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Characterizing E-Cigarette Vaping Associated Lung Injury (EVALI) in the Pediatric Intensive Care Unit

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Abstract

Objective: Adolescent e-cigarette use has risen to epidemic levels in the US, revealing a new phenomenon of e-cigarette associated vaping lung injury (EVALI). It is important to better characterize EVALI in the critically ill adolescent as this is a vulnerable and rapidly growing demographic.

Methods: This was a retrospective case series of patients ≤ 21 years old with confirmed or probable EVALI (as defined by the Centers for Disease Control) that resulted in admission to the pediatric intensive care unit (PICU) of a large tertiary academic children's hospital between August 2019 and January 2020.

Results: There were six eligible patients, with median age of 17 years. All patients reported tetrahydrocannabinol (THC) as well as nicotine e-cigarette use. Half of the patients had a preexisting diagnosis of asthma and four patient had mental health comorbidities. All patients presented with respiratory alkalosis and chest radiography showing diffuse bilateral infiltrates; two patients had pneumomediastinum, subcutaneous air and/or pneumothorax. The lowest documented ratio of oxygen saturation to inspired oxygen (SpO2:FiO2 or S/F ratio) ranged from 146 to 296. Two patients required an arterial line, with lowest ratio of arterial oxygen to inspired oxygen (PaO2:FiO2 or P/F ratio) of 197 and 165. Two patients tested positive for rhinovirus and respiratory cultures were negative for all patients. Four patients underwent chest CT imaging, which showed diffuse ground glass opacities. Every patient required non-invasive positive pressure ventilation, with one progressing to invasive ventilation. All patients received broad spectrum intravenous antibiotics and steroids, though there was considerable variability in dose, frequency and duration of steroids. The hospital length of stay ranged from 5 to 16 days (median 8.3 days) with PICU length of stay ranging from 4 to 10 days (median 5.5 days). Four patients had

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pulmonary function testing prior to discharge, two of which showed decreased diffusing capacity of lung for carbon monoxide (DLCO). There were no patient deaths.

Conclusions: This single center case series describes the presentation, course and treatment of EVALI in a pediatric intensive care unit setting. Our results show nuanced differences in the presentation and management of the critically ill adolescent, and raise many questions about the long term implications on lung health, morbidity and mortality. Importantly, these cases illustrate the critical care consequences of a public health phenomenon and should spur further research and policy to address the negative health effects of vaping.

Keywords

pediatrics; intensive care; e-cigarette vaping associated lung injury

INTRODUCTION

While cigarette smoking in teenagers has decreased, there has been a dramatic increase in e-cigarette use or “vaping” in the last decade, such that over 1 in 4 adolescents report vaping use [1]. E-cigarettes, initially patented in the United States in 2007 [2], are handheld devices that produce an aerosol from a solution typically containing nicotine, flavoring chemicals, and other additives for inhalation through a mouthpiece by the user[3]. Though there are countless models and brands, each has the essential components of a liquid reservoir that is vaporized by an atomizer heat source and powered by a battery[4]. Also called vape pens, e-hookahs or electronic nicotine delivery systems, the modern e-cigarette has high appeal to youth due to targeted social media advertising [4], sleek new e-cigarette designs [5], and promotion of fruity and novelty flavors [6]. While promoted as a smoking cessation tool, e-cigarettes are thought to contribute to future use of cigarettes [7–10] and marijuana use [11,12] in adolescents. Among these negative sequelae, e-cigarette use is associated with a newly characterized condition known as e-cigarette vaping associate lung injury (EVALI). EVALI was first described in the summer of 2019 as a constellation of constitutional, gastrointestinal and respiratory symptoms with hypoxemia and bilateral infiltrates on imaging, in the absence of infection [13].

As EVALI was being defined, the largest initial case series of 98 patients by Layden et. al. showed that the majority of patients were male with a median age of 21 years; most, but not all, reported tetrahydrocannabinol (THC) use [13]. In this initial cohort, the illness was severe, such that 95% of patients were hospitalized and 26% underwent intubation and mechanical ventilation [13]. The Centers for Disease Control (CDC) subsequently began data collection nationally, which uncovered over 2800 cases and 68 deaths as of February 2020 [14]. Similar to the sentinel case series, these cases had a male predominance with two-thirds of patients under the age of thirty-five [15].

The prevailing thought in the literature is that the compound vitamin E acetate, often a diluting agent found in tetrahydrocannabinol (THC) products, is a possible causal agent for the syndrome observed [16,17]. In fact, analysis of products used by EVALI patients frequently showed the presence of vitamin E acetate as a diluent, and follow up studies of bronchoalveolar lavage (BAL) samples showed vitamin E acetate in all samples for 29

EVALI cases in multiple states [16]. Moreover, when compared to a healthy cohort, vitamin E acetate was found in 48 of 51 patients across 16 states, but was notably absent from 99 healthy samples including 18 e-cigarette users [16]. It is hypothesized that vitamin E acetate affects surfactant (by converting from a gel to liquid crystalline state) [18,19] such that it may impair the lung's ability to maintain adequate surface tension[20–22]. While evidence is not sufficient to rule out the contribution of other chemicals of concern, it appears that vitamin E acetate is commonly found in unregulated THC-containing liquids and that there is a physiological basis for susceptibility to lung disease.

Though the current literature sheds light on the characteristics and management of primarily adult users, much less is known about EVALI in critically ill children and teenagers. It is important to understand how the pediatric population is affected as they are the most vulnerable, largest, and fastest growing population of e-cigarette users. To our knowledge, this is the first case series to characterize patients with EVALI that require pediatric intensive care unit (PICU) level care.

METHODS

This was a retrospective case series of patients admitted to the 70-bed pediatric intensive care unit (PICU) of the Children's Hospital of Philadelphia, a large tertiary academic children's hospital, between August 2019 and January 2020. This study used de-identified data and was approved by our Institutional Review Board. Data was extracted using chart review of the electronic medical record.

We included all visits by children ≤ 21 years old with confirmed or probable EVALI (as defined by the Centers for Disease Control) that resulted in PICU admission. Teenage patients were routinely screened for smoking/vaping use on admission as part of the social history and it was documented both in a social history section as well as in the history & physical. While there is a newly introduced e-cigarette screening tool built into the electronic health record, it was inconsistently used at the time of this study; for this reason, the identification of case patients was via review of documentation in the electronic health record.

The designation of confirmed or probable EVALI was made at the time of admission (not retrospectively) based on CDC guidelines. The CDC defines a confirmed case of EVALI as 1) use of an e-cigarette (vaping) in 90 days prior to symptom onset 2) presence of pulmonary infiltrates on chest radiograph or ground glass opacities on chest computed tomography 3) absence of pulmonary infection and 4) no evidence of alternative plausible diagnoses such as a cardiac, rheumatologic or neoplastic process [15]. A probable case is defined as above with exception that there may be infection identified (by means of culture or PCR) but the clinical team believes infection is not the sole cause of underlying respiratory process [15].

RESULTS

Demographics

During the study period there were six eligible patients admitted to the PICU with EVALI (Table 1). The median age was 17 (IQR 16–17) years. Half the patients were male and all but one identified as Non-Hispanic White. Half of the patients had a preexisting diagnosis of asthma and four patients had mental health comorbidities. All patients reported both nicotine and THC e-cigarette use, with 100% of patients testing positive for cannabinoids in cases where urine toxicology was obtained. The vaping history varied significantly, ranging from 4 months to 3 years, with frequency of vaping ranging from daily to weekly.

Clinical Presentation, Testing and Imaging

In addition to cough and shortness of breath, all patients presented with fever, nausea/vomiting and abdominal pain. Two of the patients presented with weight loss. Only one patient presented with chest pain. No patients presented with hemoptysis.

All patients presented with respiratory alkalosis and normal lactate. The lowest documented ratio of oxygen saturation to inspired oxygen (SpO2:FiO2 or S/F ratio) ranged from 146 to 296. Two patients required placement of an arterial line and subsequent measuring of arterial oxygen, with lowest ratio of arterial oxygen to inspired oxygen (PaO2:FiO2 or P/F ratio) of 197 and 165 respectively. Five patients presented with leukocytosis, with white blood cell counts ranging from 11–29.5 K/uL. Two patients tested positive for rhinovirus (remainder had negative respiratory viral panels) and respiratory cultures were negative for all patients. Each patient had chest radiography showing diffuse bilateral infiltrates. Two patients had air leak, characterized by pneumomediastinum, subcutaneous air or pneumothorax. Four patients underwent chest CT imaging, which universally showed diffuse ground glass opacities with intralobular septal thickening.

Management, Outcomes & Post-Discharge Course

Every patient required non-invasive positive pressure ventilation, with one progressing to invasive ventilation. No patients required extracorporeal membrane oxygenation (ECMO) and there were no patient deaths. All patients received broad spectrum IV antibiotics and IV steroids, though there was considerable variability in steroid dose (30–60 mg), frequency (every 6 hours to daily) and duration (5 to 21 days). The hospital length of stay ranged from 5 to 16 days (median 8.3 days) with PICU length of stay ranging from 4 to 10 days (median 5.5 days). No patients were readmitted within 30 days of discharge (though one patient was admitted to our hospital within 30 days of discharge from another hospital pediatric floor). Four patients had pulmonary function testing prior to discharge, two of which showed decreased diffusion capacity of lung for carbon monoxide (DLCO). There were no patient deaths.

DISCUSSION

While multiple studies have characterized the presentation, diagnosis, management and post-discharge course of adult patients, our results show nuanced differences and additional

findings in the critically ill adolescent. These differences are important to consider when caring for the ever-growing population of young vaping patients.

Clinical Presentation & Risk Factors

The clinical presentation of our patients was quite similar to what has been described in the adult literature; all patients presented with cough, fever, shortness of breath as well as gastrointestinal symptoms. Alarmingly, one patient, age 14, described a 2–3 year history of vaping revealing that EVALI must be a consideration in even younger children. Given that these symptoms are often accompanied by leukocytosis, it is difficult to distinguish from lung infections. We found that respiratory alkalosis (as opposed to respiratory acidosis or normal blood gas) accompanied EVALI as well as the presence of abdominal pain, nausea, vomiting, diarrhea or weight loss. There may be systemic toxicity, in addition to lung inflammation [23], which may contribute to why EVALI presents with symptoms similar to toxic ingestion. Unlike the adult population, chest pain was not a prominent feature, likely reflecting the absence of cardiac comorbidities in our patients as compared to older groups.

In reviewing the imaging findings, all patients had bilateral infiltrates and the four patients for whom chest CT was obtained showed ground glass opacities, in keeping with prior adult and pediatric data [13,24,25]. Interestingly, two patients experienced air leak as demonstrated by pneumomediastinum, small bilateral pneumothoraces and/or subcutaneous air. These findings were present on admission, prior to initiation of positive pressure or invasive ventilation. Air leak has been described in smaller case reports [26–28], but was not discussed in larger cohorts. The mechanism for this air leak is unclear, but is reminiscent of the known increased risk of pneumothorax associated with traditional cigarette smoking [29]. Together, these findings suggest that e-cigarette users are not protected from this harm when compared to smokers, though there is further investigation needed.

Although our cohort was too small to reasonably draw conclusions about risk factors for EVALI, we did note trends in THC use and presence of co-morbidities including mental health and asthma. All patients reported vaping THC (and all those with urine toxicology were positive for THC), in keeping with the theory that vitamin E acetate in cannabinoid compounds may be the culprit for EVALI [16,17]. That said, there was high variability in the duration, frequency and type of device/pod used by each patient so no conclusions could be made about whether more frequent or longer duration of vaping correlated with development of EVALI.

Two-thirds of our patients additionally had mental health co-morbidities, namely anxiety and bipolar disorder. While there is a strong association between mental health conditions and e-cigarette use, the evidence is limited with regard to whether this affects development of EVALI. That said, mental illness conferred increased risk of mortality in hospitalized adult EVALI patients[30], making this an important consideration for future research.

There is similar uncertainty with regard to asthma as a risk factor. While half of our patients did have a pre-existing diagnosis of asthma, it was unclear whether this translated to greater risk of EVALI compared to their non-asthmatic counterparts. Adult studies have commented on higher prevalence of asthma in EVALI cohorts as compared the general population[13] and

recent studies are finding an association between e-cigarette use and asthma in adults[31] as well as adolescents[32]. There is certainly need for further investigation into whether e-cigarette use contributes to development of asthma and/or whether asthma increases likelihood of EVALI.

Management & Post-Discharge Course

With regard to management, all patients required non-invasive positive pressure ventilation, with one patient progressing to intubation and mechanical ventilation. All patients received broad-spectrum antibiotics and systemic steroids, however the selection of antimicrobials and steroid courses varied. IV methylprednisolone doses ranged from 30–60 mg/dose, with frequency ranging from every 6 hours to daily; duration ranged from 5 days to 1 week followed by 2 week oral prednisone taper. The variability in steroid dosing is seen in adult case series as well, with steroid doses ranging from 0.5–1 mg/kg/day methylprednisolone [33] to as high as 500 mg daily [34]. Anecdotally, it seems that patients improved quickly with steroids after failing outpatient antibiotics (and went on to have negative respiratory cultures), though it is difficult assess if broad-spectrum IV antibiotics played a role in improvement. In general, the management approach at our center was broad spectrum antibiotics while infectious workup was pending and IV steroids until patient was weaned off of positive pressure ventilation. We found patients to have heterogeneous lung disease consistent with acute respiratory distress syndrome (ARDS). Indeed the P/F ratios in the two patients with arterial blood gas sampling were <200, in keeping with ARDS. The S/F (SpO2:FiO2) ratios similarly were indicative of ARDS; S/F ratios ranged from 146 to 296. Based on prior comparison of S/F ratios to P/F ratios in pediatric ARDS, criteria for acute lung injury was S/F ratio less than 264 and less than 221 for ARDS [35]. Based on this criteria, three patients met criteria for ARDS and two met criteria for acute lung injury. The subsequent ventilatory strategy utilized was the same as for ARDS (high positive end-expiratory pressure and low tidal volume), with close monitoring for new or worsening air leak. The hospital length of stay ranged from 5 to 16 days with PICU length of stay ranging from 4 to 10 days. In comparison to median PICU length of stay of two days for all-comers [36], our EVALI patients required longer ICU stays with additional days on the hospital floor. While it was observed that one patient who was admitted to our PICU a day after discharge from another hospital pediatric floor, there were overall no PICU readmissions within 30 days of discharge. This differed from the adult population, where approximately 2.7% of patients were re-hospitalized after discharge and 13.5% of EVALI deaths occurred days after discharge, highlighting the post-discharge time as high risk [37]. It is possible that the longer hospital stay for our patients preempted the complications seen in the post-discharge period seen in adults; on the other hand, adults may have increased post-discharge risk due to severity of illness and presence of comorbidities.

At discharge, two patients had abnormal pulmonary function testing (PFTs); one had preexisting asthma and showed an obstructive pattern with reduced DLCO and the other also showed decreased DLCO. Prior case series have similarly shown decreased DLCO [38,39], raising the important question of whether patients with EVALI will have lasting lung injury. Four patients presented to pulmonary follow up with one patient reporting continued vaping

use, illustrating the continued risk for lung injury and importance of managing the psychosocial aspects of substance use.

Limitations

This case series has several important limitations, namely the small sample size and inability to generalize these findings; these are cases seen at a large academic referral center, which may not represent cases seen in the community. Given this is a single center study, we are unable to see if patients followed up elsewhere with specialists or if they were readmitted to another hospital. Additionally, this series is retrospective and based on chart review, limiting the information that can be collected. Nevertheless, these cases shed light on the nature of EVALI in adolescent patients and how they may present and be managed in a pediatric ICU setting.

CONCLUSION

This single center case series describes the presentation, course and treatment of EVALI in a pediatric intensive care unit setting. Our results show nuanced differences in the presentation and management of the critically ill adolescent, and raise many questions about the long term implications on lung health, morbidity and mortality. Importantly, these cases illustrate the critical care consequences of a public health phenomenon and should spur further research and policy to address the negative health effects of vaping.

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Abbreviations:

ARDS	Acute Respiratory Distress Syndrome
EVALI	E-cigarette Vaping Associated Lung Injury
THC	Tetrahydrocannabinol
CDC	Centers for Disease Control
ICU	Intensive Care Unit
PICU	Pediatric Intensive Care Unit
IRB	Institutional Review Board
ECMO	Extracorporeal Membrane Oxygenation

CT	Computed Tomography
DLCO	Diffusing Capacity of Lung for Carbon Monoxide
PFT	Pulmonary Function Testing

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Table 1.

Characteristics, diagnostics, and management of EVALI patients

Characteristics of Study Population	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	16	17	18	17	17	14
Sex	Female	Male	Male	Female	Female	Male
Race/Ethnicity	White	White	White	White	White	Other
Preexisting diagnosis of asthma	No	Yes	Yes	Yes	No	Yes
Vaping history (duration, frequency)	7 months (2 pods/week)	2 years (1 pod per day)	2 years (1 pod per day)	4 months (1 pod per day)	Unknown (endorsed “daily use”)	2–3 years (1 pod per week)
Reported THC use	Yes	Yes	Yes	Yes	Yes	Yes
Reported Nicotine use	Yes	Yes	Yes	Yes	Yes	Yes
Reported Mental Illness	Yes (anxiety)	Yes (anxiety)	Yes (anxiety)	No	Yes (bipolar)	No
Initial Presenting Symptoms						
Constitutional						
Fever	Yes	Yes	Yes	Yes	Yes	Yes
Weight loss	No	Yes	No	Yes	No	No
Fatigue/malaise	Yes	Yes	Yes	Yes	Yes	Yes
Respiratory						
Shortness of breath	Yes	Yes	Yes	Yes	Yes	Yes
Chest pain	Yes	No	No	No	No	No
Cough	Yes	Yes	Yes	Yes	Yes	Yes
Hemoptysis	No	No	No	No	No	No
Gastrointestinal						
Nausea/Vomiting	Yes	Yes	Yes	Yes	Yes	Yes
Abdominal Pain	Yes	Yes	Yes	Yes	Yes	Yes
Diarrhea	Yes	No	Yes	No	No	No
Laboratory Findings						
White Blood Cell Count (K/uL)	17.2	23.1	25.7	11	29.5	13

Characteristics of Study Population	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Initial Blood Gas	Respiratory Alkalosis	Respiratory Alkalosis	Respiratory Alkalosis	Respiratory Alkalosis	Respiratory Alkalosis	Respiratory Alkalosis
Abnormal Lactate	No	No	No	No	No	No
Lowest SpO2/FiO2 Ratio	263	296	174	251	146	188
Lowest PaO2/FiO2 Ratio	n/a	n/a	197	n/a	165	n/a
Respiratory Viral Panel	Negative	Negative	Negative	Positive for rhinovirus	Negative	Positive for rhinovirus
Respiratory Culture	Negative	Negative	Negative	Negative	Negative	Not obtained
Urine Toxicology Screen	Positive THC	Positive THC	Positive THC	Positive THC	Not obtained	Positive THC
Bronchoscopy	Not completed	Not completed	Not completed	Not completed	Not completed	Not completed
Radiographic Findings						
Chest Radiograph						
Bilateral Infiltrates	Yes	Yes	Yes	Yes	Yes	Yes
Presence of Air Leak	No	No	Yes (pneumomediastinum and subcutaneous air)	No	Yes (pneumomediastinum, small bilateral pneumothoraces and subcutaneous air)	No
Chest CT	Yes (Diffuse ground glass opacities)	Yes (Diffuse ground glass opacities)	Not obtained	Yes (Diffuse ground glass opacities)	Yes (Diffuse ground glass opacities)	Not obtained
Treatment						
Supplemental Oxygen	Yes	Yes	Yes	Yes	Yes	Yes
Non-Invasive Positive Pressure Ventilation	Yes	Yes	Yes	Yes	Yes	Yes
Invasive Ventilation	No	No	No	No	Yes	No
ECMO	No	No	No	No	No	No
Antibiotics	Yes	Yes	Yes	Yes	Yes	Yes
Systemic Steroids	IV methylprednisolone 60 mg q12h x 5 days followed by 2 week oral prednisone taper	IV methylprednisolone 60 mg q6h x 5 days followed by one week oral prednisone taper	IV methylprednisolone 30 mg q6h for 5 days	IV methylprednisolone 60 mg q6h x 5 days followed by 2 week oral prednisone taper	IV methylprednisolone 30 mg q12h x7 days followed by 14 day oral prednisone taper	IV methylprednisolone 30 mg q6h (then 40 mg oral prednisone BID for 5 day course, with 2 day taper)
Outcomes						
Hospital Length of Stay	8 days	7 days	9 days	5 days	16 days	5 days
PICU Length of stay	5 days	4 days	6 days	6 days	10 days	4 days

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Characteristics of Study Population	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Pulmonary Function Test at Discharge	Obstructive pattern with reduced DLCO	Decreased DLCO	Not completed	Not completed	Normal	Normal
Vaping Cessation at Time of Pulmonary follow up visit	Yes	No	Yes	No follow up recorded	No follow up recorded	Yes
Readmission within 30 days of PICU discharge	No	No	No	No (of note, was admitted to PICU one day after discharge from another hospital's general pediatric floor)	No	No
Death	No	No	No	No	No	No