*Project S E.N.S.O.R. News

Volume 30 No. 4 Fall 2019

Vaping and Acute Lung Disease

On 9/6/19, the Centers for Disease Control and Prevention (CDC) announced that 450 possible cases with five deaths of acute lung disease from vaping had been reported from 33 states, including Michigan, and one territory. Although some newspaper reports have discussed infectious agents, the 9/6/2019 CDC announcement stated that "no evidence of infectious disease has been identified; therefore, lung illnesses are likely associated with a chemical exposure."

The CDC public health case definition is shown in Table 1. Since the case reports do not require a lung biopsy, the underlying pathology of the 450 possible cases are not clear. The CDC is expected to start reporting only confirmed and probable cases so the number of reported cases in the future, at least initially, is expected to decrease. The diagnosis of six cases reported in September from Utah (Maddock et al., 2019) and five cases from North Carolina (Davidson et al., 2019) was lipoid pneumonia. All these patients had vaped cannabinoid products. Nine of these 11 patients had bronchoscopy and evaluation of their lavage fluid; all nine had lipid-containing macrophages consistent with the diagnosis of lipoid pneumonia.

On 9/6/2019, a New England Journal of Medicine article reported on 53 cases from Illinois and Wisconsin (Layden et al. 2019). The authors reported that 84% of the cases had vaped tetrahydro cannabinoid products. Only three of the patients had a lung biopsy with a range of findings: Case 1 had "mild and nonspecific inflammation, acute diffuse alveolar damage and foaming macrophages"; Case 2 had "interstitial and nonspecific inflammation, acute diffuse alveolar damage and foaming macrophages"; and Case 3 had "interstitial and peribronchiolar granulomatosis pneumonitis." Of the 14 cases with data on lavage cells, none had increased eosinophils and only two noted moderate lipid-laden macrophages. Eighty one percent of these 53 patients had gastrointestinal symptoms in addition to respiratory symptoms.

Prior to the current concern about vaping, there have been 17 case reports in the medical literature; Acute Eosinophilic Pneumonia (4 cases), Organizing Pneumonia (3 cases), Lipoid Pneumonia (3 cases), Diffuse Alveolar Hemorrhage (2 cases), Hypersensitivity Pneumonitis (2 cases), Respiratory Bronchiolitis Interstitial Lung Disease (1 case), Pneumonia (1 case), and Bronchitis (1 case). These reports are summarized in Table 2. Unlike the current cases, the cases in previous publications did not report gastrointestinal symptoms and only one of these 17 previous cases reported the use of cannabinoid products.

Table 1. CDC Case Definition for Confirmed and Probable Cases (Not for Clinical Diagnosis)

Confirmed	♦ Using an e-cigarette ("vaping") or dabbing* in 90 days prior to symptom onset **AND** ♦ Pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest CT **AND** ♦ Absence of pulmonary infection on initial work-up: Minimum criteria include negative respiratory viral panel, or influenza PCR or rapid test if local epidemiology supports testing. All other clinically indicated respiratory ID testing (e.g., urine Antigen for *Streptococcus pneumoniae* and *Legionella*, sputum culture if productive cough, bronchoalveolar lavage (BAL) culture if done, blood culture, HIV-related opportunistic respiratory infections if appropriate) must be negative **AND** ♦ No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic or neoplastic process).
Probable	♦ Using an e-cigarette ("vaping") or dabbing* in 90 days prior to symptom onset **AND** ♦ Pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest CT **AND** Infection identified via culture or PCR, but clinical team** believes this is not the sole cause of the underlying respiratory disease process ***OR*** Minimum criteria to rule out pulmonary infection not met (testing not performed) and clinical team** believes this is not the sole cause of the underlying respiratory disease process **AND** ♦ No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic or neoplastic process).
Footnotes	*Using an electronic device (e.g., electronic nicotine delivery system (ENDS), electronic cigarette, e-cigarette, vaporizer, vape (s), vape pen, dab pen, or other device) or dabbing to inhale substances (e.g., nicotine, marijuana, THC, THC concentrates, CBD, synthetic cannabinoids, flavorings, or other substances). **Clinical team caring for the patient.

E-cigarettes and vaping are relatively recent forms of smoking; they were first commercially available in the United States in 2007. It has become increasingly popular with young individuals. In fact, e-cigarettes are the most common tobacco product used by high school students with 20.8% using in the prior 30 days up from about 3% in 2011 (Gentzke et al., 2019). The increased use of e-cigarettes as a nicotine delivery product as well as to deliver cannabinoids has clearly increased the population at risk. How possible changes in both legal formulations or contaminants in the products contributed to the recent cases is under active investigation. The reports in the current cases of gastrointestinal symptoms and the exposure to marijuana products may be clues to determine the etiology of the current cases. For example, vitamin E acetate oil was found in multiple cannabinoid samples and has been suggested as the cause of lipoid pneumonia in some individuals with acute lung disease associated with vaping.

E-cigarettes contain multiple types of chemicals including nicotine, carbonyls, and solvents. Previous examples of lung disease caused by chemicals that can be potentially found in e-cigarettes include microwave popcorn lung (bronchiolitis obliterans) from exposure to diacetyl and 2, 3 pentanediol flavoring agents (Van Roon et al., 2007; PS News v.18 (4), Fall 2007) and waterproof spraying lung (chemical pneumonitis and pulmonary edema) from exposure to solvents in boot or tent waterproofing products (CDC, 2006; PS News v. 19 (#1), Winter 2007-2008).

Given the uncertainty of the etiology of the lung disease associated with vaping, healthcare providers should strongly discourage their patients from vaping. To assist in determining the etiology, providers are encouraged to report all suspected cases of lung disease associated with vaping to public health officials. Ways to report are shown in Table 3. Michigan will be sharing de-identified data of the reported cases with the CDC. The CDC will be examining the cases from all states, including reviewing the epidemiology and pathological findings, along with a review of the results of the FDAs laboratory analysis of the components of the vaping products associated with the cases of lung disease.

CDC. Brief Report: Respiratory Illness Associated with Boot Sealant Products – Five States, 2005-2006. MMWR 2006; 55: 488-490.
Davidson K, Brancato A, Heetderks P, et al. Outbreak of Electronic-Cigarette–Associated Acute Lipoid Pneumonia — North Carolina, July–August 2019. MMWR ePub: 6 September 2019. DOI: http://dx.doi.org/10.15585/mmwr.mm6836e.
Gentzke AS, Creamer M, Cullen KA, et al. *Vital Signs:* Tobacco Product Use Among Middle and High School Students — United States, 2011–2018. Morb Mortal Wkly Rep 2019; 68: 157–164.
Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin-Preliminary Report. N Engl J Med 2019 Sep 6. doi: 10.1056/NEJMc1911614. [Epub ahead of print].
Maddock SD, Cirulis MM, Callahan SJ, et al. Pulmonary Lipid-Laden Macrophages and Vaping. N Engl J Med 2019 Sep 6. doi: 10.1056/NEJMc1912038. [Epub ahead of print].
Meiman J. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Preliminary Report. N Engl J Med. 2019 Sep 6. doi: 10.1056/NEJMoa1911614. [Epub ahead of print].
Microwave Popcorn Lung. Fall 2007; 18 (4). https://oem.msu.edu/images/newsletter/ProjectSensor/Sv18n4.pdf
Van Rooy GJ, Rooyackers JM, Prokop M, et al. Bronchiolitis Obliterans Syndrome in Chemical Workers Producing Diacetyl for Food Flavorings. Am J Respir Crit Care Med 2007; 176: 498-504.
Waterproofing Lung. PS News Winter 2007-2008; 19 (1). https://oem.msu.edu/images/newsletter/ProjectSensor/Sv19n1.pdf.

Table 3. Public Health Reporting Instructions *The following information on your patient with severe pulmonary disease of unclear etiology and history of e-cigarette/vaping within the last 90 days should be reported*

Reports can be submitted in one of three ways:

1. By calling your Local Health Department (see www.malph.org for directory)
2. By providing a completed reporting form to your hospital's Infection Preventionist, who will make sure it gets to the right Local Health Department, or
3. By faxing a report to 517-335-8509. Obtain the reporting form at: www.michigan.gov/cdinfo

Lung disease from chemical exposure is a reportable condition under Administrative Rules R 325.71-75. Reporting of patients with this condition falls under the HIPAA public health exception [section 1264.512 (b)]; and disclosure by you or your hospital is exempt from "patient consent, authorization, or opportunity to agree or object."

NIH Award to Investigate the Etiology of Hypersensitivity Pneumonitis – Actively Recruiting Study Subjects

Hypersensitivity Pneumonitis (HP) can be a difficult disease to diagnose, particularly since there are limited ways to identify the causal antigen. Commercially available HP precipitating antibody panels have limited utility due to their lack of sensitivity and specificity. Melissa Millerick-May, PhD, an environmental exposure scientist at MSU, has a 5-year NIH award to investigate a novel approach to identify causal antigens for patients with HP. Activity includes: comprehensive exposure assessment, home/workplace evaluations, and environmental sample collection. Blood from each study subject (and designated exposure matched control) will be utilized in immunoassays to determine the presence of offending antigen in samples collected. Results will be used to develop a targeted exposure avoidance plan.

All test results and the resulting exposure avoidance plans will be shared with both the patient and the referring physician. We will subsequently contact the referring physician to determine the clinical status of the patient and to evaluate if the testing and plan to reduce/eliminate exposures proved useful in managing the patient. If you would like additional information about this project, including our criteria for patient recruitment/enrollment and/or details pertaining to the sampling and laboratory methods used, please contact Melissa Millerick-May, PhD. If you have diagnostic or management questions about a possible HP patient, please contact Kenneth Rosenman, MD. Both can be reached at 1-800 446-7805.

Table 2. Seventeen Case Reports of Lung Disease and Vaping Reported Prior to 2019

Acute Eosinophilic Pneumonia (4) There have been four case-reports of acute eosinophilic pneumonia related to vaping; one from Hawaii (2), one from California (5), and two from Japan (1,4). There is a much more extensive literature that acute eosinophilic pneumonia is associated with cigarette smoking (3). The 20-year-old male from California was a healthy active duty sailor who had a three-day history of a persistent cough, shortness of breath and facial flushing. His symptoms occurred within one hour after smoking an e-cigarette. He had apical ground glass opacities on a chest CT scan. He had 74% eosinophils in bronchial lavage fluid. He had significant improvement after treatment with steroids. The 18-year-old female from Hawaii had fever, non-productive cough, difficulty breathing and pleuritic chest pain. She had begun vaping in the prior two months. She had diffuse ground glass patchy airspace disease and coalescing nodules. She had 26% eosinophils in her bronchial lavage fluid and had significant improvement after treatment with steroids. One case reported from Japan was a 20-year-old man who was admitted to the hospital with acute respiratory failure He had begun vaping six months previously. He had bilateral infiltrates and pleural effusion on chest CT scan. He had 60% eosinophils in his bronchial lavage fluid. On the fourth day of steroids he was markedly improved. The other case reported from Japan was a 16-year-old male with asthma, who was hospitalized with severe cough, fatigue and shortness of breath that began after vaping for two weeks. He had ground glass opacities and was intubated, meeting the criteria for ARDS. Bronchial lavage fluid contained 14.7% eosinophils. This did not meet the diagnostic criteria for acute eosinophilic pneumonia but the authors stated the marked increase in peripheral eosinophils on the seventh day of hospitalization was consistent with acute eosinophilic pneumonia. He had resolution of symptoms and clearing of his chest CT scan by the ninth day of steroid treatment. 1) Aokage T, et al. Heat-not-burn cigarettes induce fulminant acute eosinophilic pneumonia requiring extracorporeal membrane oxygenation. Respir Med Case Rep 2018; 26: 87-90. 2) Arter ZL, et al. Acute eosinophilic pneumonia following electronic cigarette use. Respir Med Case Rep 2019; 27: 100825. doi: 10.1016/j.rmcr.2019.100825. 3) De Giacomi F, et al. Acute Eosinophilic Pneumonia: Correlation of Clinical Characteristics with Underlying Cause. Chest 2017; 152: 379-385. 4) Kamada T, et al. Acute eosinophilic pneumonia following heat-not-burn cigarette smoking. Respirol Case Rep 2016; 4(6): e00190. doi: 10.1002/rcr2.190. 5) Thota D, et al. Case report of electronic cigarettes possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor. J Emerg Med 2014; 47: 15-17.

Hypersensitivity Pneumonitis (2) There are two reports of hypersensitivity pneumonitis associated with vaping; one from New Hampshire (1), and one from Pennsylvania (2). The report from New Hampshire was of a 60-year-old male with weakness, chills and cough who had bilateral ground glass opacities predominantly in his upper lobes. His symptoms improved within 24 hours and resolved within 72 hours. He declined to have bronchoscopy. He had used a flavored e-cigarette prior to onset of his symptoms. The Pennsylvania report was of an 18-year-old woman with two days of progressive dyspnea, cough and pleuritic chest pain. She had a history of mild intermittent asthma. She had begun using e-cigarettes two to three weeks prior to the onset of her symptoms. Her chest radiograph showed patchy bilateral pulmonary infiltrates and her chest CT scan showed "dependent opacities in both lung bases, superimposed smooth interlobular septal thickening and bilateral small-to-moderate pleural effusions". She was intubated and met diagnostic criteria for ARDS. Bronchial lavage showed cellular debris and reactive mononuclear cells. The differential of white cells in her lavage fluid was 26% neutrophils, 13% lymphocytes, 14% monocytes, 25% mononuclear cells and 22% eosinophils. All tests for viruses, bacteria and fungus were negative. She was treated with steroids and weaned from the ventilator over a five-day period. 1) Atkins G, et al. Acute Inhalational Lung Injury Related to the Use of Electronic Nicotine Delivery System (ENDS). Chest 2015; 148 (Suppl): 83A. 2) Sommerfeld CG, et al. Hypersensitivity Pneumonitis and Acute Respiratory Distress Syndrome From E-Cigarette Use. Pediatrics 2018; 141(6). pii: e20163927. doi: 10.1542/peds.2016-3927.

Diffuse Alveolar Hemorrhage (2) There are two case reports of diffuse alveolar hemorrhage; one from Guam of a 33-year-old male (1) and the other a 70-year-old- man from West Virginia (2). The man from Guam had diabetes and a seizure disorder. He had been vaping for two months before onset of dyspnea and hemoptysis. On chest CT, he had diffuse ground glass opacities and bilateral patching consolidation. Work up for inflammatory conditions and microbial disease was negative. Bronchial lavage and a right wedge resection lung biopsy showed "bland pulmonary hemorrhage with no evidence of capillaritis or diffuse alveolar damage". Steroids were tapered and two weeks later his CT scan was normal.

The 70-year-old had begun using electronic cigarettes four weeks prior to developing rapidly progressive dyspnea and cough. He had COPD and previously had a left upper lobectomy for lung cancer. Sequential bronchial lavage revealed increasing hemorrhagic return consistent with diffuse alveolar hemorrhage. Lavage fluid contained a large number hemosiderin –laden macrophages. Infectious and inflammatory causes were excluded. He developed refractory hypoxemia and died. 1) Agustin M, et al. Diffuse Alveolar Hemorrhage Induced by Vaping. Case Rep Pulmonol 2018; 2018: 9724530. doi: 10.1155/2018/9724530. 2) Long JL, et al. Diffuse Alveolar Hemorrhage Due to Electronic Cigarette Use. Am J Resp Crit Care Med 2016; 193: A1862.

Lipoid Pneumonia (3) There are three case reports of lipoid pneumonia, one from Oregon (1), one from West Virginia (2), and one from the United Kingdom (3). The case from the United Kingdom was a 34-year-old woman with a three-month history of progressive shortness of breath, daily productive cough and hemoptysis who was an ex-smoker; she had been vaping for three years. She had congenital dimorphism with thrombocytopenia, iron deficiency anemia and previously had closure of a ventricular septal defect at the age of one. She had diffuse lung infiltrates on a chest radiograph and diffuse ground glass opacities and subpleural cysts on a high resolution CT scan. A video assisted thoroscopic lung biopsy showed extensive lipid-filled macrophages and deposition of cholesterol clefts with some inflammation. She was treated with 40 mg prednisone daily and advised to stop vaping but continued to vape and remained on steroids with only slight improvement in her pulmonary function test values. The individual from West Virginia was 31-years-old and had vaped for three months. She had ground glass opacities on her CT scan and lipid laden alveolar macrophages in her bronchial lavage fluid. Testing for bacteria and viruses was negative. She had rapid improvement with steroids and cessation of vaping. The individual from Oregon was 42-years-old and had vaped for seven months. She had rheumatoid arthritis, fibromyalgia, schizoaffective disorder, and hypertension. She had ground glass opacities on her CT scan and lipid laden alveolar macrophages in her bronchial lavage fluid. Testing for bacteria and viruses was negative. She ceased vaping and a follow up chest radiograph was normal but she continued to have a reduced diffusing capacity. 1) McCauley L, et al. An unexpected consequence of electronic cigarette use. Chest 2012; 141:1110–1113. 2) Viswam D, et al. Case report: Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. BMJ Case Rep 2018. doi:10.1136/bcr-2018-224350. 3) Modi S, et al. Acute Lipoid Pneumonia Secondary to E-Cigarettes Use: An Unlikely Replacement for Cigarettes. Chest 2015; 148: 382A.

Organizing Pneumonia (3) Three cases of organizing pneumonia (Bronchiolitis Obliterans Organizing Pneumonia (BOOP)) have been reported; one from New York (1), one from Ohio (2), and one from Virginia (3). Their ages ranged from 27 – 54 years and they had vaped for one month to several years. The 54-year-old from New York developed acute onset of dyspnea and hemoptysis six hours after vaping cannabis. He had extensive focal airspace opacities and a centrilobular pattern ("tree in bud"). His transbronchial biopsy showed organizing pneumonia. Infectious causes were ruled out. He rapidly recovered and was not treated with steroids. Two weeks later his repeat chest CT was normal. The other two patients used e-cigarettes, had abnormal chest CT scans; one with "innumerable pulmonary nodules" and the other with "multifocal discrete and confluent ground glass opacities". Both had biopsies showing organizing pneumonia. Both recovered; one within days and the other within two weeks. The Ohio patient had a repeat chest CT scan two weeks later, which was normal. 1) He T, et al. "Tree-in-Bloom": Severe Acute Lung Injury Induced by Vaping Cannabis Oil. Ann Am Thorac Soc 2017; 14: 468-470. 2) Khan MS, et al. Organizing pneumonia related to electronic cigarette use: A case report and review of literature. Clin Respir J 2018;12: 1295-1299. 3) Mantilla RD, et al. Vapor Lung: Bronchiolitis Obliterans Organizing Pneumonia (BOOP) in Patient with E-Cigarette Use. Am J Resp Crit Care Med 2016; 193: A6513.

Other Conditions (3) A 33-year-old male who had been treated with chemotherapy for testicular cancer was reported from Australia (1). Nine months after chemotherapy and three months after he began vaping, a chest CT scan performed as part of routine follow-up showed multiple new pulmonary nodules with "fluffy" parenchymal opacification. An open lung biopsy was interpreted as showing respiratory bronchiolitis-associated interstitial lung disease. He ceased vaping and had resolution of his radiographic findings. A 43-year-old male was reported from France with shortness of breath (2). He had a decrease in his values on pulmonary function testing but a normal chest radiograph. His symptoms began after he began vaping. He did not have a chest CT scan, bronchoscopy or a biopsy. A case of bilateral pneumonia with pleural effusions was reported from Florida in a 43-year-old male (3). He had vaped for three days. He did not have bronchoscopy or a biopsy. He was treated with antibiotics and discharged after two days. 1) Flower M, et al. Respiratory bronchiolitis-associated interstitial lung disease secondary to electronic nicotine delivery system use confirmed with open lung biopsy. Respirol Case reports 2017; 5: e00230. doi: 10.1002/rcr2.230. 2) Hureaux J, et al. A case report of subacute bronchial toxicity induced by an electronic cigarette. Thorax 2014; 69: 596-597. 3) Moore K, et al. Bilateral Pneumonia and Pleural Effusions Subsequent to Electronic Cigarette Use. Open Journal of Emergency Medicine 2015; 03:18-22. doi: 10.4236/ojem.2015.33004.

*Project SENSOR News

Michigan State University
College of Human Medicine
West Fee Hall
909 Wilson Road, Room 117
East Lansing, MI 48824-1316
Phone (517) 353-1846

In this issue: V30n4: Vaping and Acute Lung Disease

*P*S* *Remember to report all cases of occupational disease!*

Printed on recycled paper.

Michigan Law Requires the Reporting of Known or Suspected Occupational Diseases

Reporting can be done by:

Web
www.oem.msu.edu

E-Mail
ODREPORT@ht.msu.edu

FAX
(517) 432-3606

Telephone
1-800-446-7805

Mail
Michigan Occupational Safety & Health Administration (MIOSHA)
Management and Technical Services Division
P.O. Box 30649
Lansing, MI 48909-8149

Reporting forms can be obtained by calling 1-800-446-7805

The Project SENSOR News is published quarterly by Michigan State University-College of Human Medicine with funding from the National Institute for Occupational Safety and Health and is available at no cost. Suggestions and comments are welcome.

(517) 353-1846
MSU-CHM
West Fee Hall
909 Wilson Road, Room 117
East Lansing, MI 48824-1316