 (88%) of 60 patients presented with constitutional symptoms, 59 (98%) with respiratory symptoms, and 54 (90%) with gastrointestinal symptoms. 54 (90%) of 60 were given antibiotics and 57 (95%) were given steroids. Six (10%) of 60 patients were readmitted to an ICU or hospital within 2 weeks, three (50%) of whom had relapsed with vaping or e-cigarette use. Of 26 patients who were followed up within 2 weeks, despite clinical and radiographic improvement in all, many had residual abnormalities on chest radiographs (ten [67%] of 15) and pulmonary function tests (six [67%] of nine). Two patients died and lung injury associated with e-cigarettes or vaping was thought to be a contributing factor, but not the cause of death, for both.

Interpretation Lung injury associated with e-cigarettes or vaping is an emerging illness associated with severe lung injury and constitutional and gastrointestinal symptoms. Increased awareness has led to identification of a broad spectrum of severity of illness in patients who were treated with antibiotics and steroids. Despite improvement, at short-term follow-up many patients had residual abnormalities. Lung injury associated with e-cigarettes or vaping remains a clinical diagnosis with symptoms that overlap infectious and other lung diseases. Maintaining a high index of suspicion for this disease is important as work continues in understanding the cause or causes, optimal therapy, and long-term outcomes of these patients.

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Introduction

An ongoing outbreak of lung injury associated with e-cigarettes or vaping (also known as E-VALI or VALI) has been reported in the USA, starting in March, 2019, and including 1888 cases as of Oct 29, 2019.[1]

An initial case series of 53 patients described severe acute lung injury in those who had vaping exposure in the past 90 days.[2] The cause of lung injury associated with e-cigarettes or vaping is still unknown, and thus the original case definition described in the case series remains the basis for diagnosing the condition—namely, lung injury associated with e-cigarettes or vaping is a clinical diagnosis that comprises use of an e-cigarette (ie, vaping) in the 90 days before symptom onset, pulmonary infiltrates on plain chest radiograph or chest CT, and absence of another known cause, such as infection.[2]

Although the cause of lung injury associated with e-cigarettes or vaping remains unclear, patterns consistent with toxic inhalational pulmonary injury suggest direct injury rather than an infectious cause.[1,3] Lipoid pneumonia due to vaping has been previously reported,[4] and initial reports of this outbreak have reported lipid laden macrophages staining with oil red O on bronchoalveolar lavage samples;[5] however, the clinical course and radiographic[6] and pathological samples[7] do not support lipoid pneumonia as the mechanism of the lung injury in this outbreak of lung injury associated with e-cigarettes or vaping.

Research in context

Evidence before this study

A nationwide outbreak of lung injury associated with e-cigarettes or vaping was first reported in March, 2019, in the USA and more than 1880 cases have been reported to date. Although vaping is widespread globally, almost all cases have been reported in the USA. Initial reports noted severe cases of acute lung injury with constitutional and gastrointestinal symptoms, otherwise negative infectious diagnostic testing, and potential improvement with steroids. Increased disease recognition has led to subsequent small case series outlining the cases assessed at single institutions and public health reports of demographic data and vaping or e-cigarette use information. No pathognomonic test for this disease exists and bronchoscopy findings are non-specific. Uncertainty remains about disease course, appropriate diagnostic testing, the need for invasive testing, and treatment recommendations.

Added value of this study

In this study, we report the largest single health system cohort of patients with lung injury associated with e-cigarettes or vaping to date. Public awareness of the outbreak has led to increased recognition, and an evolving clinical picture of disease severity at presentation. Milder disease at presentation, whether due to earlier recognition or other reasons, was associated with less invasive testing (such as bronchoscopy) and shorter courses of lower doses of steroids. Most patients were treated with antibiotics and steroids, with perceived clinical improvement within days. We showed that a system resource (telecritical care) could be used to rapidly identify patients across multiple hospitals in an integrated health system, expediting recognition of this outbreak in one state in the USA. Using a specialised task force, we assessed cases at the system level rather than at individual hospitals, which facilitated validation of cases, shared expertise on the disease across the system, reporting of health outcomes to national bodies, and development of a standardised system approach around a guideline for diagnosis and treatment of lung injury associated with e-cigarettes or vaping. We also developed, and share, a practical clinical guideline for the diagnosis and treatment of lung injury associated with e-cigarettes or vaping.

Implications of all the available evidence

The collective evidence points to a possible opportunity to modify disease course in lung injury associated with e-cigarettes or vaping by faster recognition, cessation of vaping exposure at first symptom onset, and prompt initiation of steroid therapy. Additionally, in less severely ill patients with rapid improvement on steroids, extensive invasive testing, or even admission to hospital might not be necessary. Furthermore, while health systems globally determine whether this outbreak could be affecting their patients, the use of a system resource might help identify and increase the speed of response to an outbreak in which few severe cases accumulate at any single facility.

The prevalence of vaping tetrahydrocannabinol and nicotine compounds has been increasing among children and adults since 2014; however, the scale and severity of this new outbreak of acute lung injury indicates a more recent change in the composition of the e-liquid, and thus e-cigarette vapour, being vaped.[1,8,9] The number of cases of lung injury associated with e-cigarettes or vaping in Utah, USA, is one of the highest in the USA, despite the state having a similar proportion of adults who use e-cigarettes as the national average and being among the least populated states in the country.[10]

In 2017, 5·1% (95% CI 4·5–5·7; age-adjusted 4·9% [4·4–5·5]) of adults in Utah reported currently using e-cigarettes compared with 4·6% nationally.[11] The US Centers for Disease Control and Prevention (CDC), the US Food and Drug Administration, and other bodies are attempting to identify the chemical, metal, or other substances newly present in e-devices that might be causing this outbreak.[1,9]

Vaping involves heating an e-liquid that contains solvents such as glycol and propylene glycol; active agents, such as nicotine and tetrahydrocannabinol; flavourings; and other additives. The e-liquid is heated and aerosolised, creating an e-cigarette vapour for inhalation.[8]

With increased awareness, clinicians are more consistently obtaining vaping histories in patients who present with acute lung injury in medical centres throughout the USA and building experience with individual case series of patients with lung injury associated with e-cigarettes or vaping.[12] However, individual medical centres are most likely to recognise only the most severe cases in any outbreak and might not have the broader picture of the full range of disease presentations.[2,13]

Telehealth has been increasingly implemented across different hospital systems with resulting standardisation of care and intensive care unit (ICU) processes, and improvements in mortality and clinical care have been observed.[14] However, the role of telecritical care in expediting recognition of outbreaks and rapid dissemination in core competencies of treatment has not been previously reported.

The objectives of this study were to report the clinical course, treatment, and outcomes of the largest single health system cohort of patients with lung injury associated with e-cigarettes or vaping to date. Additionally, we note the key role of telecritical care in facilitating the rapid recognition of an outbreak, establishment of a system response via a specialised task force, dissemination of knowledge, and implementation of a proposed guideline for evaluation and treatment of lung injury associated with e-cigarettes or vaping for clinicians in an integrated health system.

Methods

Study design and patients

In this prospective observational cohort study, we collected data on all patients with lung injury associated with e-cigarettes or vaping seen at Intermountain Healthcare, Salt Lake City, UT, USA, between June 27 and Oct 4, 2019. Intermountain Healthcare is a Utah-based, not-for-profit, integrated health system comprising 24 hospitals (including one virtual hospital) and approximately 160 clinics serving patients throughout the state of Utah and parts of Idaho, Wyoming, and Nevada. In 2018, nearly 500 000 people visited the emergency department and over 130 000 people were admitted into the system as acute inpatients.[15] In 2018, over 22 000 people were admitted to Intermountain Healthcare ICUs (Grissom CK, personal communication).

We used the case series definition for lung injury associated with e-cigarettes or vaping of pulmonary infiltrates (on chest radiograph or chest CT, or both) in a patient with history of e-cigarette use or vaping in the 90 days before symptom onset, and exclusion of alternative diagnosis.[2] Patients who denied a history of vaping at initial presentation, but subsequently reported a recent history of vaping, were included.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. It was approved by the Institutional Review Board at Intermountain Healthcare (1051214). Release of Utah Department of Health data is allowable under Utah admin code 26-6-27(2)(c) with data sharing related to public health efforts to interrupt transmission of disease.[16] The need for individual patient consent was waived by the Insitutional Review Board.

Procedures

Eligible patients were identified by clinicians during routine care at hospitals, ICUs (including the virtual hospital ICU service), emergency departments, and outpatient clinics. After the index case at Intermountain Healthcare was identified, the telecritical care service became the central repository and resource for data collection and public reporting. A task force was formed, comprising five pulmonary and critical care physicians.

All patients identified were referred to a member of the task force and whether they met inclusion criteria was reviewed and validated before acceptance into the cohort. Inclusion criteria were standardised among the task force members. Patients with an unclear history of vaping were provisionally tracked and over the course of their disease either included if history of vaping emerged or excluded.

In cases of ambiguity or disagreement, additional review by another member of the task force was sought, although no such situations have occurred to date. Reviews of patients included prospective and concurrent chart review for validation to ensure that the case definition for lung injury associated with e-cigarettes or vaping was met.

Initial notification of ICUs that an outbreak of lung injury associated with e-cigarettes or vaping had been noted occurred via routine shift hand-over between telecritical care physicians who monitor the most patients in the ICU in our system and who are also in-hospital clinicians in the ICU at our four major hospitals. As the outbreak evolved, the system ICU operational lane medical director (CKG) sent out a formal communication to all ICU directors and critical care physicians in the system via email. This communication directed all clinicians to refer patients suspected as having lung injury associated with e-cigarettes or vaping to a member of the task force to track outcomes and ensure public reporting, and reported current information on the state of the outbreak in our system. Subsequent email communications were sent by other system leaders about the outbreak to all emergency departments, hospitals, and pulmonary physicians in the system.

Vaping exposure history, signs and symptoms at presentation, laboratory and microbiological tests, bronchoscopy results, imaging findings, treatment, clinical course, and follow-up data were obtained via chart review in a standardised fashion. A shared web-based data repository in the system with controlled access enabled standardised data collection. All patient data were extracted prospectively via individual chart review by a group of trained clinicians who were part of the telecritical care team who had frequent reviews with the task force. One investigator (DPB), as part of routine clinical care, took detailed pulmonary exposure histories.

All patients with suspected or confirmed lung injury associated with e-cigarettes or vaping were reported to the Utah Department of Health (Salt Lake City, UT, USA) who did an independent investigation. Additional vaping exposure history was also obtained via standardised questionnaires by a Utah Department of Health staff member from patients or their proxy (eg, a family member) and some of these data are reported here.

All patients were treated according to the judgment of their clinician based on their clinical status, improvement, severity of illness, and other clinical factors. Telecritical care support was provided in consultation for ICU patients and others when requested.

As system-wide experience with lung injury associated with e-cigarettes or vaping increased, a proposed guideline for standardised assessment and treatment was developed (appendix pp 1–2) and circulated via email through the beforementioned system communication channels, first circulated on Oct 2, 2019, with updates as needed thereafter. These actions were implemented rapidly in the 2 months after recognition of the outbreak (Aug 6, 2019).

See Online for appendix

Statistical analysis

We report the presenting symptoms, signs, clinical course, treatment, and outcomes using descriptive statistics. We report continuous variables as medians with IQRs. We described the duration of symptoms

before presentation among patients admitted to an ICU compared with those who were not admitted to an ICU.

Due to the exploratory and descriptive nature of these analyses, no p values are reported. We did all statistical analyses using Stata, version 16.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

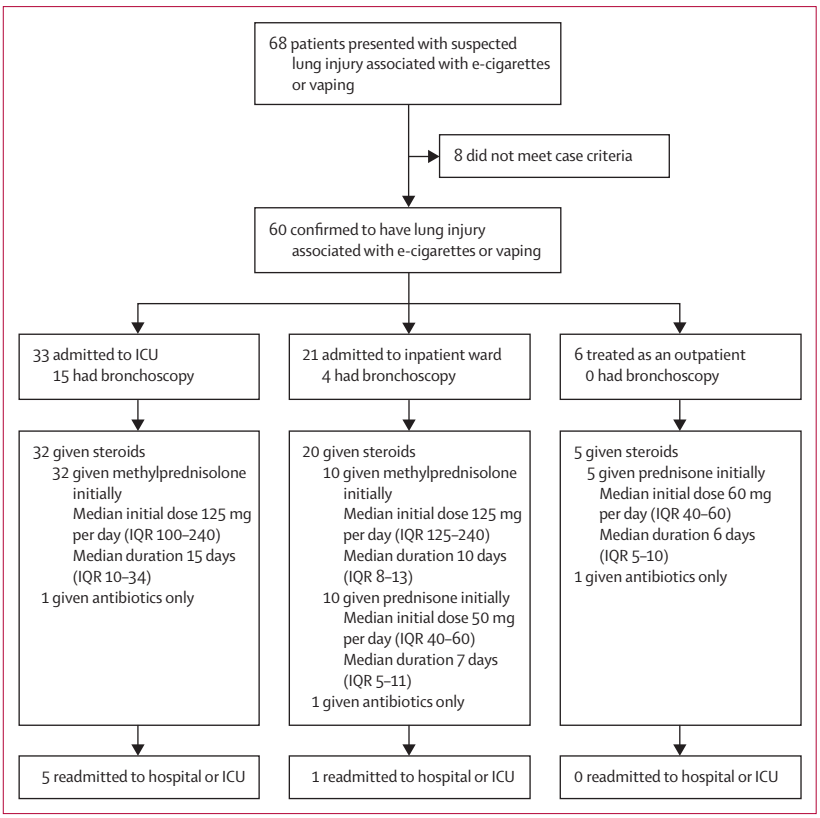

Figure 1: **Screening, admittance, and treatment of patients with lung injury associated with e-cigarettes or vaping**
ICU=intensive care unit.

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

68 patients with suspected lung injury associated with e-cigarettes or vaping were referred to the task force. On review, eight patients did not meet the case definition and were excluded. Thus, 60 patients with confirmed lung injury associated with e-cigarettes or vaping, who presented to 13 hospitals or outpatient clinics in the integrated health system, were included in this analysis (figure 1). This cohort comprises most of the reported cases of the condition in the state of Utah, with 71 cases identified as of Sept 30, 2019.[17]

The index patient who was admitted to Intermountain Healthcare was recognised as part of a cluster of patients with the condition on Aug 6, 2019, by a physician (DH) who subsequently identified other patients with the condition at other hospitals via change in shift hand-overs between telecritical care clinicians over the next day. The rapid dissemination of information via that centralised system service led to multiple other patients being referred by colleagues, including some who were identified retrospectively.

The first patient with lung injury associated with e-cigarettes or vaping at Intermountain Healthcare presented on June 27, 2019, but was not initially recognised as part of an outbreak. Another patient presented at that same hospital on July 21, 2019, again before recognition of the outbreak. Not until Aug 11, 2019, 5 days after the index patient was identified, did a single hospital identify multiple cases at once, with one hospital admitting three patients with the condition, a number that we speculate might have been sufficient for a single hospital to recognise a cluster of patients and hence a potential outbreak (figure 2).

Patients were identified at different hospitals throughout the state of Utah (figure 3), which were all part of the Intermountain Healthcare integrated health system.

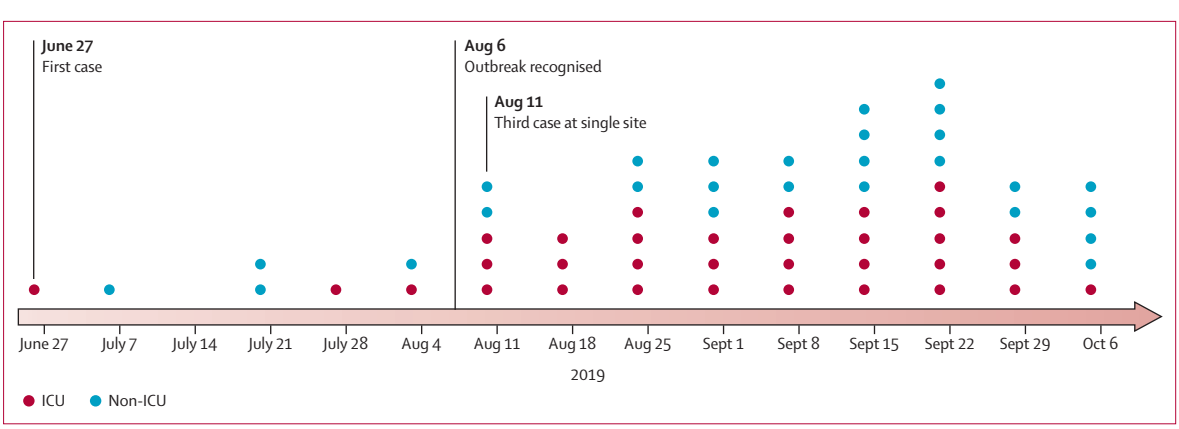

Figure 2: **Timeline of identification of patients with lung injury associated with e-cigarettes or vaping and recognition of outbreak**
Each dot represents an individual patient. ICU=intensive care unit

35 (58%) of 60 patients presented to tertiary hospitals in the health system and 17 (28%) were transferred from smaller facilities. However, eight (32%) of 25 patients who presented to smaller facilities were able to remain locally for treatment.

Demographic and presenting signs and symptoms among our cohort (table 1) were similar to those in other reports.[2,12,18] Notably, 12 (20%) of 60 patients were women and patients were young, with a median age of 27 years (IQR 22–36), without clinically significant comorbidities. 14 (23%) patients had a history of asthma, which is similar to the proportion of patients in previous reports.[2] All patients had vaping exposure to nicotine, tetrahydrocannabinol, or both, as required by the case definition.

Almost all patients presented with respiratory, constitutional, and gastrointestinal symptoms (table 1). For two patients, abdominal symptoms were their reason for presenting to the emergency department. The only notable abnormalities on their abdominal CT were bilateral ground glass opacities in the lung bases, which led to them having a chest CT, obtaining the vaping history, and a diagnosis of lung injury associated with e-cigarettes or vaping.

Hypoxaemia (peripheral capillary oxygen saturation ≤88%), tachypnoea (>20 breaths per min), and tachycardia (heart rate >100 beats per min) were common (table 1). Although 33 (55%) of 60 patients were admitted to an ICU, only ten (17%) were given mechanical ventilation. Laboratory abnormalities included mild increases in liver function tests, and leucocytosis with white blood cell counts above 11 000 per mm³.

Notably, when measured, inflammatory markers were often severely high, with a median C-reactive protein concentration of 31 mg/L (IQR 21–33), and median erythrocyte sedimentation rate of 92 mm/h (IQR 65–103). However, additional inflammatory serologies (antinuclear antibody, antiglomerular basement membrane, and antineutrophil cytoplasmic antibodies) were negative. Additionally, urinalysis was done in 46 patients, of whom 13 (28%) had 5 white blood cells per high powered field (hpf) or higher, and eight (17%) had 5 red blood cells per hpf or higher. Only two (3%) of 58 patients who had creatinine measured had concentrations higher than 2 mg/dL on presentation, one with 2·4 mg/dL and one with 9·6 mg/dL.

Although 33 (55%) of 60 patients presenting with lung injury associated with e-cigarettes or vaping were quite ill (ie, admitted to an ICU), the severity of illness varied, with six (10%) patients being treated in the outpatient setting. The frequency of bronchoscopy varied depending on where patients were admitted (figure 1).

A detailed exposure history was undertaken by the Utah Department of Health in 27 patients (table 2). The most commonly reported vaping devices were Juul for nicotine and Dank Vapes for tetrahydrocannabinol. Patients commonly purchased their vape liquid via an online dealer, social media app, or friends. Patients often used a variety of e-liquids, with tetrahydrocannabinol oil being the most common.

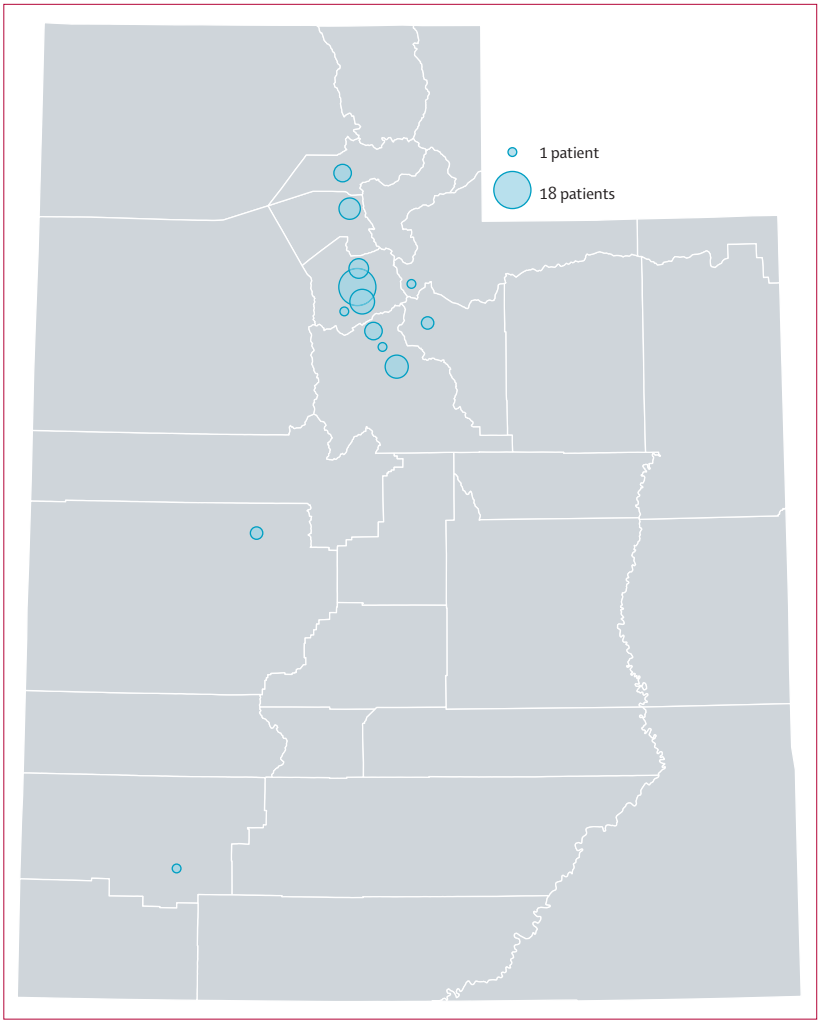

Figure 3: **Geographical distribution of patients with lung injury associated with e-cigarettes or vaping**
The health-care facilities where patients were identified are shown. Circles are proportional to the number of patients identified, ranging from one to 18 patients per centre.

Most patients used prefilled cartridges or premade liquids, with only one (5%) of 21 patients who responded reporting that they mixed their own liquid. Although some patients reported they had only started vaping or using an e-cigarette in the past year (one as part of an attempt to discontinue smoking cigarettes), many others noted they had been vaping for several years (table 2).

The longest reported period of vaping was 5 years before presentation, with a median of 225 days (IQR 90–620) before presentation. Frequency of vaping varied from one or two times per week to over 50 times per day, with some reporting use "constantly" and "every 5 mins". Of the 24 patients who reported frequency, ten (42%) reported use more than 24 times per day, and the most commonly reported use was three puffs at a time.

	Total cohort (n=60)
Demographic	
Sex	
Male	48 (80%)
Female	12 (20%)
Age, years	27 (22–36)
Race	
White, not Hispanic	43 (72%)
Hispanic	13 (22%)
Asian	1 (2%)
Unknown	2 (3%)
Declined	1 (2%)
Clinical	
Medical history	
Asthma	14 (23%)
Depression or anxiety	19 (32%)
E-cigarette use in previous 90 days	
E-nicotine use	40 (67%)
Only e-nicotine use	10 (17%)
E-tetrahydrocannabinol use	47 (78%)
Only e-tetrahydrocannabinol use	18 (30%)
Both e-nicotine and e-tetrahydrocannabinol use	29 (48%)
E-cannabidiol oil use	4 (5%)
Presenting symptoms	
Duration of symptoms before presentation, days	6 (3–9)
Any respiratory symptom	59 (98%)
Dyspnoea	51 (85%)
Chest pain	26 (43%)
Pleurisy	21 (35%)
Cough	47 (78%)
Haemoptysis	7 (12%)
Any gastrointestinal symptom	54 (90%)
Nausea	45 (75%)
Emesis	43 (72%)
Abdominal pain	28 (47%)
Any constitutional symptom	53 (88%)
Subjective fever	46 (78%)
Chills	28 (48%)
Weight loss	7 (12%)
Fatigue	29 (48%)
Headache	11 (18%)
Presenting signs and hospital data	
Febrile, temperature ≥38°C	34 (57%)
Heart rate >100 beats per min	50 (83%)
Respiratory rate >20 breaths per min	43 (72%)
SpO_2 while breathing room air*	
≥95%	8 (13%)
89–94%	19 (32%)
≤88%	31 (52%)
White blood cell count >11 000 per mm^3	46 (77%)
Erythrocyte sedimentation rate >30 mm/h	21/21 (100)
Erythrocyte sedimentation rate, mm/h (n=21)	92 (65–103)
C-reactive protein, mg/L (n=23)	31 (21–33)
Aspartate aminotransferase or alanine aminotransferase, or both	
>35 U/L	21 (35%)
>105 U/L	8 (14%)
Procalcitonin, µg/L (n=22)	0·30 (0·09–0·74)
Creatinine, mg/dL (n=58)	0·85 (0·72–0·96)
Abnormal chest radiograph	57/59 (97%)
Abnormal chest CT	45/45 (100%)
Triage and management	
Participated in detailed interview with Utah Department of Health	27 (45%)
Admitted to hospital	54 (90%)
Admitted to ICU	33 (55%)
Given bronchoscopy	19 (32%)
Given antibiotics	54 (90%)
Given steroids	57 (95%)
Given supplemental oxygen	53 (88%)
Given high-flow nasal cannula	28 (47%)
Given non-invasive positive pressure ventilation	17 (28%)
Given mechanical ventilation	10 (17%)
Clinical outcomes	
Hospital length of stay, days	5 (3–8)
ICU length of stay, if admitted to ICU, days	4 (0–7)
Days on ventilator, if received mechanical ventilation	3 (3–5)
Died	2 (3%)
Discharged on supplemental oxygen	17 (29%)
Readmission to hospital or ICU	6/58 (10%)

Data are n (%), n/N (%), or median (IQR). SpO_2=peripheral capillary oxygen saturation. ICU=intensive care unit. *Elevation in Utah is approximately 1500 m.

Table 1: **Demographic characteristics, symptoms, evaluation, and clinical course of patients with lung injury associated with e-cigarettes or vaping**

As previously reported,[2] bronchoalveolar lavage studies were non-specific and ruled out infection and alternative diagnoses, with no bronchoalveolar lavage test recovering organisms on fungal, viral, acid-fast-bacilli, aspergillus, or galactomannan testing (table 3).

Fitting with the case definition, no patients had a microbiologically confirmed infectious pneumonia diagnosis (table 3). Lipid laden macrophages on oil red O staining were present in the eight (89%) of nine bronchoscopy samples assessed. As part of routine clinical care, three patients were interviewed by one of the investigators (DPB) in detail on pulmonary exposure history, two of whom also reported using essential oil diffusers at home. Patients admitted to an ICU did not have longer duration of symptoms before presentation than those admitted to a hospital (7 days [IQR 4–9] *vs* 5 days [IQR 3–10]). Although clinicians reported that patients appeared to be presenting earlier in their disease course and with milder disease over time as news of the outbreak became public, we did not observe an association between the date of presentation

and duration of symptoms before presentation (appendix p 3). Similarly, we did not observe that fewer patients were admitted to the ICU in the first half of observation period than in the second half (figure 2).

Pneumothorax and pneumomediastinum were noted in 11 (18%) of 60 patients: six had pneumothorax, two had pneumomediastinum, one had both pneumothorax and pneumomediastinum, one had a pneumatocele that developed as a sequela of his lung injury and subsequently became infected, and one had emphysematous gastritis.

Billing codes based on the International Classification of Disease (ICD) that were used to describe these patients were inconsistent and many patients had multiple codes, which is to be expected given the current lack of specific ICD code for lung injury associated with e-cigarettes or vaping. The most common ICD code, in 30 (50%) of 60 patients, was acute hypoxic respiratory failure (J96.01). Additionally, acute respiratory failure (J96.00); respiratory failure caused by fumes (J68.9); systemic inflammatory response syndrome (R65.1); adult respiratory distress syndrome (J80); pneumonitis (J18.9); chemical pneumonitis due to chemicals, gases, fumes, and vapours (J68.0); acute lung injury (S27.309A); and hypersensitivity pneumonitis (J67.9) were commonly used. Codes that were used only once included hypersensitivity pneumonitis due to e-cigarette use (J80), pneumonitis due to inhalation of oils (J69.1), and inhalational injury (T14.90XA). Overall, 21 overlapping ICD codes were used.

Most patients received antibiotics, steroids, and oxygen (figure 1, table 1). The main therapy that treating clinicians believed led to rapid improvement within days was steroids. The initial steroid dosing and duration of therapy varied with severity of illness at presentation (figure 1, table 4). Patients admitted to an ICU were given higher doses and longer courses of steroids, whereas outpatients had short bursts of oral steroids (figure 1). 54 (90%) of 60 patients were given antibiotics due to overlapping presentation and diagnostic uncertainty.

Six (10%) of 60 patients were readmitted to hospital or an ICU at least 2 weeks after discharge, three (50%) of whom were readmitted due to vaping relapse (figure 1). One patient relapsed with vaping and was readmitted with pneumothorax and had a subsequent readmission for lung abscess and empyema. A second patient was not initially treated with steroids (diagnosed retrospectively in July, 2019) and was later readmitted to the hospital with pneumothorax and lung abscess. A third patient was readmitted to the hospital with an infected pneumatocele, which was a sequela of his lung injury associated with e-cigarettes or vaping and evolved over several weeks.

A fourth patient relapsed with vaping and was readmitted to the hospital with cholecystitis and underwent cholecystectomy (which was unremarkable on pathological examination). He was diagnosed with haemophagocytic lymphohistiocytosis and developed liver failure and died from multiorgan system failure 2 weeks after his original discharge.

	Patients who agreed to interview (n=27)
Length of use	
<1 year	10/23 (43%)
1–<2 years	4/23 (17%)
2–<3 years	6/23 (26%)
≥3 years	3/23 (13%)
Type of device used	
Disposable e-cigarette	5/23 (22%)
Reusable device for liquids	16/22 (73%)
Reusable device for wax or dry herbs	9/23 (39%)
Vape rig (for competitive vaping and stronger vape)	5/22 (23%)
Vaping salts	3/23 (13%)
Reported inhalation device	
Juul (nicotine)	7 (26%)
Smok (nicotine)	2 (7%)
Nicotine E-Juice (various brands)	7 (26%)
Golden Gorilla (tetrahydrocannabinol)	4 (15%)
Smart Cart (tetrahydrocannabinol)	3 (11%)
Cereal (tetrahydrocannabinol)	1 (4%)
Dank Vapes (tetrahydrocannabinol)	6 (22%)
Rove (tetrahydrocannabinol)	6 (22%)
Other brands of inhalation device (tetrahydrocannabinol)	11 (41%)
Where vape liquid purchased	
A Utah vape shop	4 (15%)
Dealer	4 (15%)
Online dealer or social media app	7 (26%)
Out of state dispensary	2 (7%)
Friend	5 (19%)
Convenience store	2 (7%)
Vape liquid or e-liquid used	
Prefilled cartridges	18/23 (78%)
Dank Vapes	10/22 (45%)
A variety of liquids	16/20 (80%)
Premade liquid	13/22 (59%)
Nicotine	17/25 (68%)
Tetrahydrocannabinol oil	22/25 (88%)
Marijuana	10/21 (48%)
Cannabidiol oil	10/23 (44%)
Synthetic marijuana	18/21 (86%)
Mixed own vape liquid	1/21 (5%)
If using tetrahydrocannabinol, using for medicinal reasons	7/11 (64%)

Data are n/N (%) or n (%) and are from patients who agreed to participate in a detailed interview with the Utah Department of Health. All answers given are non-exclusive, with patients often reporting more than one exposure.

Table 2: **Selected history on e-cigarette or vaping exposure**

Whether this death was a manifestation of severe systemic effects of vaping injury in a patient who relapsed, or whether lung injury associated with e-cigarettes or vaping had a contributory role in his death, but was not the primary cause, is not clear. One other

	Patients who underwent bronchoscopy (n=19)
Macrophage predominant	4/19 (21%)
Neutrophil predominant	12/19 (63%)
Eosinophil predominant	2/19 (11%)*
Bacteria recovered (α-haemolytic Streptococcus)	4/19 (21%)
CD4 to CD8 cell ratio (n=7)	2·43 (1·16–2·79)
Lipid-laden macrophages positive on oil red O staining	8/9 (89%)
Bronchioalveolar lavage cell count and differential	
White blood cells per μL	279 (101–520)
Red blood cells per μL	1224 (299–3669)
Monocyte and macrophage, %†	21% (9–25)
Neutrophil, %†	61% (38–69)
Lymphocytes, %†	12% (7–19)
Eosinophils, %†	0·5% (0–4)
Basophils, %†	0% (0–0)

Data are n/N (%) or median (IQR). *Eosinophil percentage in the two patients with eosinophilic predominant patterns were 39% and 74%, and for all other patients who underwent a bronchoscopy was 0–6%. †Reported as differential percentages between 1% and 100%.

Table 3: **Bronchoscopy findings**

	Total cohort (n=60)
Received intravenous methylprednisolone	41 (71%)
Initial daily dose, mg per day (n=41)	125 (120–240)
Duration before tapering dose or stopping, days	2 (1–4)
Patients whose dose was increased	8 (15%)
Initial daily dose of oral prednisone when started, mg (n=15)	40 (40–60)
Total duration of therapy, days	11 (6–18)
Clinical improvement attributed to steroids	48/57 (84%)

Data are n (%) or median (IQR).

Table 4: **Steroid treatment details**

patient died from cardiac arrest after a transcatheter aortic valve replacement, and although lung injury associated with e-cigarettes or vaping was determined by the in-hospital clinical team to be a probable contributor, it was not thought to be the cause of death.

Because these two deaths can be attributed to an alternative plausible diagnosis, they are not attributed to lung injury consistent with the CDC definition for death due to lung injury associated with e-cigarettes or vaping.[19] The sixth patient had recurrence of lung injury associated with e-cigarettes or vaping when he resumed vaping, which was treated with vaping cessation and steroids.

Short-term follow-up occurred at 2 weeks after hospital discharge and 26 patients were followed up as of Oct 10, 2019, and were seen 2 weeks or more after hospital discharge. Notably, one (4%) of 26 patients was still vaping. All patients reported improvement compared with their initial admission to hospital and radiographs showed improvement in acute findings even when residual abnormalities remained. Residual abnormalities in radiographic imaging, pulmonary function tests, and respiratory symptoms remained in most patients, with ten (67%) of 15 patients who had follow-up chest radiographs having abnormal results, six (67%) of nine having abnormal pulmonary function tests, and 14 (54%) of 26 having residual symptoms of dyspnoea or cough, or both.

Among the patients who had abnormal follow-up chest radiographs, the findings were still a substantial improvement in radiographic findings compared with previous imaging during their initial hospital stay, with some residual abnormalities of bilateral interstitial and alveolar opacities (nine [90%] of ten), or residual bronchial wall thickening (one [10%] of ten) still present. In addition to the abovementioned radiographic improvements, two patients had chest radiographs that showed improvement in complications, one with improvement in pneumothorax and one with improvement in lung abscess.

Although most patients had not yet had pulmonary function tests at short-term follow-up (some due to a concern for pneumomediastinum and pneumothorax resolution), six (67%) of nine who had the tests had abnormalities. The most common pulmonary function test abnormality was reduced diffusing capacity of the lung for carbon monoxide (DLCO) seen in five (83%) of six patients.

Three (50%) of six patients with abnormalities had normal spirometry with reduced DLCO, one (17%) had obstruction with normal DLCO, one (17%) had reduced DLCO with non-specific pattern (normal forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] ratio, mildly reduced FEV_1 and normal FVC and normal total lung capacity), and another (17%) had obstruction with reduced DLCO.

Overall the abnormalities on pulmonary function tests at short-term follow-up were relatively mild, with one patient having severely reduced DLCO (with moderate obstruction), while four others had only mild DLCO reduction. Six (23%) of 26 patients who were followed up still required supplemental oxygen at follow-up (elevation in Utah is approximately 1500 m), and three (12%) were still tapering off of oral steroids. One patient who had presented with abdominal symptoms had residual, but improved, abdominal symptoms at follow-up.

Discussion

The rapid recognition of the outbreak in an integrated health system, formation of a specialised task force, and centralisation of data collection and reporting mechanisms led to accumulated experience in diagnosing and treating patients with lung injury associated with e-cigarettes or vaping.

While each individual physician might have seen fewer than ten patients with the condition, as a system many more were seen. To disseminate this expertise,

we developed a proposed guideline for diagnosis and treatment of lung injury associated with e-cigarettes or vaping (appendix pp 1–2). This draft flow chart was shared with clinicians via email and will be iteratively updated as the outbreak evolves.

The causes of lung injury associated with e-cigarettes or vaping remain unknown, and our understanding of its possible cause, disease course, and progression is evolving. As such, the biggest limitation of our findings is that the diagnosis of the condition remains one of exclusion as defined by the current case definition.[2] Our findings support those of other reports in which patients with vaping exposure (e-tetrahydrocannabinol or e-nicotine, or both) had constitutional, gastrointestinal, and respiratory symptoms.[1,2,12] Nearly a quarter of patients who presented with lung injury associated with e-cigarettes or vaping had a history of asthma, rasing several questions about the association between asthma and vaping or e-cigarette use. For instance, is the relatively high prevalence of asthma in patients with lung injury associated with e-cigarettes or vaping due to the general prevalence of asthma? Do young people diagnosed with asthma turn to vaping over conventional smoking, believing it to be safer? Do those who vape or use e-cigarettes have a higher incidence of developing asthma than those who do not? Or does asthma predispose people to lung injury associated with e-cigarettes or vaping? More work is needed to begin to answer these questions.

We also found a relatively high incidence of pneumothorax and pneumomediastinum (11 [18%] of 60 patients). Most of the patients we identified with lung injury associated with e-cigarettes or vaping were young men. The demographics of our cohort affected by the outbreak are similar to the demographics of those who vape in Utah, with most being male and aged 18–34 years.[11]

If the relatively low proportion of women affected by the condition in our study reflects demographics of people who vape or use tetrahydrocannabinol in particular,[20] some aspect of how a contaminant and supply might spread among people, or an underlying biological difference in susceptibility between the sexes remains unknown. If, like obesity,[21] vaping among young people spreads via a network, and if that network is gendered, are also unknown, but the social factors of vaping and e-cigarette use should be considered, in addition to plausible biological factors, when looking for explanations for the prevalence of this condition in young men versus young women.

Real-time syndrome surveillance by telehealth has been proposed as a method to rapidly identify emerging infectious threats and bioterrorism.[22] The University of California, San Francisco (San Francisco, CA, USA) used telehealth to disseminate information and tightly coordinate a consistent response to the 2015 Zika virus epidemic.[23] However, telecritical care has not previously been reported as a real-time syndrome surveillance tool in an emerging outbreak. Our use of this system-centralised resource to rapidly identify and respond to an outbreak could serve as a model for how telehealth could be leveraged by an integrated health system to support rural and small hospitals.

Our increased detection of patients with lung injury associated with e-cigarettes or vaping over the course of the study period might be attributable to an increased awareness and ability to detect the condition across our health system. However, in the absence of a specific test for lung injury associated with e-cigarettes or vaping, increased clinical diagnoses might also in part be the result of attributing the condition to symptoms of other idiopathic, infectious, or inflammatory pneumonias in patients who now have a known history of vaping.

With no known cause, no specific pathognomonic test exists to confirm lung injury associated with e-cigarettes or vaping. The case definition for the condition remains a clinical, working case definition and not all patients had exhaustive infectious and inflammatory testing, especially those who were less sick on presentation.

Two things stand out as we consider our experience. First, as recognition of lung injury associated with e-cigarettes or vaping has spread, not only among clinicians but among patients and the public, the general clinical impression is that we are identifying milder cases of the condition earlier than at the beginning of the outbreak.

The number of cases remains too small to make any inferences other than to generate hypotheses. With appropriate follow-up, some patients might be safely treated in the outpatient setting and many do not require bronchoscopy or admission to hospital only for a diagnosis of lung injury associated with e-cigarettes or vaping, and could be treated with relatively short courses of steroids at moderate doses.

The severe complications and subsequent deaths we noted were in patients who were severely ill initially and often required admission to an ICU. Only a few patients were readmitted, and half of those readmissions were associated with a relapse in vaping after initial improvement. For the benefit of readers, we have provided our proposed guideline for initial standardising of the diagnosis and treatment of lung injury associated with e-cigarettes or vaping based on these experiences and observations (appendix pp 1–2).

Most patients with lung injury associated with e-cigarettes or vaping in our cohort improved clinically while in the hospital or during follow-up, and the clinical notes of the treating physicians typically attribute the administration of steroids to rapid clinical improvement within days, which is as yet unvalidated. Given our poor understanding of this disease or syndrome, offering any recommendations on steroid dosage here would be premature and further study is warranted.

However, notably, several patients who presented with mild manifestations were treated with short courses of

moderate amounts of steroids and appeared to have good clinical outcomes.

Second, we are intrigued by the substantial gastrointestinal abnormalities observed in this cohort. Most patients presented with abdominal symptoms and for some these symptoms were the reason for their presentation. Additionally, the frequency of pneumothorax and pneumomediastinum and the development of pneumatocele and lung abscess as possible sequelae of lung injury associated with e-cigarettes or vaping are of interest, especially considering the emphysematous gastritis diagnosis in one patient.

Emphysematous gastritis is most commonly caused by corrosive ingestion but has been reported as a consequence of trauma and gastric infarction.[24] The additional minor transaminase abnormalities perhaps suggest that a more systematic approach should be adopted to monitoring and evaluation of abdominal signs and symptoms in these patients.

If this aspect of lung injury associated with e-cigarettes or vaping will lead to better understanding of disease is unknown; however, emphasising to the public and clinicians that flu-like and abdominal symptoms might be presentations of lung injury associated with e-cigarettes or vaping, and that discontinuing vaping is the best treatment intervention, even in the absence of severe pulmonary symptoms. Increasing awareness of these symptoms will be especially important during influenza season.

Although we report the clinical presentation, treatment, and outcomes in the largest cohort of patients with lung injury associated with e-cigarettes or vaping in an integrated health system to date, our study has some limitations. First, our cohort consists of only 60 patients and does not capture indolent disease that has not reached the severity to present to a hospital or outpatient clinic. The paucity of studies in so-called healthy vapers or e-cigarette users (which could be a control group for lung injury associated with e-cigarettes or vaping studies) restricts some of the inferences we can make on the condition, including the finding of lipid-laden macrophages on oil red O staining, which might be present in the lungs of healthy vapers simply as a marker of inhalation of oil.

Although a case-control study might help overcome some of these limitations, the lack of a specific billing code for lung injury associated with e-cigarettes or vaping and lack of consistent vaping or e-cigarette histories restrict the ability to find controls. Additionally, vaping and e-cigarette exposure histories can be variable and change over time, so our reports of use are limited by what was captured by self-reporting, which itself can be confounded by stigma and legal concerns. For instance, because of the varying legality and lack of regulation of tetrahydrocannabinol products in the USA, patients are unable to reliably self-report consumption habits even if they so desired, with many patients reporting uncertainty about the origins of their vaping liquids. Furthermore, given the recency of presentation, outcome data including the number of readmissions are incomplete.

Finally, since the cause of lung injury associated with e-cigarettes or vaping is unknown, additional important, but as yet unknown, aspects of history or diagnostic assessment might be missing from this report. Despite these limitations, our study shows that patients who are less severely ill who undergo less exhaustive assessments can have good outcomes, which might suggest that not every patient needs an extensive invasive diagnostic assessment before rapid empiric treatment with steroids is initiated, even with the lack of a disease-specific confirmatory test.

In summary, we report the largest single health system cohort study of patients with lung injury associated with e-cigarettes or vaping to date. We categorised patients on the basis of their severity of illness at presentation. We found that patients who are more severely ill at presentation are more likely to have complications.

An integrated health system resource, such as telecritical care service, could be of use for early detection and a standardised response to an emerging outbreak across an integrated health system. We also note the prominence of the gastrointestinal findings and suggest that both clinicians and the public should consider lung injury associated with e-cigarettes or vaping in patients who present predominantly with constitutional and gastrointestinal symptoms.

Although the specific cause of the outbreak remains unknown, abstinence from all vaping and e-cigarette products remains the best way to prevent primary and recurrent lung injury associated with e-cigarettes or vaping.

Contributors

DPB, DH, CKG, and MJL conceived and designed the study. DH, DPB, MJL, and ACD contributed clinical data. MJL, DPB, and DH analysed the data. DPB, MJL, and DH wrote the manuscript. All authors read the final manuscript and approved submission.

Declaration of interests

We declare no competing interests.

Data sharing

To protect patient privacy and comply with relevant regulations, identified data are unavailable. Requests from qualified researchers with appropriate ethics board approvals and relevant data use agreements for de-identified data will be processed by the Intermountain Healthcare Office of Research. To request access please contact the office by email: officeofresearch@imail.org.

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