[ Thoracic Oncology Special Feature ]

CHEST

# Pulmonary and Critical Care Considerations for E-Cigarette, or Vaping, Product Use-Associated Lung Injury

*Don Hayes Jr, MD, FCCP; Amy Board, DrPH; Carolyn Calfee, MD; Sascha Ellington, PhD, MSPH; Lori A. Pollack, MD, MPH; Hasmeena Kathuria, MD; Michelle N. Eakin, MD; David N. Weissman, MD; Sean J. Callahan, MD; Annette M. Esper, MD; Laura E. Crotty Alexander, MD; Nirmal S. Sharma, MD; Nuala J. Meyer, MD; Lincoln S. Smith, MD; Shannon Novosad, MD; Mary E. Evans, MD, MPH; Alyson B. Goodman, MD, MPH; Eleanor S. Click, MD, PhD; Richard T. Robinson, PhD; Gary Ewart, MHS; and Evelyn Twentyman, MD, MPH*

**BACKGROUND:** In 2019, the United States experienced a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI). More than one-half of these patients required admission to an ICU.

**RESEARCH QUESTION:** ■■■

**STUDY DESIGN AND METHODS:** To synthesize information critical to pulmonary/critical care specialists in the care of patients with EVALI, this study examined data available from patients hospitalized with EVALI between August 2019 and January 2020; reviewed the clinical course and critical care experience with those patients admitted to the ICU; and compiled opinion of national experts.

**RESULTS:** Of the 2,708 patients with confirmed or probable EVALI requiring hospitalization as of January 21, 2020, a total of 1,604 (59.2%) had data available on ICU admission; of these, 705 (44.0%) were admitted to the ICU and are included in this analysis. The majority of ICU patients required respiratory support (88.5%) and in severe cases required intubation (36.1%) or extracorporeal membrane oxygenation (6.7%). The majority (93.0%) of these ICU patients survived to discharge. Review of the clinical course and expert opinion provided insight into: imaging; considerations for bronchoscopy; medical treatment, including use of empiric antibiotics, antiviral agents, and corticosteroids; respiratory support, including considerations for intubation, positioning maneuvers, and extracorporeal membrane oxygenation; and patient outcomes.

**INTERPRETATION:** Review of the clinical course of patients with EVALI requiring ICU admission and compilation of expert opinion provided critical insight into pulmonary/critical care-specific considerations for this patient population. Because a large proportion of patients hospitalized with EVALI required ICU admission, it is important to remain prepared to care for patients with EVALI.

CHEST 2022; ■(■):■-■

**KEY WORDS:** critical illness; e-cigarette; ICU; lung injury; vaping

**ABBREVIATIONS:** CDC = Centers for Disease Control and Prevention; CXR = chest radiograph; ECMO = extracorporeal membrane oxygenation; EVALI = E-cigarette, or vaping, product use-associated lung injury; ORO = Oil-Red-O; PCR = polymerase chain reaction; PEEP = positive end-expiratory pressure; THC = tetrahydrocannabinol

**AFFILIATIONS:** From the Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine (D. Hayes), Cincinnati, OH; Epidemic Intelligence Service, National Center for Injury Prevention and Control (A. Board), Atlanta, GA; University of California at San Francisco School of Medicine (C. Calfee), San





REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089

In August 2019, the Centers for Disease Control and Prevention (CDC) along with the US Food and Drug Administration, state and local health departments, and public health and clinical stakeholders initiated an investigation into a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI).[1-6] EVALI was subsequently found to be strongly linked with vitamin E acetate, an oily substance with an appearance similar to cannabis oil sometimes used as a diluent or "cutting agent" in tetrahydrocannabinol (THC)-containing e-cigarette, or vaping, products.[7] However, in some of the reported EVALI cases, the evidence is not sufficient to rule out the contribution of other chemicals of concern, including chemicals in either THC or non-THC products.[5] Declines in the number of EVALI cases reported to the CDC were observed every week following a peak in mid-September 2019, which was likely due to multiple factors, including: rapid public health action to increase public awareness of the risk associated with THC-containing e-cigarette, or vaping, products; actions by consumers to reduce this risk; and actions by manufacturers to remove vitamin E acetate from these products.[5,8-10]

Substantial guidance has been published to aid the general medical community and first-line health-care providers in the care and treatment of patients with EVALI.[11-13] However, an opportunity remains to provide a synthesis of information for the diagnosis and management of patients with EVALI-related critical illness. The current report provides information for the diagnosis and management of critically ill patients with EVALI.

## Patients and Methods

### Definitions

In accordance with the CDC EVALI case definitions,[14] confirmed EVALI cases met the following criteria: (1) reported using an e-cigarette, or vaping, product (eg, e-cigarette, vape pen) to inhale substances such as nicotine, marijuana, THC, or cannabidiol within 90 days prior to symptom onset; (2) pulmonary infiltrate, such as opacities, on chest radiograph (CXR) or ground-glass opacities on chest CT imaging; (3) absence of pulmonary infection on initial examination, including, at a minimum, a negative respiratory viral panel and a negative influenza polymerase chain reaction (PCR) or rapid test result; (4) negative results on all other clinically indicated respiratory infectious disease testing; and (5) no evidence in medical history of an alternative plausible diagnosis. Probable EVALI cases were not required to meet criteria 3 and 4; instead, if pulmonary or respiratory infection was identified or the minimum criteria to rule out infection was not met (eg, testing not performed) but the clinical team believed that infection was not the sole cause of the underlying lung injury, the case would be classified as probable.

### Data Analysis

Data on patients hospitalized with confirmed and probable EVALI were reported to the CDC voluntarily by all 50 states, the District of Columbia, Puerto Rico, and the US Virgin Islands from August 2019 through January 2020 by using established data collection tools as described in previously published articles.[5,6] All data in the current analyses were collected from patients treated prior to the onset of the SARS-CoV-2 pandemic. Presenting symptoms, clinical course, product use history, and medical history were obtained from patient medical record abstraction and interviews of patients or proxies (eg, spouses or parents) if a patient was too ill or had died.

Descriptive analyses on patient characteristics (age, sex, and race/ethnicity) and clinical course (presentation, history, imaging, infectious disease testing, type of first care visit, medical treatment, respiratory support, and patient outcome) by percentages and distributions of categorical and continuous indicators were conducted by using SAS version 9.4 (SAS Institute, Inc.).

### Compilation of Expert Opinion

To compile clinical perspective from those caring for patients with EVALI, the CDC collaborated with national adult and pediatric pulmonary and critical care medicine experts designated by professional medical societies to participate in the Lung Injury Response Clinical Working Group.[11] This group met from October to December 2019, weekly to biweekly, and developed multiple guidance documents to address the EVALI outbreak.[11-13] An additional collaboration was formed in November 2019 with the CDC and pulmonary and critical care experts to identify, document, and synthesize potential best practices in the diagnosis and management of EVALI-related critical illness.

## Results

Of 2,708 patients with confirmed or probable EVALI requiring hospitalization from August 2019 to January 2020, a total of 1,604 (59.2%) had data available

Francisco, CA; Centers for Disease Control and Prevention (S. Ellington, L. A. Pollack, S. Novosad, M. E. Evans, A. B. Goodman, E. S. Click, and E. Twentyman), Atlanta, GA; Boston University Medical Center (H. Kathuria), Boston, MA; Johns Hopkins University School of Medicine (M. N. Eakin), Baltimore, MD; Respiratory Health Division, National Institute for Occupational Safety and Health (D. N. Weissman), Morgantown, WV; University of Utah School of Medicine (S. J. Callahan), Salt Lake City, UT; Emory University School of Medicine (A. M. Esper), Atlanta, GA; University of California at San Diego School of Medicine (L. E. Crotty Alexander), San Diego, CA; Brigham and Women's Hospital (N. S. Sharma), Boston, MA; University of Pennsylvania Perelman School of Medicine (N. J. Meyer), Philadelphia, PA; Seattle Children's Hospital and University of Washington School of Medicine (L. S. Smith), Seattle, WA; The Ohio State University College of Medicine (R. T. Robinson), Columbus, OH; and the American Thoracic Society (G. Ewart), New York, NY.

**CORRESPONDENCE TO:** Don Hayes Jr, MD, FCCP; email: Don.Hayes@cchmc.org



**DOI:** https://doi.org/10.1016/j.chest.2022.02.039





REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089

**TABLE 1** ] Demographic Characteristics of Patients With EVALI Admitted to the ICU, August 2019 to January 2020

| Characteristic | ICU Patients (N = 705) |
|---|---|
| Age group (n = 701), y | |
| ≤ 17 | 124 (17.7%) |
| 18-24 | 219 (31.2%) |
| 25-34 | 172 (24.5%) |
| 35-44 | 87 (12.4%) |
| 45-64 | 77 (11.0%) |
| ≥ 65 | 22 (3.1%) |
| Sex (n = 700) | |
| Female | 273 (39.0%) |
| Male | 427 (61.0%) |
| Race/ethnicity (n = 550) | |
| Asian, Native Hawaiian, or other Pacific Islander | 13 (2.4%) |
| Black, non-Hispanic | 28 (5.1%) |
| Hispanic | 76 (13.8%) |
| Other[a] | 17 (3.1%) |
| White, non-Hispanic | 416 (75.6%) |

EVALI = E-cigarette, or vaping, product use-associated lung injury.
[a]Cell details are not displayed because of small numbers (n = 1-4), which do not meet standards for maintaining confidentiality.

regarding ICU admission; of these, 705 (44.0% [705 of 1,604]) were admitted to the ICU and are included in this analysis. Most ICU patients were aged 18 to 34 years (55.7%), male (61.0%), and non-Hispanic White (75.6%) (Table 1). Table 2 outlines the presenting symptoms and clinical course for patients with EVALI admitted to the ICU. The majority of those admitted to the ICU presented with GI (76.1%), respiratory (96.8%), and/or constitutional (92.0%) symptoms. For patients with medical history data available (either reported in the medical record or via patient or proxy self-report), prior anxiety and/or depression was reported for approximately one-third of patients admitted to the ICU (35.5% and 30.4%, respectively, with 22.8% of patients missing anxiety medical history and 22.6% of patients missing depression medical history), and prior respiratory diseases (28.5%, with 18.7% of patients missing respiratory medical history). Almost all patients had imaging demonstrative of bilateral rather than unilateral findings, with 97.7% of chest CT scans and 90% of CXRs revealing bilateral abnormalities. Subpleural sparing was noted in 34.3% of patients with data available. Almost one-half (45.0%) of patients underwent bronchoscopy. Most patients had negative infectious disease test results. Advanced respiratory support was provided to more than one-third of patients admitted to the ICU, with 36.1% intubated and 6.7% receiving extracorporeal membrane oxygenation (ECMO). For the minority of patients admitted to the ICU with data available on length of ICU stay (n = 130), the median length of stay was 6 days (range, 0-74 days) (data not shown). Of the 705 patients diagnosed with EVALI who were admitted to the ICU, 656 (93.0%) had survival data available. Of these 656 patients, 610 (93.0%) survived, and 46 (7.0%) died.

## *Diagnosis and Management*

**Patient History:** Patients with EVALI may present with respiratory symptoms (cough, shortness of breath, and chest pain), GI symptoms (nausea, vomiting, abdominal pain, and diarrhea), or constitutional symptoms (fever, chills, and weight loss).[11,12] Patients often report having more than one symptom.[11] In this analysis, each of these symptoms was reported by the majority of ICU patients (76.1% with GI symptoms, 96.8% with respiratory symptoms, and 92.0% with constitutional symptoms). EVALI symptoms may be similar to those associated with respiratory infections, including COVID-19[15] and influenza.[12] EVALI should be suspected in patients with a history of using e-cigarette, or vaping, products within the last 3 months, a pneumonia-like illness, progressive dyspnea, and/or worsening hypoxemia.[11]

In obtaining a history of e-cigarette, or vaping, product use, confidentiality is key. Maintenance of confidentiality can be challenging in the critical care setting.[16,17] Specific details regarding e-cigarette, or vaping, product use include the following: start of product use, last use of product, method of use (eg, aerosol, dabbing, dripping), duration of use, daily frequency of puffs, and concomitant combustible tobacco use.[18] In addition, it is important to obtain information regarding the device, such as the product brand, the delivery system, types of substances used (eg, THC, cannabidiol, cannabis, nicotine, modified products, addition of substances not produced by the manufacturer), and product source. Most patients with EVALI reported a history of using THC-containing products; however, some patients reported exclusive use of nicotine-containing products.[1,12] Products obtained off the street or from other informal sources are linked to most EVALI cases.[3] In addition to details about e-cigarette, or vaping, product use, patient history should include recent travel, other environmental exposures, medications, presence of underlying disease,





REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089

**TABLE 2** ] Clinical Presentation and Clinical Course of Patients With EVALI Admitted to the ICU, August 2019 to January 2020

| Variable | ICU Patients (N = 705) |
|---|---|
| Presenting symptoms | |
| GI symptoms (n = 640) | 487 (76.1%) |
| Respiratory symptoms (n = 655) | 634 (96.8%) |
| Constitutional symptoms (n = 641) | 590 (92.0%) |
| Medical history | |
| Respiratory diseases (n = 573) | 163 (28.5%) |
| Heart diseases (n = 550) | 72 (13.1%) |
| Anxiety (n = 544) | 193 (35.5%) |
| Depression (n = 546) | 166 (30.4%) |
| Other chronic diseases (n = 493) | 286 (58.0%) |
| Imaging | |
| CT scan performed (n = 560) | 514 (91.8%) |
| Opacities present (n = 323) | 321 (99.4%) |
| Location of abnormal finding (n = 307) | |
| Bilateral | 300 (97.7%) |
| Unilateral | 7 (2.3%) |
| Subpleural sparing (n = 67%) | 23 (34.3%) |
| Chest radiograph performed (n = 567) | 555 (97.9%) |
| Opacities present (n = 325) | 311 (95.7%) |
| Location of abnormal finding (n = 322) | |
| Bilateral | 291 (90.4%) |
| Unilateral | 20 (6.2%) |
| Bronchoscopy | 317 (45.0%) |
| Infectious disease testing | |
| Respiratory viral panel positive (n = 373) | 47 (12.6%) |
| Influenza positive (n = 396) | 5 (1.3%) |
| Blood culture positive (n = 347) | 11 (3.2%) |
| Legionella positive (n = 291) | 2 (0.7%) |
| *Streptococcus pneumoniae* positive (n = 216) | 0 (0.0%) |
| *Mycoplasma pneumoniae* positive (n = 219) | 13 (5.9%) |
| Medical treatment | |
| Corticosteroids (n = 582) | 533 (91.6%) |
| Antibiotics (n = 512) | 508 (99.2%) |
| Antivirals (n = 164) | 10 (6.1%) |
| Advanced respiratory support given (n = 538) | |
| ECMO (n = 417) | 28 (6.7%) |
| Intubation (n = 538) | 194 (36.1%) |
| Bilevel pressure ventilation/CPAP/ high-flow oxygen (n = 403) | 167 (41.4%) |
| Patient outcome | |
| Survival to discharge (n = 656) | 610 (93.0%) |

ECMO = extracorporeal membrane oxygenation; EVALI = E-cigarette, or vaping, product use-associated lung injury.

and all forms of substance use. Resources are available for clinicians and the public to define the terms used to describe e-cigarette use, or vaping, as well as associated products.[18,19]

**Physical Examination:** In assessing a patient with suspected EVALI, the physical examination should include an evaluation of vital signs, pulse oximetry, and respiratory system assessment. Tachycardia, tachypnea, and hypoxemia have been reported in cases of EVALI.[13] According to data reported to the CDC, 56% of patients had an oxygen saturation < 95%, and 55% patients had tachycardia.[11] Pulmonary findings on auscultation may be unremarkable.

**Bronchoscopy:** Although bronchoscopy is not routinely recommended in the evaluation of EVALI, indications for bronchoscopy can be reviewed in consultation with a pulmonologist and the decision to pursue bronchoscopy made on a case-by-case basis.[11] Among ICU patients included in this analysis, 45.0% underwent bronchoscopy (Table 2). The median number of days from hospitalization or ICU admission to bronchoscopy was 3 days (range, 0-88 days) (data not shown). Early in the outbreak, numerous hospitals performed bronchoscopy regularly when confronted with suspected EVALI, and CDC interim guidance recommended considering it in the diagnostic workup. Because EVALI is a diagnosis of exclusion, bronchoscopy has been used by clinicians to aid in EVALI diagnosis and to rule-out





REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089

alternative diagnoses. For example, other acute syndromes in which a patient may present with diffuse parenchymal involvement, hypoxemia, and constitutional symptoms include hypersensitivity pneumonitis, eosinophilic pneumonia, diffuse alveolar hemorrhage, and ARDS from another source (eg, pancreatitis).[20,21] EVALI is a syndrome of distinct clinical manifestations; whereas the most typical pulmonary manifestations include organizing pneumonia and the broader spectrum of acute lung injury, EVALI may also present with phenotypes resembling hypersensitivity pneumonitis, eosinophilic pneumonia, and others.[22] When the pretest probability of one of these alternative diagnoses is high (eg, in a patient with hemoptysis and suspected diffuse alveolar hemorrhage or a patient with immunosuppression and a suspected opportunistic infection), diagnostic bronchoscopy may aid evaluation.

Contraindications to bronchoscopy in patients with suspected EVALI include situations in which patients are too hypoxemic to undergo bronchoscopy or tolerate sedation and history of recent myocardial infarction.[23] In addition, some experts believe bronchoscopy induces airway hyperreactivity that is an unacceptably high-risk consequence of the procedure.[24] The following sections provide considerations for lung tissue examination, cellular analysis, and identification of lipid-laden macrophages in the context of bronchoscopy as an aid to diagnosis.

**Lung Tissue:** Two series of bronchoscopic and surgical lung biopsy specimens have been published, both showing a constellation of airway-centric damage and acute lung injury. These include high rates of fibrinous pneumonitis, organizing pneumonia, bronchiolitis obliterans, and diffuse alveolar damage, all of which are nonspecific findings seen in a variety of conditions.[25,26] These findings are expected given the pathophysiological underpinnings of EVALI and do not aid physicians trying to solidify a diagnosis of EVALI.[27] Thus, routine biopsies are not recommended in patients with suspected EVALI because the findings do not differentiate it from other illnesses.

**Cellular Analysis:** Cellular analysis of BAL specimens has had limited diagnostic utility in the context of EVALI. There is no "typical" cellular differential on cytology; BAL samples have variously yielded neutrophil-, lymphocyte-, eosinophil-, or macrophage-predominant cell differentials.[26,28-31] The differential among published case series shows a neutrophil predominance, consistent with an acute inflammatory pattern. This pattern is nonspecific to EVALI as it can also be seen in ARDS, multifocal infectious pneumonia, and other diagnoses.[32] A lymphocyte- or eosinophil-predominant differential is also nonspecific and not helpful in ruling out EVALI, as cases of hypersensitivity pneumonitis or eosinophilic pneumonia phenotypes have been identified.[20]

**Lipid-Laden Macrophages:** Oil-Red-O (ORO) staining is a method in which macrophages are stained to evaluate for lipid deposition, a finding commonly seen in lipoid pneumonia. Historically, its clinical use has been limited secondary to poor specificity, as "lipid-laden macrophages" may be witnessed in a host of conditions, including amiodarone toxicity, ARDS, and others.[33] However, early in the EVALI outbreak, a number of reports described lipid-laden macrophages in EVALI cases, leading to initial consideration of EVALI as an exogenous lipoid pneumonia.[31,34,35] Lipid-laden macrophages do appear with high frequency,[25,26,28-30] suggesting a high sensitivity despite very poor specificity; physicians encountering a positive ORO stain must decipher whether the findings represent EVALI vs alternative causes that yield lipid-laden macrophages. Data suggest, for example, that this finding may represent an endogenous response to e-cigarette, or vaping, product constituents.[9,26,27] If bronchoscopy with BAL is pursued for separate reasons, ORO staining of BAL cells could be ordered for patients with suspected EVALI.

**Pulmonary Imaging:** A CXR should be obtained for all patients with a history of e-cigarette, or vaping, product use, who have respiratory or GI symptoms, particularly when chest pain, dyspnea, or decreased oxygen saturation are present.[11] Bilateral opacities are the most common CXR findings in this analysis. In a published description of 53 patients from Illinois and Wisconsin, 91% of patients had an abnormal CXR[30]; in this analysis, close to 96% of ICU patients had an abnormal CXR. However, a normal CXR does not conclusively rule out EVALI.

CT imaging of the chest might be obtained when the CXR is normal.[11,12] In the case series from Illinois and Wisconsin, chest CT imaging was abnormal 100% of the time.[27] In this national analysis, 99.4% of chest CT scans revealed opacities, and among cases with data available for location of abnormal findings, 97.7% of findings were bilateral. Among the relatively few patients with data available regarding the presence of subpleural





REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089

sparing (n = 67), subpleural sparing was reported in 34.3%. In cases in which abnormalities on CXR are sufficient for diagnosis, a chest CT scan should be considered on a case-by-case basis.[11] Chest CT imaging may be used to evaluate for alternate or coexisting etiologies, such as infection or pulmonary embolism, worsening disease, or for complications such as pneumothorax. A contrast or noncontrast chest CT scan may be indicated depending on what alternative etiologies or potential findings are being considered.

Pneumomediastinum, pleural effusions, and pneumothorax have been seen in a minority of patients; a published description of 34 cases reported a variety of imaging patterns that correlated with pathologic investigations, including acute eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia, and lipoid pneumonia, but noted that most of the patterns identified had basilar-predominant consolidation and ground-glass opacity, often with areas of lobular or subpleural sparing.[20] In one case series from Utah of 60 patients with EVALI, pneumothorax or pneumomediastinum was identified in 18%.[28]

**Other Diagnostic Testing:** When evaluating a patient with suspected EVALI, the principal alternative diagnosis to consider is an infectious agent presenting with diffuse lung involvement. Fever is a common presenting symptom in patients with suspected EVALI.[4,36,37] Most infectious etiologies can be diagnosed by means other than bronchoscopy as the sensitivity of nasopharyngeal PCR viral testing for many viruses approaches 100%.[38,39] Atypical pneumonias such as mycoplasma or chlamydia may present in a similar manner (eg, diffuse infiltrates, hypoxemia) and may be detected via PCR-based assays of nasal swabs or sputum.[39] Other infectious agents to consider are fungal organisms such as *Pneumocystis jirovecii* and endemic mycoses.[40,41] These latter organisms should be considered in the appropriate context, including immunosuppression in the former, and appropriate geographic location or travel history in the latter.

It may be difficult to differentiate EVALI from COVID-19,[15] influenza, or other infections, and EVALI may occur in the presence of infection. In this analysis, 12.6% of patients had a positive respiratory viral panel, 5.9% were *Mycoplasma pneumoniae* positive, 1.3% were influenza positive, 3.2% had positive blood culture findings, and 0.7% were positive for *Legionella pneumophila*. In addition to these infectious etiologies, case series of patients with EVALI have identified evidence of concomitant infections with *Candida albicans*, rhinovirus, and nontuberculous mycobacteria.[37,42-44] Additional testing for infections should be based on individual patient factors, clinical evaluation, and geographic risk factors. In addition, HIV testing can be considered, particularly when the differential includes opportunistic infections.

Multiple other laboratory test results have been reported as abnormal in patients with EVALI. However, these tests are not diagnostic and generally nonspecific. In a report of 53 early cases from Illinois and Wisconsin, 87% had elevated WBC (median WBC, 15,900/mm$^3$), 93% had an elevated erythrocyte sedimentation rate, and 50% of patients had elevated liver transaminase levels.[30] These laboratory abnormalities are similar to those seen in other published case series.[28,36] Furthermore, neutrophil predominance is common, while eosinophilia is rarely seen.[36] Although elevated procalcitonin levels have been speculated to help rule out EVALI, elevation may be highly variable. In a case series by Aberegg et al,[45] for example, the median procalcitonin level was 0.3 ng/mL with an interquartile range of 0.1 to 0.7 ng/mL. The complete clinical presentation of patients, rather than any single laboratory test, is of greatest diagnostic utility.

**Level of Care:** Although the CDC has previously reported that 96% of patients with EVALI were hospitalized,[11] there may be underreporting of less fulminant cases, and thus both ambulatory and inpatient providers are encouraged to consider the diagnosis. Outpatient management can be considered for patients with normal oxyhemoglobin saturation (> 95% on room air), without significant comorbidity, and with strong social support and reliable access to health care. These last two points are critical as very close follow-up, within 24 to 48 h, is recommended based on observations that many patients deteriorated substantially over a short time course and subsequently required hospitalization and even intensive care.[13] Hospitalization is advised for any patient with suspected EVALI who has a new supplemental oxygen requirement, labored breathing, or significant comorbidity, or if the patient lacks the means for timely follow-up. Once hospitalized, decisions about caring for the patient on a general ward compared with an ICU may be determined according to local resources and staffing. Given the high rate of respiratory failure with presentations indistinguishable from ARDS,[30] ICU admission may be advisable for patients with severe tachypnea, oxygen requirements > 4 L by nasal cannula, any assisted ventilatory requirement (high-flow nasal





REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089

cannula, noninvasive ventilation, or invasive ventilation), or the development of nonpulmonary organ failure, including encephalopathy, shock, severe liver injury, or renal failure.

### Pharmacotherapy

**Antimicrobials:** In this study, almost all (99.2%) ICU patients received antibiotics, and 6.1% received antiviral agents. Because the disease course can mimic bacterial or viral pneumonia in previously healthy patients, early initiation of coverage for community-acquired pneumonia should be considered, and antiviral therapy such as for viral pneumonia if caused by influenza should be considered in the appropriate season.[11] If the patient has risk factors for hospital-associated pneumonia and appears critically ill, empiric antimicrobial therapy should be adjusted to cover common nosocomial pathogens in accordance with society guidelines.[46]

**Corticosteroids:** In the current study, almost all (91.6%) ICU patients received corticosteroids. An earlier analysis of observational data found that 82% of patients with suspected EVALI who were treated with corticosteroids improved,[11] although corticosteroid treatment in EVALI has not been prospectively evaluated.[47] Two histopathologic series of patients with EVALI undergoing biopsy noted that a majority met pathologic criteria for diffuse alveolar damage with a bronchiolocentric distribution,[25,26] consistent with ARDS. Corticosteroids have produced inconsistent findings for unspecified ARDS cases,[48-50] whereas corticosteroids have been found to be beneficial in ARDS due to COVID-19 specifically.[51,52] Although clinical trials have not been conducted to compare different corticosteroid dosing regimens, commonly reported doses for hospitalized patients requiring supplemental oxygen are between 40 and 60 mg of prednisone daily for durations ranging from a few days to 2 weeks.[45] If corticosteroids are being used, clinicians are encouraged to carefully consider all infections prior to starting therapy.

### Respiratory Support

In this study, more than one-third of ICU patients (36.1%) required intubation. Initial ventilator management for patients with EVALI should adhere to the principles of ARDS ventilation: adequate oxygenation (oxyhemoglobin saturation > 90%) with the least necessary $F_{IO_2}$; limit tidal volume and plateau pressures in an effort to avoid ventilator-induced lung injury; and seek to achieve ventilator synchrony to decrease oxygen consumption.[53] Less certainty exists regarding recommendations for titrating positive end-expiratory pressure (PEEP) for patients with suspected EVALI. Considerations for PEEP titration include: the degree and diffuseness of the consolidated lung, with more diffuse consolidation potentially favoring a higher PEEP strategy[54]; how lung compliance changes with the addition of PEEP[55]; and whether the patient has evidence of barotrauma at the outset of ventilation. General recommendations are to minimize mean airway pressure in the presence of pneumothorax and persistent air leak. Whether mean airway pressure must be limited in cases of isolated pneumomediastinum or pulmonary interstitial emphysema is unclear, but limiting PEEP to provide expansion could be considered.

For patients with a $P_{aO_2}$:$F_{IO_2}$ ratio < 150 despite adequate sedation and ventilation in accordance with best ARDS practices,[54] prone positioning should be considered, which has been shown to reduce mortality.[56] For patients who remain difficult to oxygenate, or who have difficulty achieving ventilator synchrony, neuromuscular blockade can be added. However, as shown in the Reevaluation of Systemic Early Neuromuscular Blockade (ROSE)-Prevention and Early Treatment of Acute Lung Injury (PETAL) trial, early institution of neuromuscular blockade did not reduce mortality compared with a lighter sedation strategy without obligatory neuromuscular blockade.[57]

When confronted with severe ARDS not responding favorably to traditional ARDS ventilation strategies or when significant barotrauma precludes the ability to deliver adequate PEEP, early consideration for venovenous ECMO should be considered. In the current analysis, 6.7% of ICU patients underwent ECMO. Early decisions of ECMO candidacy and prompt initiation allow for operative planning and the safest possible transition.[58] In the event that the patient's lungs are unrecoverable from damage by EVALI or manifest a rapidly fibrotic ARDS subtype, lung transplantation is a consideration.

In this study, 41.4% of ICU patients received noninvasive ventilation and/or high-flow nasal cannula. Less severe cases of EVALI may respond well to noninvasive forms of supplemental oxygen; typical practice is to administer oxygen via high-flow nasal cannula in patients requiring oxygen that exceeds a 4 L/min flow rate and/or for patients with a very high respiratory rate (> 26 breaths/min), particularly when





REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089

patients do not have $CO_2$ retention or obstructive lung disease.[58] Noninvasive ventilation can also be considered, and is often selected, if the patient has a component of cardiogenic pulmonary edema, $CO_2$ retention, or airflow obstruction.[59]

## Limitations

This analysis was subject to several limitations: (1) considerable missing data among several clinical variables, including ICU admission and specific diagnoses within category of underlying medical condition, may limit the generalizability of these findings; (2) EVALI definition is intentionally sensitive to capture all potential cases, and thus possible misdiagnosis may occur; and (3) data collection tools and state-specific data management systems evolved throughout the outbreak, leading to variations in variable reporting and completeness between the start and end period of data collection. At the beginning of the EVALI response, data were collected in a system previously used for collecting limited line list data during multistate foodborne outbreaks, and they were then transitioned into a larger system and migrated into a secure online platform. In addition, as public health knowledge of factors influencing EVALI risk changed over the course of the outbreak, the case report form changed as well. As state-level responses evolved, some states built their own data collection systems around earlier or later versions of the case report form. Each of these factors affected reporting, data collection, and variation in data across states and over the course of the outbreak.

## Conclusions

Since the identification of the primary cause of EVALI, the number of hospitalized EVALI cases has decreased considerably in the United States. However, pulmonary and critical care specialists continue to face challenges related to patient use of e-cigarette, or vaping, products, and it is critically important that these specialists and all clinicians remain prepared to address EVALI and its potential complications.

## Acknowledgments

**Financial/nonfinancial disclosures:** None declared.

## References


1. Ghinai I, Pray IW, Navon L, et al. E-cigarette product use, or vaping, among persons with associated lung injury—Illinois and Wisconsin, April-September 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:865-869.
2. Perrine CG, Pickens CM, Boehmer TK, et al. Characteristics of a multistate outbreak of lung injury associated with E-cigarette use, or vaping—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:860-864.
3. Moritz ED, Zapata LB, Lekiachvili A, et al. Update: characteristics of patients in a national outbreak of E-cigarette, or vaping, product use-associated lung injuries—United States, October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:985-989.
4. Chatham-Stephens K, Roguski K, Jang Y, et al. Characteristics of hospitalized and nonhospitalized patients in a nationwide outbreak of E-cigarette, or vaping, product use-associated lung injury—United States, November 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:1076-1080.
5. Krishnasamy VP, Hallowell BD, Ko JY, et al. Update: characteristics of a nationwide outbreak of E-cigarette, or vaping, product use-associated lung injury—United States, August 2019-January 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:90-94.
6. Mikosz CA, Danielson M, Anderson KN, et al. Characteristics of patients experiencing rehospitalization or death after hospital discharge in a nationwide outbreak of E-cigarette, or vaping, product use-associated lung injury—United States, 2019. *MMWR Morb Mortal Wkly Rep*. 2020;68:1183-1188.
7. Kiernan E, Click ES, Melstrom P, et al. A brief overview of the national outbreak of E-cigarette, or vaping, product use-associated lung injury and the primary causes. *Chest*. 2021;159(1):426-431.
8. Blount BC, Karwowski MP, Shields PG, et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *N Engl J Med*. 2020;382:697-705.
9. Taylor J, Wiens T, Peterson J, et al. Characteristics of E-cigarette, or vaping, products used by patients with associated lung injury and products seized by law enforcement—Minnesota, 2018 and 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:1096-1100.
10. US Food and Drug Administration. Lung illnesses associated with use of vaping products. April 30, 2020 [cited 2020 September 30]. https://www.fda.gov/news-events/public-health-focus/lung-injuries-associated-use-vaping-products
11. Siegel DA, Jatlaoui TC, Koumans EH, et al. Update: interim guidance for health care providers evaluating and caring for patients with suspected e-cigarette, or vaping, product use associated lung injury—United States, October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:919-927.
12. Jatlaoui TC, Wiltz JL, Kabbani S, et al. Update: interim guidance for health care providers for managing patients with suspected E-cigarette, or vaping, product use-associated lung injury—United States, November 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:1081-1086.
13. Evans ME, Twentyman E, Click ES, et al. Update: interim guidance for health care professionals evaluating and caring for patients with suspected E-cigarette, or vaping, product use-associated lung injury and for reducing the risk for rehospitalization and death following hospital discharge—United States, December 2019. *MMWR Morb Mortal Wkly Rep*. 2020;68:1189-1194.
14. Centers for Disease Control and Prevention. 2019 Lung Injury Surveillance Primary Case Definitions. Atlanta, Georgia: Health and Human Services; 2019.
15. Callahan SJ, Harris D, Collingridge DS, et al. Diagnosing EVALI in the time of COVID-19. *Chest*. 2020;158(5):2034-2037.
16. Pérez-Cárceles MD, Pereñiguez JE, Osuna E, Luna A. Balancing confidentiality and the information provided to families of patients in primary care. *J Medical Ethics*. 2005;31:531-535.
17. Lisseman I. Maintaining confidentiality and information-giving in intensive care. *Nursing Crit Care*. 2000;5:187-193.
18. Centers for Disease Control and Prevention. E-cigarette, or vaping, products visual dictionary. 2019 [cited 2020 September 1]. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf
19. Choi H, Lin Y, Race E, Macmurdo MG. Electronic cigarettes and alternative methods of vaping. *Ann Am Thorac Soc*. 2021;18:191-199.






REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089

20. Henry TS, Kanne JP, Kligerman SJ. Imaging of vaping-associated lung disease. *N Engl J Med*. 2019;381:1486-1487.
21. Henry TS, Kligerman SJ, Raptis CA, Mann H, Sechrist JW, Kanne JP. Imaging findings of vaping-associated lung injury. *AJR Am J Roentgenol*. 2020;214:498-505.
22. Kligerman SJ, Kay FU, Raptis CA, et al. CT findings and patterns of e-cigarette or vaping product use-associated lung injury: a multicenter cohort of 160 cases. *Chest*. 2021;160:1492-1511.
23. Du Rand IA, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. *Thorax*. 2013;68(suppl 1):i1-i44.
24. Diaz CD, Carroll BJ, Hemyari A. Pulmonary illness related to E-cigarette use. *N Engl J Med*. 2020;382:384-385.
25. Mukhopadhyay S, Mehrad M, Dammert P, et al. Lung biopsy findings in severe pulmonary illness associated with E-cigarette use (vaping). *Am J Clin Pathol*. 2020;153:30-39.
26. Butt YM, Smith ML, Tazelaar HD, et al. Pathology of vaping-associated lung injury. *N Engl J Med*. 2019;381:1780-1781.
27. Dries DJ, Endorf FW. Inhalation injury: epidemiology, pathology, treatment strategies. *Scand J Trauma Resusc Emerg Med*. 2013;21:31.
28. Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study. *Lancet (London, England)*. 2019;394:2073-2083.
29. Triantafyllou GA, Tiberio PJ, Zou RH, et al. Vaping-associated acute lung injury: a case series. *Am J Respir Crit Care Med*. 2019;200:1430-1431.
30. Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related to E-cigarette use in Illinois and Wisconsin—final report. *N Engl J Med*. 2020;382:903-916.
31. Maddock SD, Cirulis MM, Callahan SJ, et al. Pulmonary lipid-laden macrophages and vaping. *N Engl J Med*. 2019;381:1488-1489.
32. Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *Am J Respir Crit Care Med*. 2012;185:1004-1014.
33. Pambuccian SE. Testing for lipid-laden macrophages in bronchoalveolar lavage fluid to diagnose vaping-associated pulmonary injury. Are we there yet? *J Am Soc Cytopathol*. 2020;9:1-8.
34. Davidson K, Brancato A, Heetderks P, et al. Outbreak of electronic-cigarette-associated acute lipoid pneumonia—North Carolina, July-August 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68:784-786.
35. Shields PG, Song MA, Freudenheim JL, et al. Lipid laden macrophages and electronic cigarettes in healthy adults. *EBioMedicine*. 2020;60:102982.
36. Kalininskiy A, Bach CT, Nacca NE, et al. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. *Lancet Respir Med*. 2019;7:1017-1026.
37. Kass AP, Overbeek DL, Chiel LE, Boyer EW, Casey AMH. Case series: adolescent victims of the vaping public health crisis with pulmonary complications. *Pediatr Pulmonol*. 2020;55:1224-1236.
38. Hakki M, Strasfeld LM, Townes JM. Predictive value of testing nasopharyngeal samples for respiratory viruses in the setting of lower respiratory tract disease. *J Clin Microbiol*. 2014;52:4020-4022.
39. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373:415-427.
40. Orlowski HLP, McWilliams S, Mellnick VM, Bhalla S, Lubner MG, Pickhardt PJ, Menias CO. Imaging spectrum of invasive fungal and fungal-like infections. *Radiographics*. 2017;37:1119-1134.
41. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med*. 2014;371:1619-1628.
42. Aldy K, Cao DJ, Weaver MM, Rao D, Feng SY. E-cigarette or vaping product use-associated lung injury (EVALI) features and recognition in the emergency department. *J Am Coll Emerg Physicians Open*. 2020;1:1090-1096.
43. Rao DR, Maple KL, Dettori A, et al. Clinical features of E-cigarette, or vaping, product use-associated lung injury in teenagers. *Pediatrics*. 2020:146.
44. Chen L, Arens R, Chidambaram AG, et al. Vaping associated pulmonary nontuberculous mycobacteria. *Lung*. 2021;199:21-27.
45. Aberegg SK, Cirulis MM, Maddock SD, et al. Clinical, bronchoscopic, and imaging findings of e-cigarette, or vaping, product use-associated lung injury among patients treated at an academic medical center. *JAMA Netw Open*. 2020;3:e2019176.
46. Kalil AC, Metersky ML, Klompas M, et al. Executive summary: management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016;63:575-582.
47. Smith ML, Gotway MB, Crotty Alexander LE, Hariri LP. Vaping-related lung injury. *Virchows Arch*. 2021;478:81-88.
48. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354:1671-1684.
49. Peter JV, John P, Graham PL, Moran JL, George IA, Bersten A. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ (Clinical Research Ed)*. 2008;336:1006-1009.
50. Villar J, Belda J, Añón JM, et al. Evaluating the efficacy of dexamethasone in the treatment of patients with persistent acute respiratory distress syndrome: study protocol for a randomized controlled trial. *Trials*. 2016;17:342.
51. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384:693-704.
52. WHO Rapid Evidence Appriasal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341.
53. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307:2526-2533.
54. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195:1253-1263.
55. Constantin JM, Grasso S, Chanques G, et al. Lung morphology predicts response to recruitment maneuver in patients with acute respiratory distress syndrome. *Crit Care Med*. 2010;8:1108-1117.
56. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368:2159-2168.
57. Moss M, Huang DT, Brower RG, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med*. 2019;380:1997-2008.
58. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378:1965-1975.
59. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J*. 2017;50.






REV 5.6.0 DTD ■ CHEST4944_proof ■ 26 March 2022 ■ 2:38 pm ■ EO: CHEST-21-2089