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## Electrotonic-Cigarette or Vaping Product Use Associated Lung Injury: Diagnosis of Exclusion

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### *Abstract*

The first reports of lung injury attributable to vaping date back to 2012, but the ongoing outbreak of electrotonic-cigarette or vaping product use associated lung injury (EVALI) began in 2019. It is a diagnosis of exclusion. In this case report, we describe a patient with history of excessive vaping for the last 3 weeks who was admitted to the intensive care unit for acute hypoxic respiratory failure. The patient was diagnosed with EVALI given the history of vaping in the setting of negative infectious work-up and radiographic imaging that showed lung opacities.

### *Case Presentation*

A 37-year-old man with no significant past medical history initially presented to the emergency department (ED) with “chest pain and trouble breathing.” He reported first feeling chest pain localized to the substernal region 5 days prior to presentation; described it as pleuritic in nature; and rated intensity as severe. The patient stated deep breaths and laying flat aggravated his pain, while leaning forward relieved it. He also reported associated subjective fevers, non-productive cough, nausea and diarrhea but denied any lower extremity swelling, calf pain, prolonged immobilization, or history of congestive heart failure (CHF) or venous thromboembolism (VTE).

The patient denied any past medical or surgical history and reported not being on any medications or over-the-counter supplements. He denied any medication, diet, or environmental allergies. He lives in

an apartment (built in the 1990s) with his wife, and does not have any pets. He works full-time at a box manufacturing facility where he processes shipping labels, reports drinking approximately 5 to 6 beers a day, denies any history of illicit drug use. He smoked one pack per day for the past ten years, but reported to have quit smoking over the last month.

Due to his significantly worsening shortness of breath and severe chest pain, he was prompted to present to the ED. Upon presentation, he was febrile (38.9 degrees Celsius), hypoxic (saturating at 88%) in the setting of tachypneic (22 breaths per minute), tachycardic (117 beats per minute), and normotensive (systolic of 105 mmHg). Patient was started on supplemental oxygen, 4 Liters (L) nasal cannula (NC), yet had been noted to continue to desaturate in the mid-80’s. Despite being transitioned to 11L non-rebreather mask, he remained tachypneic and hypoxic, and was subsequently started on

high flow nasal cannula (HFNC), 50L at 0.50 fraction of inspired oxygen (FiO<sub>2</sub>).

Physical examination was significant for a man who appeared about the stated age in respiratory distress. He was noted to have scleral icterus, yellow skin discoloration, supraclavicular retraction, increased respiratory exertion, and fine bibasilar crackles. S1 & S2 were heard but no additional heart sounds or friction rubs were noted. His abdomen was soft, nondistended, nontender to superficial or deep palpation, without organomegaly, but with normal bowel sounds. No superficial venous dilation or telangiectasia was noted. Upper and lower extremities were without edema or tenderness. Homan's sign was negative.

Initial laboratory investigations were significant for leukocytosis (white blood cell count of 12.6 K/uL), normocytic anemia (hemoglobin 8.2 g/dl) with an INR of 1.25, D-dimer 415 ng/ml DDU, troponin 0 ng/ml, hyponatremia (serum sodium 130 mmol/L), potassium 3.8 mmol/L, creatinine 0.79 mg/dL, BUN of 7mg/dL, alanine transaminase 21 IU/L, aspartate transaminase 63 IU/L, alkaline phosphatase 178 IU/L, gamma-glutamine transaminase 224 IU/L, total bilirubin 6.9 mg/dL (direct bilirubin 5.9 mg/dL). His lactic acid was elevated at 3.76 mEq/L. SARS-CoV-2 polymerase chain reaction (PCR) nasal swab was negative. Urine analysis was positive for moderate bilirubin. Urine toxicology was negative.

Arterial blood gas while on HFNC showed pH 7.45, pCO<sub>2</sub> 27 mmHg, pO<sub>2</sub> 68 mmHg and HCO<sub>3</sub> 21 mEq/L. His PaO<sub>2</sub>:FiO<sub>2</sub> was calculated to be 136, significant for moderate acute respiratory distress syndrome (ARDS).

Electrocardiogram (ECG) showed normal sinus rhythm, rate of 99 beats per minute, no ST segment changes or T wave inversions, without axis devious or conduction abnormalities.

Chest X-Ray (CXR) was significant for extensive patchy bilateral multifocal patchy infiltrates in the mid and lower lobes. Computer tomography (CT) of the chest without contrast (Figure 1) was significant for severe multifocal pneumonia with small bilateral pleural effusions.

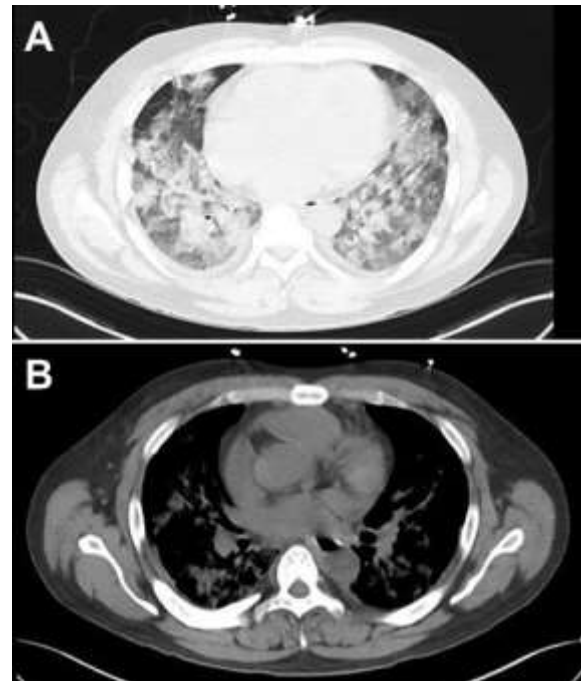


Figure 1. Representative images from the computer tomography (CT) of the chest without contrast in (A) lung windows and (B) soft tissue widows. The CT was significant for severe multifocal pneumonia with small bilateral pleural effusions.

CT of the abdomen and pelvis with contrast was significant for hepatomegaly with diffuse fatty infiltrated, moderate gallbladder distention without intra or extra hepatic duct dilatation non-concerning for obstruction. Ultrasound (US) of the gallbladder revealed a distended gallbladder without evidence of stone or wall thickening, but was significant for sludge.

The patient was admitted to the intensive care unit (ICU) with severe sepsis and acute hypoxic respiratory failure likely secondary to presumed viral versus bacterial community acquired pneumonia (CAP) requiring

HFNC. Blood cultures were collected, and the patient was started on fluid resuscitation and broad-spectrum antibiotics. Sputum cultures, respiratory viral panel, atypical pneumonia serologies and urine for legionella and pneumococcal antigens were ordered.

His Well's score was calculated at 1.5 placing him at a low risk for pulmonary embolism (PE) with a D-dimer of 415 ng/ml DDU, likely secondary to septic-inflammatory state. However, given his continued high oxygen requirement, saturating in the high-80s to the low-90s while on HFNC 50L of 60% FiO<sub>2</sub>, and increased respiratory effort, chest CT angiography was ordered but negative for PE or acute aortic pathology. Transthoracic echocardiogram (TTE) demonstrated a preserved left ventricular function with an ejection fraction of 60%, without valvular disease or pericardial effusion.

Repeat CXR showed worsening diffuse multifocal infiltrates concerning for progressive ARDS. He was started on a 5-day course of systemic steroids (dexamethasone) given his worsening oxygen requirements and CXR findings. SARS-CoV2 nasal PCR was repeated as well, which remained negative. Cryptococcus, coccidiomycosis & QuantiFERON-Gold were ordered. His oxygen requirements improved,. Labs revealed normalization of lactic acid and bilirubin with down-trending liver enzymes with correlating resolution of patient's jaundice and icterus. He also reported significant improvement in his gastrointestinal symptoms. Subsequently, he was transferred from the ICU to the telemetry unit.

Infectious work-up (including *Streptococcus pneumoniae*, chlamydia psittaci, chlamydia pneumonia, mycoplasma pneumonia, *Legionella pneumoniae*, cryptococcus, aspergillosis, cryptococcus, histoplasmosis, human immunodeficiency virus, *Pneumocystis jiroveci* pneumonia (PCP), and tuberculosis), respiratory viral panel and

cultures were all negative. Of note, the patient's wife reported that over the course of the last few weeks, the patient had started vaping e-cigarettes. Upon discussion, he that he started vaping a nicotine-containing product in order to quit smoking cigarettes 3-weeks ago, states that he has been "excessive vaping for the last 2-3 weeks."

Given newfound history of vaping in the setting of negative infectious work-up and CT imaging that showed dense ground glass opacities throughout, differential diagnosis now included E-cigarette, or vaping product, use associated lung injury (EVALI) versus respiratory bronchiolitis associated interstitial lung disease (RB-ILD) secondary to smoking. He was treated with high dose systemic steroids (methylprednisolone) and PCP prophylaxis with trimethoprim-sulfamethoxazole. The broad-spectrum antibiotics were discontinued.

He started to demonstrate significant improvement in his oxygen requirement and in his clinical symptoms, was no longer coughing and was able to ambulate without dyspnea. Repeat CT scan demonstrated interval improvement in pulmonary infiltrates, although radiographic findings on CT were still significant for diffuse pulmonary infiltrates. The patient had near-complete resolution of symptoms, was titrated down to 2L NC, was transitioned to room air, and discharged on hospital day 21 on a steroid taper and PCP prophylaxis.

### *Discussion*

The first reports of lung injury attributable to vaping date back to 2012, but the ongoing outbreak of electrotonic-cigarette or vaping product use associated lung injury (EVALI) began in 2019 (1). By February 2020, the Center for Disease Control (CDC) documented over 2800 EVALI hospitalizations, amongst which 68 patients died (2). E-cigarettes function to aerosolize

various chemicals (including nicotine, tetrahydrocannabinol, favoring and other additives) for inhalation (3). EVALI is a form of acute or subacute lung injury whose pathogenesis is unknown and is thought to be a spectrum of disease, rather than a single process (4,11). The histopathological patterns include acute fibrinous pneumonitis, diffuse alveolar damage and organizing pneumonia, more commonly bronchiolocentric with accompanying bronchiolitis (5). This spectrum of nonspecific acute lung injury commonly presents with cough, dyspnea, gastrointestinal symptoms with accompanying constitutional symptoms (1).

Radiographic findings of EVALI demonstrate a spectrum of nonspecific acute lung injury patterns. Bilateral opacities are typically seen, the majority of chest radiographs demonstrate diffuse hazy or consolidative opacities (6). CT opacities are typically ground glass in density and may spare subpleural spaces. Pleural effusions are less common findings (7). Other radiographic patterns have been noted suggestive of one or more disease processes: diffuse alveolar damage (dependent consolidation, diffuse ground glass and air bronchograms), acute eosinophilic pneumonitis (centrilobular ground glass opacities in the anterior lung fields, confluent ground glass opacities in dependent areas and lobules of mosaic attenuation) and organizing pneumonia (diffuse, multifocal discrete and confluent) (7).

EVALI is a diagnosis of exclusion; thus, pulmonary infectious causes and other etiologies of progressive respiratory insufficiency should be excluded (7). Currently CDC criteria for a confirmed case of EVALI include: (1) Use of e-cigarette or related products in the last 90 days, (2) Lung opacities on CXR or CT, (3) Exclusion of lung infection, including negative influenza polymerase chain reaction (PCR) or rapid test (unless out of season), viral respiratory

panel, and if clinically indicated, urine antigen tests for *Legionella* and *Streptococcus pneumoniae*, blood & sputum cultures, bronchoalveolar lavage and HIV-related opportunistic infections, (4) absence of likely alternative diagnosis including cardiovascular disease, rheumatologic disease and neoplastic (2).

Supportive care initially focuses on management of hypoxia with supplemental oxygen at a goal saturation of 88 to 92% (3). Empiric antibiotics should also be initiated to cover likely pathogens for CAP. Although the optimal treatment of EVALI is not yet known, systemic glucocorticoids have been used in the majority of patients with varying efficacy (9). Given the possible efficacy and low incidence of adverse effects, systemic glucocorticoids should be considered in EVALI cases with progressively worsening symptoms and hypoxemia (7,10). Flexible bronchoscopy may be utilized in excluding other causes of non-resolving or progressive pneumonitis; however, bronchoscopy is generally reserved for patients with progressive or severe symptoms despite treatment.

Our patient's initial complaint of chest pain upon presentation raised concerns for cardiovascular disease. ECG without any signs of acute ischemia in the setting of a troponin of 0.000 ng/ml was not indicative of acute coronary syndrome. Marginally elevated D-dimer in the setting of worsening hypoxemia and tachycardia was concerning for PE, but CTA was non-significant for any PE or aortic pathology. TTE without pericardial effusion and ECG without PR segment depression or ST segment elevations, ruled out pericarditis. The initial chest CT raised concerns for multifocal pneumonia; however, infectious, and autoimmune workup were negative. Given the patient's history of vaping within the last 90 days, diffuse dense ground glass opacities on CT, absence of infectious etiology and

absence of alternative diagnosis, the patient met the CDC Criteria for EVALI and started on treatment. Given the patient's clinical improvement and reduced oxygen requirements while on systemic steroids, flexible bronchoscopy was deferred.

### *Conclusion*

While alternative causes of respiratory illness may be more prevalent, it is important to consider and assess for pulmonary illness associated with vaping, particularly in patients where no other cause can be clearly identified. Patients reporting respiratory complaints as well as gastrointestinal symptoms should be questioned about any recent e-cigarette to assess for possible EVALI given the appropriate clinical scenario, radiographic findings, and absence of pulmonary infectious etiologies and other causes progressive respiratory insufficiency.

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