Acute Lung Injury

- Cori Daines, MD
- Pediatric Pulmonary and Sleep Medicine
- University of Arizona
- SEAHEC November 17, 2020
Definition

• EVALI—E-cigarette or vaping product related acute lung injury
• Officially recognized by the CDC in the summer of 2019
• Peaks in incidence June through September 2019 with a decrease since, likely due to information/surveillance
WHAT ARE E-CIGARETTES?

- E-cigarettes are known by many different names. They are sometimes called “e-cigs,” “e-hookahs,” “mods,” “vape pens,” “vapes,” “tank systems,” and “electronic nicotine delivery systems.”

- Some e-cigarettes are made to look like regular cigarettes, cigars, or pipes. Some resemble pens, USB sticks, and other everyday items.

- E-cigarettes produce an aerosol by heating a liquid that usually contains nicotine—the addictive drug in regular cigarettes, cigars, and other tobacco products—favorings, and other chemicals that help to make the aerosol. Users inhale this aerosol into their lungs. Bystanders can also breathe in this aerosol when the user exhales into the air.

- E-cigarettes can be used to deliver marijuana and other drugs.

![Diagram of e-cigarettes and related products](image)
EVALI—National Statistics

• As of February 18, 2020
  • 2807 hospitalizations—all states
  • 68 deaths—29 states, not AZ, age range 15-75
• Hospitalizations: 66% male, median age 24, range 13-85 years, 15% under 18 y.o., 37% 18-24 y.o., 24% 25-34 y.o., 24% over 35 years
• As of January 14, 2020
  • 82% using THC products, 33% exclusively—78% getting “informally”
  • 57% using nicotine products, 14% exclusively—69% getting commercially
Number of Hospitalized Lung Injury Cases Reported to CDC as of December 17, 2019

Legend
- 0 cases
- 1-9 cases
- 10-49 cases
- 50-69 cases
- 100-149 cases
- 150-199 cases
- 200-249 cases

States and territories are color-coded according to the number of cases per state.
Pathology

- Acute fibrinous pneumonitis, diffuse alveolar damage, organizing pneumonia
- Acute eosinophilic pneumonia
- Diffuse alveolar hemorrhage
- Lipoid pneumonia
- Bronchiolar interstitial lung disease
- All suggest more than one mechanism and a continuum of disease
THE MANY FLAVORS OF EVAL...

HYPERSENSITIVITY PNEUMONITIS
- Often symmetrical
- Mid-to-upper lung ground-glass mosaic
- Ill-defined centrilobular nodules

ORGANIZING PNEUMONIA
- Often dense and/or ground-glass consolidations
- Often peripheral or peri-lobular distribution
- Classically subpleural shadows

DIFFUSE ALVEOLAR DAMAGE
- Heterogeneous consolidations
- Clefts, fissures, ground-glass, etc.
- Gravity-dependent
- Organizing phase with traction bronchiectasis and fistulations

DIFFUSE ALVEOLAR HEMORRHAGE
- May have centrilobular nodules
- Ground-glass
- Consolidations
- Combination of any of above

LIPID PNEUMONIA
- Usually suppurative parenchymal
- May contain any of any of above
- Crusts, purple lacy
- Ground-glass
- Consolidations

ACUTE EOSINOPHILIC PNEUMONIA
- Symmetrical ground-glass with septal thickening and pleural, extrinsic murmur
- Perihilar eosinophilia absent on presentation
- Diagnosis clinched by BAL with >5% eosinophils
<table>
<thead>
<tr>
<th>E-liquid component</th>
<th>Chemical or compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier solution</td>
<td>- Propylene glycol</td>
</tr>
<tr>
<td></td>
<td>- Vegetable glycerin</td>
</tr>
<tr>
<td></td>
<td>- Diacetyl</td>
</tr>
<tr>
<td></td>
<td>- 2,3-Pentanedione</td>
</tr>
<tr>
<td></td>
<td>- Acetin</td>
</tr>
<tr>
<td>Flavourants</td>
<td>- Nicotine</td>
</tr>
<tr>
<td></td>
<td>- Tetrahydrocannabinol</td>
</tr>
<tr>
<td></td>
<td>- Cannabidiol</td>
</tr>
<tr>
<td></td>
<td>- Butane hash oil</td>
</tr>
<tr>
<td>Additives</td>
<td>- Other oil-rich additives</td>
</tr>
<tr>
<td></td>
<td>- Vitamin E acetate (tetrahydrocannabinol adulterant)</td>
</tr>
<tr>
<td>Aerosol emissions</td>
<td>- Carbonyls from heating propylene glycol and vegetable glycerin</td>
</tr>
<tr>
<td></td>
<td>- Trace metal elements</td>
</tr>
<tr>
<td></td>
<td>- Particulates</td>
</tr>
<tr>
<td></td>
<td>- Volatile organic compounds</td>
</tr>
<tr>
<td>Contaminants</td>
<td>- Bacterial endotoxins</td>
</tr>
<tr>
<td></td>
<td>- Fungal glucans</td>
</tr>
</tbody>
</table>
Risks

• THC—present in lung lavage samples from 75-80% of acute injury victims
• Vitamin E acetate—used as a thickener, usually with THC—present in lung lavage of over 90% of acute injury victims
• Nicotine—present in lung lavage of over 60% of acute injury victims. Also present in lavage of smokers without symptoms
• Other elements—CBD, plant oils, medium chain triglycerides, petroleum products, byproducts
Figure 1. The known and unknown health effects of vaping in comparison to cigarette smoke. The major toxic effects of compounds found in cigarette smoke (Right lung) and in vaping aerosols (Left lung) are lung inflammation, oxidative stress, cell death, impaired immune response, DNA damage and epigenetic modifications. The respiratory diseases caused by cigarette smoke (lung cancer, COPD [emphysema and/or obstruction of airways]) are not yet established to be caused by vaping (represented by question marks in the left lung). The presence of lipid-laden macrophages is a feature predominantly associated with vaping products containing THC and has been a feature of EVALI.
Patterns of disease shown in case reports of vaping-associated pulmonary illnesses: an overview of the medical literature up to Oct. 30, 2019*.

<table>
<thead>
<tr>
<th>Type of lung injury or predominant disease pattern</th>
<th>No. of cases</th>
<th>Age and sex</th>
<th>Associated imaging findings</th>
<th>Level of care required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organizing pneumonia</td>
<td>12</td>
<td>64M, 40F, 54M, 22M, 20M, 21M, 23M, 15M, 55M, 39M, 35M, 35M, 95M</td>
<td>1 patchy infiltrates, 11 diffuse GGO, 1 tree in bud, 1 pneumothorax with bilateral central opacities, bilateral reticulonodular opacities with subpleural sparing</td>
<td>7 hospital ward, 2 ICU, 3 unknown</td>
</tr>
<tr>
<td>Acute fibroinflammatory pneumonitis with organizing pattern</td>
<td>3E</td>
<td>44M, 42M, 53M, 25M, 23M, 34F, 28M, 34F, 67M, 19M, 45M</td>
<td>1 diffuse GGO, 2 bilateral centrilobular GGO, 1 peribilar GGO, 1 tree in bud, 1 diffuse bronchocentriacinar micronodular GGO, 1 diffuse bilateral opacities</td>
<td>11 unknown</td>
</tr>
<tr>
<td>Acute alveolitis or diffuse alveolar damage</td>
<td>5I</td>
<td>40M, 33M, 35M, 41M, 47F, 21M, 34F, 20M</td>
<td>1 bilateral diffuse GGO, 1 traction bronchiectasis</td>
<td>1 hospital ward, 6 ICU, 1 unknown</td>
</tr>
<tr>
<td>Pneumomediastinum or pneumomediastinum with pneumothorax</td>
<td>6</td>
<td>17M, 16M, 21M, 15M, 16M, 16M</td>
<td>1 pneumomediastinum, 1 tension pneumothorax, 1 pneumothorax, 1 pneumothorax</td>
<td>6 hospital ward</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td>4</td>
<td>73F, 10F, 23M, 10F</td>
<td>2 diffuse GGO, 2 septal thickening, 1 traction bronchiectasis, 1 honeycombing, 1 diffuse nodules</td>
<td>2 hospital ward, 1 ICU with ECMO, 1 ICU without ECMO</td>
</tr>
<tr>
<td>Granulomatous disease</td>
<td>2</td>
<td>43F, 34F</td>
<td>2 bilateral nodules</td>
<td>2 hospital ward</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>2</td>
<td>18F, 20M</td>
<td>2 diffuse GGO, 1 airspace disease, 1 cavitating nodules</td>
<td>1 ICU, 1 hospital ward</td>
</tr>
<tr>
<td>Status asthmaticus</td>
<td>2</td>
<td>16M, 14F</td>
<td>2 pneumomediastinum</td>
<td>2 hospital ward, 1 ICU with ECMO</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2</td>
<td>43M, 56F</td>
<td>1 no acute abnormality, 1 diffuse GGO, 1 “crazy paving”</td>
<td>1 outpatient, 1 hospital ward</td>
</tr>
<tr>
<td>Inhaled occupational injury</td>
<td>2</td>
<td>35M, 60M</td>
<td>1 nodular infiltrate, 1 mediastinal adenopathy, 1 bilateral GGO</td>
<td>1 ICU with ECMO, 1 hospital ward</td>
</tr>
<tr>
<td>Respiratory bronchiolitis–associated interstitial lung disease</td>
<td>1</td>
<td>33M</td>
<td>1 blood</td>
<td>1 hospital ward</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>1</td>
<td>33M</td>
<td>Diffuse GGO</td>
<td>ICU</td>
</tr>
<tr>
<td>Hypersensitivity pneumonia</td>
<td>1</td>
<td>18F</td>
<td>NA</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Transient nodules in lung and liver</td>
<td>1</td>
<td>45F</td>
<td>Multiple pulmonary and hepatic nodules</td>
<td>Hospital ward</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1</td>
<td>43M</td>
<td>Left-sided pleural effusion</td>
<td>Hospital ward</td>
</tr>
<tr>
<td>Severe persistent airflow obstruction in a long-standing smoker</td>
<td>1</td>
<td>45M</td>
<td>Patchy GGO, mosaic attenuation</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Upper airway damage</td>
<td>1</td>
<td>30M</td>
<td>Moderate vocalis and edema of the paratracheal musculature</td>
<td>ICU</td>
</tr>
</tbody>
</table>


**Case reports** refers to individual cases reported with pathology and imaging findings. Table 1 does not include the 53 patient cases included by Jayson et al. of 106 cases reported by Torres et al.*
Patterns of disease shown in case reports of vaping-associated pulmonary illnesses: an overview of the medical literature up to Oct. 30, 2019*.

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<th>Level of care required</th>
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</thead>
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<tr>
<td>Organizing pneumonia¹⁰,¹³,¹⁶</td>
<td>12</td>
<td>64M, 40F, 54M, 22M, 20M, 21M, 28M, 19M, 28M, 38M, 35M, 39M</td>
<td>1 patchy infiltrates, 11 diffuse GGO, 1 tree in bud, 1 pneumothorax with bilateral central opacities, bilateral reticulonodular opacities with subpleural sparing</td>
<td>7 hospital ward, 2 ICU, 3 unknown</td>
</tr>
<tr>
<td>Acute fibrinous pneumonitis with organization¹⁶</td>
<td>11†</td>
<td>44M, 42M, 51M, 25M, 21M, 34F, 28M, 54F, 67M, 19M, 44M</td>
<td>5 diffuse GGO, 2 bilateral centrilobular GGO, 1 perihilar GGO, 1 tree in bud, 1 diffuse bronchocentric micronodular GGO, 1 diffuse bilateral opacities</td>
<td>11 unknown</td>
</tr>
<tr>
<td>Acute alveolitis or diffuse alveolar damage⁹,¹³,¹⁶-²⁸</td>
<td>8¶</td>
<td>46M, 33M, 35M, 61M, 47F, 21M, 34F, 28M</td>
<td>6 bilateral diffuse GGO, 1 traction bronchiectasis</td>
<td>1 hospital ward, 6 ICU, 1 unknown</td>
</tr>
<tr>
<td>Pneumomediastinum or pneumothorax²⁹-³³</td>
<td>6</td>
<td>17M, 16M, 21M, 15M, 16M, 18M</td>
<td>2 pneumomediastinum, 1 tension pneumothorax, 3 nontension pneumothorax</td>
<td>6 hospital ward</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis⁵-⁸</td>
<td>4</td>
<td>73F, 16F, 23M, 19F</td>
<td>2 diffuse GGO, 2 septal thickening, 1 traction bronchiectasis, 1 honeycombing, 1 diffuse nodules</td>
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</tr>
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</table>

*Simon T. Landman et al. CMAJ 2019;191:E1321-E1331

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Patterns of disease shown in case reports of vaping-associated pulmonary illnesses: an overview of the medical literature up to Oct. 30, 2019.

<table>
<thead>
<tr>
<th>Granulomatus disease(^{34,35})</th>
<th>2</th>
<th>43f, 34(F)</th>
<th>2 bilateral nodules</th>
<th>1 hospital ward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic pneumonia(^{15,16})</td>
<td>2</td>
<td>18f, 20M</td>
<td>2 diffuse GGO, 1 airspace disease, 1 coalescing nodules</td>
<td>ICU, 1 hospital ward</td>
</tr>
<tr>
<td>Status asthmaticus(^{36})</td>
<td>2</td>
<td>16M, 14F</td>
<td>2 pneumomedistinum</td>
<td>ICU with ECGO</td>
</tr>
<tr>
<td>Bronchitis(^{3,38})</td>
<td>2</td>
<td>43M, 56F</td>
<td>1 no acute abnormality, 1 diffuse GGO, 1 &quot;crazy paving&quot;</td>
<td>outpatient, 1 hospital ward</td>
</tr>
<tr>
<td>Inhalational injury(^{39,40})</td>
<td>2</td>
<td>35f, 60M</td>
<td>1 nodular infiltrates, 1 mediastinal adenopathy, 1 bilateral GGO</td>
<td>ICU with ECGO, hospital ward</td>
</tr>
<tr>
<td>Respiratory bronchiolitis-associated interstitial lung disease(^{41})</td>
<td>1</td>
<td>33M</td>
<td>Tree in bud</td>
<td>Hospital ward</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage(^1)</td>
<td>1</td>
<td>33M</td>
<td>Diffuse GGO</td>
<td>ICU</td>
</tr>
<tr>
<td>Hypereosinophilia with eosinophilic asthma(^{42})</td>
<td>1</td>
<td>48F</td>
<td>NA</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Transient nodules in lung and liver(^4)</td>
<td>1</td>
<td>45F</td>
<td>Multiple pulmonary and hepatic nodules</td>
<td>Hospital ward</td>
</tr>
<tr>
<td>Pleural effusion(^{44})</td>
<td>1</td>
<td>63M</td>
<td>Left-sided pleural effusion</td>
<td>Hospital ward</td>
</tr>
<tr>
<td>Severe persistent airflow obstruction in a long-standing smoker(^{45})</td>
<td>1</td>
<td>45M</td>
<td>Patchy GGO, mosaic attenuation</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Upper airway damage(^{46})</td>
<td>1</td>
<td>30M</td>
<td>Moderate uvulitis and edema of the paratracheal muscle</td>
<td>ICU</td>
</tr>
</tbody>
</table>

Simon T. Landman et al. CMAJ 2019;191:E1321-E1331

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Presentation, Characteristics, and Outcome of Six Patients in Utah with Pulmonary Illness Related to E-Cigarette Use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>20</td>
<td>25</td>
<td>29</td>
<td>23</td>
<td>23</td>
<td>47</td>
</tr>
<tr>
<td>Approximate time from symptom onset to presentation(^1)</td>
<td>9 days</td>
<td>9 days</td>
<td>2 wk</td>
<td>2 mo</td>
<td>5 days</td>
<td>6 wk</td>
</tr>
<tr>
<td>Initial laboratory studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood white-cell count (per mm(^3))</td>
<td>16,300</td>
<td>18,200</td>
<td>10,600</td>
<td>4800</td>
<td>12,100</td>
<td>13,800</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Granulocytes</td>
<td>92.0</td>
<td>93.7</td>
<td>92.2</td>
<td>84.5</td>
<td>90.2</td>
<td>89.2</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.5</td>
<td>3.8</td>
<td>6.0</td>
<td>8.9</td>
<td>5.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.9</td>
<td>0.0</td>
<td>0.3</td>
<td>2.9</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>ESR (mm/hr) (^2)</td>
<td>NA</td>
<td>122</td>
<td>105</td>
<td>90</td>
<td>128</td>
<td>60</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>30.7</td>
<td>20.4&lt;sup&gt;4&lt;/sup&gt;</td>
<td>22.6</td>
<td>28.0</td>
<td>25.8</td>
<td>21.7</td>
</tr>
<tr>
<td>Bronchovascular lavage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-laden macrophages (%)</td>
<td>&gt;50</td>
<td>Approx. 50</td>
<td>30</td>
<td>25</td>
<td>&gt;75</td>
<td>Approx. 60</td>
</tr>
<tr>
<td>Macrophages</td>
<td>32</td>
<td>70</td>
<td>71</td>
<td>51</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>Bronchial lining cells</td>
<td>12</td>
<td>2</td>
<td>7</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>49</td>
<td>18</td>
<td>19</td>
<td>26</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Management and outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical therapy</td>
<td>Antibiotics; high-dose glucocorticoids</td>
<td>Antibiotics; high-dose glucocorticoids</td>
<td>Glucocorticoids; antibiotics&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Glucocorticoids; antibiotics&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Antibiotics</td>
<td>None</td>
</tr>
<tr>
<td>Other interventions</td>
<td>Mechanical ventilation, venovenous ECMO</td>
<td>High-flow nasal cannula</td>
<td>None</td>
<td>Supplemental oxygen by nasal cannula</td>
<td>Supplemental oxygen by nasal cannula</td>
<td>Supplemental oxygen by nasal cannula</td>
</tr>
<tr>
<td>Outcome</td>
<td>Alive; hypoxemia resolved</td>
<td>Alive; oxygen at discharge</td>
<td>Alive; fevers resolved</td>
<td>Alive; hypoxemia resolved</td>
<td>Alive; hypoxemia resolved</td>
<td>Alive; hypoxemia resolved</td>
</tr>
</tbody>
</table>

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<sup>1</sup> ECOMO denotes extracorporeal membrane oxygenation; ESR erythrocyte sedimentation rate, and NA not available.
<sup>2</sup> Shown are data at admission to our facility.
<sup>3</sup> The reference range is 0.0 to 10 mm per hour.
<sup>4</sup> Shown are data for high-sensitivity C-reactive protein; the reference range is less than 0.3 mg per deciliter.
<sup>5</sup> With respect to glucocorticoids, a short course of prednisone was prescribed by an outpatient provider before hospitalization.

### Laboratory Studies on Initial Presentation

<table>
<thead>
<tr>
<th>Test</th>
<th>Median (QD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count/µL</td>
<td>11 500 (12 300-17 900)</td>
</tr>
<tr>
<td>Differential, red (QD), %</td>
<td></td>
</tr>
<tr>
<td>Granulocytes</td>
<td>90.3 (88.0-92.4)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>5.7 (4.2-7.9)</td>
</tr>
<tr>
<td>Monocytes</td>
<td>2.4 (2.1-3.2)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>0.3 (0.1-0.9)</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>23.8 (13.7-19.2)</td>
</tr>
<tr>
<td>ESR/eosinophils</td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>25/24 (96%)</td>
</tr>
<tr>
<td>CRP</td>
<td>27/26 (100%)</td>
</tr>
<tr>
<td>ESR &gt;100 mm/h</td>
<td>26/25 (100%)</td>
</tr>
<tr>
<td>Procalcitonin ng/ml</td>
<td>0.3 (0.1-0.7)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.85 (0.73-1.04)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>1.0 (0.6-1.6)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>31 (20-57)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>24 (10-59)</td>
</tr>
<tr>
<td>Erythrocytes, No/total No. (%)</td>
<td>6/9 (69)</td>
</tr>
<tr>
<td>AST</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>ALT</td>
<td>7/30 (24)</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>85 (72-114)</td>
</tr>
<tr>
<td>HIV 1, 2 antigen or antibody</td>
<td></td>
</tr>
<tr>
<td>Negative, No/total No. (%)</td>
<td>10/16 (62)</td>
</tr>
<tr>
<td>ESR performed, No/total No. (%)</td>
<td>24/31 (77)</td>
</tr>
<tr>
<td>Cytologic differential, %</td>
<td></td>
</tr>
<tr>
<td>Macrophages</td>
<td>53 (37-79)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>28 (21-48)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>6 (2-12)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Presence of LMs, No/total No. (%)</td>
<td>2/13 (91)</td>
</tr>
<tr>
<td>LMs, median (QD), %</td>
<td>52 (33-76)</td>
</tr>
<tr>
<td>Unnatural cause, No/total No. (%)</td>
<td>10/11 (91)</td>
</tr>
<tr>
<td>Marijuana</td>
<td>11/11 (100)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0/11</td>
</tr>
<tr>
<td>Heroin</td>
<td>0/1</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Narcotics</td>
<td>2/1 (100)</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>0/11</td>
</tr>
<tr>
<td>Methadone</td>
<td>0/11</td>
</tr>
<tr>
<td>Bisoprololil</td>
<td>0/11</td>
</tr>
</tbody>
</table>

### Computed Tomography Findings

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organizing pneumonia</strong></td>
<td>26 (100%)</td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hypersensitivity</strong></td>
<td>5 (19%)</td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Eosinophilic</strong></td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>Lung injury</strong></td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>Exogenous lipid pneumonia</strong></td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>Diffuse alveolar hemorrhage</strong></td>
<td>0</td>
</tr>
<tr>
<td><strong>Subpleural sparing</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (39)</td>
</tr>
<tr>
<td>Some</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Any</td>
<td>15 (58)</td>
</tr>
<tr>
<td>No</td>
<td>11 (42)</td>
</tr>
<tr>
<td><strong>Airway wall thickening</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (81)</td>
</tr>
<tr>
<td>No</td>
<td>5 (19)</td>
</tr>
</tbody>
</table>

Aberegg SK et al, *JAMA Network Open* 2020
Computed Tomographic Scans of the Chest Obtained from Patients with Vaping-Associated Lung Injury.

Chest Radiographs and High-Resolution Computed Tomographic Imaging in a 17-Year-Old Male Patient with Diffuse Lung Disease.

EVALI—Clinical Features

- Shortness of breath
- Cough
- Chest pain
- Pleuritic chest pain
- Hemoptysis
- Fever and chills
- Nausea, vomiting, diarrhea
- Abdominal pain
- Present days to months ahead of acute process
Clinical Characteristics of Nonhospitalized Patients

- 85% (47/55) initially experienced respiratory symptoms
  - e.g., cough, chest pain, and shortness of breath

- 57% (27/47) had gastrointestinal symptoms
  - e.g., abdominal pain, nausea, vomiting, and diarrhea

- 76% (41/54) had symptoms accompanied by constitutional symptoms
  - e.g., fever, chills, and weight loss
Proposed criteria for EVALI

Confirmed case

- Use of an e-cigarette ("vaping") or "dabbing" in the previous 90 days*

- Lung opacities on chest radiograph or computed tomography

- Exclusion of lung infection based on:
  - Negative influenza PCR or rapid test (unless out of season)
  - Negative respiratory viral panel
  - Negative testing for clinically-indicated respiratory infections (eg, urine antigen test for \textit{Legionella} and \textit{Streptococcus pneumoniae}, blood cultures, sputum cultures if producing sputum, and bronchoalveolar lavage if performed)
  - Negative testing for HIV-related opportunistic respiratory infections (if appropriate)

- Absence of a plausible alternative diagnosis (eg, cardiac, neoplastic, rheumatologic)

Probable case

- Use of an e-cigarette ("vaping") or "dabbing" in the previous 90 days*

- Lung opacities on chest radiograph (diffuse hazy or consolidative opacities) or computed tomography (ground glass or consolidative opacities)

- Infection identified via culture or PCR, but clinical team believes this infection is not the sole cause of the underlying lung injury

  \textbf{OR}

  Minimum criteria to rule out pulmonary infection not met (testing not performed) and clinical team believes infection is not the sole cause of the underlying lung injury

- Absence of a plausible alternative diagnosis (eg, cardiac, neoplastic, rheumatologic)
EVALI or COVID-19

- Symptoms similar: cough, chest pain, shortness of breath, hypoxia
- Even fever, nausea, vomiting, diarrhea, fatigue
- Maybe different: nasal congestion, loss of taste/smell
- Lab findings of inflammation in both
- Imaging may be similar
• ACE2 is a receptor protein on epithelial cells
• Breaks down large protein angiotensin II which causes inflammation and bronchoconstriction
• In smokers and likely vapers, ACE2 is upregulated—more receptors
• ACE2 is also the target of the SARS-CoV-2 virus, so more ACE2 means more sites for virus to bind
• Rates of ICU hospitalization and ventilator need in COVID-19 are 2 times higher in smokers
<table>
<thead>
<tr>
<th></th>
<th>Ever-use of inhaled tobacco and...</th>
<th>Past 30-day use of inhaled tobacco and...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COVID-19 -related symptoms (n = 4,043)</td>
<td>COVID-19 test (n = 4,048)</td>
</tr>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Inhaled tobacco products</td>
<td>Cigarettes only</td>
<td>1.40 (0.83, 2.38)</td>
</tr>
<tr>
<td></td>
<td>E-cigarettes only</td>
<td>1.18 (0.80, 1.73)</td>
</tr>
<tr>
<td></td>
<td>Dual use</td>
<td>1.36 (0.90, 2.04)</td>
</tr>
<tr>
<td></td>
<td>Never used</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Children and youth 13-24 yrs
More common symptoms if smoked and vaped – cough, fever, fatigue, difficulty breathing
And more likely to get a COVID-19 test
But even more likely to have a POSITIVE COVID-19 test

Giaha SM, et al J Adol Health 2020
Treatment

- Hospitalization
- Include or exclude viral illnesses—Influenza, SARS-CoV-2
- Respiratory support—oxygen, ventilation, ECMO
- Antibiotics to cover community acquire pneumonia
- Consider steroids
- Prognosis – complete resolution to death—no clear associations
Management algorithm

Patient arrives with signs and symptoms such as: fever, cough, sore throat, shortness of breath, muscle aches, headaches, fatigue, nausea, or vomiting

Ask if patient uses e-cigarette, or vaping, products

Evaluate and manage patient as clinically indicated

Initial clinical assessment
- Obtain pulse oximetry with vital signs
- Focused history and physical exam
- Evaluate for other possible etiologies

Is patient a candidate for outpatient management?
- Normal O₂ saturation (≥95%)
- No respiratory distress
- No comorbidities that may compromise pulmonary reserve
- Reliable access to care/strong social support system
- Able to follow-up within 24–48 hours

Outpatient clinical evaluation
- Consider CXR (chest pain, dyspnea, clinical exam findings)
- Consider influenza testing per established guidelines

Outpatient clinical management
- Manage for possible EVALI
- Discontinue use of e-cigarette, or vaping, products
- Consider corticosteroids with caution
- Manage other possible infections, if present
- Consider early initiation of antivirals for possible influenza or appropriate antibiotics for community acquired pneumonia
- Ensure follow-up within 24–48 hours
- Emphasize importance of routine influenza vaccination
- Offer cessation services

COVID-19 Testing

Inpatient clinical evaluation
- Conduct laboratory and infectious disease testing guided by clinical findings
- Obtain a chest X-ray and consider CT if chest X-ray is normal
- Consider consultation with specialists
- Additional testing with bronchoalveolar lavage or lung biopsy as clinically indicated, in consultation with pulmonary specialists

Inpatient clinical management
- Discontinue use of e-cigarette, or vaping, products
- Consider empiric use of antibiotics, antivirals, or both
- Consider corticosteroids with timing, depending on severity
- Offer cessation services
- Ensure follow-up no later than 1–2 weeks after discharge
- Emphasize importance of routine influenza vaccination
Ask about Use

- Ask about the use of e-cigarette, or vaping, products and types of substances used
- Confidentiality is essential especially for young adults and adolescents
- Empathetic, nonjudgmental, and private questioning of patients*
- Continue to ask questions during follow-up encounters

*AAFP Article on Patient-Centered Communication and Interview Tool for Adolescents
Exposure History

- **Types of substances used**
  - THC/cannabis [oil, dabs], nicotine, modified products or the addition of substances not intended by the manufacturer

- **Where products were obtained**
  - THC containing products obtained through informal sources such as friends, family members, or in-person or online-dealers have been implicated

- **Clinicians might seek additional information to inform the ongoing investigation**
Physical Examination

- Should include vital signs and pulse-oximetry
  - Vital signs findings include tachycardia, tachypnea, $O_2$ saturation <95% at rest on room air
- Pulmonary findings on auscultation exam have been unremarkable, even among patients with severe lung injury
Considerations for Management Setting

- Some patients may be candidates for outpatient management
  - Normal oxygen saturation (≥95%)
  - No respiratory distress
  - No comorbidities that might compromise pulmonary reserve
  - Reliable access to care, strong social support systems
  - Ensure follow-up within 24–48 hours
Outpatient Clinical Evaluation

- Consider influenza testing
- Consider chest radiograph (CXR), if indicated by
  - Chest pain
  - Dyspnea
  - Clinical exam findings

*Consider modifying factors such as altitude to guide interpretation of measured O₂ saturation.

Consider COVID-19 Testing
Outpatient Management: Manage Possible EVALI

- Advise patient to discontinue use of e-cigarette, or vaping, products
  - Some patients have had recurrences with continue use
- Corticosteroids might worsen respiratory infections and should be considered with caution in the outpatient setting
  - Not well studied; consider with caution
  - Might worsen commonly seen respiratory infections
  - Most patients had rapid improvement with corticosteroids
  - Some patients who have not received corticosteroids had clinical improvement with e-cigarette cessation

Outpatient Management: Manage Other Infections

- Manage other infections, if present, in accordance with established guidelines*
  - Early initiation of antivirals for possible influenza
  - Appropriate antibiotics for community acquired pneumonia

* CDC Summary of Influenza Antiviral Medications; IDSA Clinical Practice Guidelines for Seasonal Influenza; Pneumonia guidelines; Pneumonia guidelines for infants and children
Co-Management of COVID-19

- Supportive—oxygen, ventilation
- Prone positioning
- Both EVALI and COVID-19 should receive steroids
- Remdesivir
- Convalescent plasma
Outpatient Management: Cessation Counseling

- Offer or connect all patients to services to stop using e-cigarette, or vaping, products
- Adults tobacco smokers should be
  - advised not to return to smoking cigarettes, if using e-cigarette, or vaping, products to quit cigarette smoking
  - provided with evidence-based interventions: behavioral counseling, FDA-approved cessation medications
- Adolescents and young adults might benefit from specialized services like
  - addiction treatment services
  - providers who have experience with counseling and behavioral health
Outpatient Management: Follow-Up Instructions

- Ensure follow-up within 24-48 hours; additional follow-up might be indicated, based on clinical findings
- Patients should return immediately if they develop new or worse respiratory symptoms
- Emphasize importance of routine influenza vaccination
Inpatient Clinical Evaluation

- Urine toxicology, influenza testing, other laboratory and infectious disease testing guided by clinical findings
- Obtain a chest x-ray and consider CT if chest x-ray is normal
- Consultation with pulmonary, critical care, medical toxicology, infectious disease, and others
- Consider bronchoalveolar lavage or lung biopsy as clinically indicated
Inpatient Clinical Management

- Discontinue use of e-cigarette, or vaping, products
- Consider empiric use of antibiotics, antivirals, or both, in accordance with established guidelines
- Consider corticosteroids, with timing depending on severity
- Offer cessation services
- Ensure follow-up no later than 1-2 weeks after discharge from hospital
- Emphasize importance of routine influenza vaccination
Follow-up From Hospital Admission

- Initial: within 1–2 weeks after discharge
  - Repeat pulse-oximetry
  - Consider repeat CXR
- Additional follow-up: 1–2 months after discharge
  - Consider spirometry, diffusion capacity testing, and CXR
- Long-term effects and the risk of recurrence of EVALI are not known
  - Many patients have symptom resolution
  - Some patients relapsed during corticosteroid tapers or with resumption product use
  - Some had hypoxemia requiring home oxygen and pulmonary follow up
  - Some treated with high-dose corticosteroids might require monitoring of adrenal function and endocrinology follow up
Residual symptoms 65%
Persistent radiographic abnormalities 40%
Abnormal PFT’s 44%

Aberegg SK et al, *JAMA Network Open* 2020
Risks to Our Children
Tobacco Product Use Among High School Students

- Any tobacco product: 31.2%
- E-cigarettes: 27.5%
- Cigars: 7.6%
- Cigarettes: 5.8%
- Smokeless tobacco: 4.8%
- Hookah: 3.4%
- Pipe tobacco: 1.1%

Learn more at bit.ly/NYTS-2019

Source: National Youth Tobacco Survey, 2019
7 out of 10 middle and high school students who currently use tobacco have used a FLAVORED product.

64% of students who currently use e-cigarettes have used flavored e-cigarettes.

61% of students who currently use hookah have used flavored hookah.

1.6 million (970,000)

Source: Morbidity and Mortality Weekly Report, 06/12/19
For Educators

E-cigarettes are the most commonly used tobacco product among U.S. middle and high school students.

Some e-cigarettes don’t look like tobacco products, so some kids use them unnoticed in schools, including in classrooms and bathrooms.

An increasingly popular e-cigarette, called JUUL, is shaped like a USB flash drive.

JUUL delivers a high dose of nicotine. Nicotine is highly addictive and can harm adolescent brain development.

TOBACCO PRODUCT USE IN ANY FORM, INCLUDING E-CIGARETTES, IS UNSAFE FOR YOUTH.
What Else—Cigarette Smoking

• Declining but still 12% of high school students actively smoking cigarettes
• Over 80% of adolescent smokers persist into adulthood
• Symptoms—chronic cough, exacerbations of asthma, pulmonary exacerbations, atherosclerosis
• Clear risk of development of lung cancer and many other cancers as well as heart disease and COPD
• Nicotine dependence—as little as 100 cigarettes
• 31% of adolescent cigarette smokers vaped previously
And—Marijuana

- Current use of 12th graders 23%
- Prevalence of vaping marijuana at 14% in 2019
- Combustibles of tar and hydrocarbons
- Youth are using THC in vaping devices more and more
Cannabis Lung Manifestations

- Symptoms—cough, sputum productions, wheezing, dyspnea
- Acutely actually increased FEV1 and decreased EIB in asthma patients
- Chronic use associated with obstructive lung disease with decreased FEV1, decreased MMEF, decreased airway conductance and diffusing capacity
- Associated with lung cancer
- Much higher likelihood of EVALI if used via vaping vs nicotine products alone
Outpatient Management: Cannabis Use Disorder

- People with cannabis use disorder should receive evidence-based interventions, such as
  - Cognitive-behavioral therapy
  - Contingency management
  - Motivational enhancement therapy
  - Multidimensional family therapy
  - Addiction medicine services consultation

Our Children at Risk

- Previous experimentation
- Previous vaping
- Smoking by parents and peers
- Attitudes and beliefs about the social implications and health consequences of smoking
- Depression
- Poor school performance
- Adverse experiences
- Substance use disorder
Our Children at Risk

• Children with underlying lung disease at increased risk
• Children and adolescents believe vaping to be “safer”
• Approximately 30% of children and adolescents who are actively vaping have asthma—may be more prone to EVALI
• Approximately 5-10% of adolescents with cystic fibrosis smoke cigarettes or vape
The 6 A’s

- Anticipate the risk of initiating
- Ask about smoking/vaping/exposure
- Advise risks and cessation
- Assess readiness to quit
- Assist those ready to quit—develop a plan
- Address nicotine withdrawal or other barriers
CDC Public Health Recommendations

- CDC recommends that people should **NOT**
  - Use e-cigarette, or vaping, products that contain THC
  - Buy any type of e-cigarette, or vaping, products, particularly those containing THC, from informal sources (such as family, friends, or in-person or online dealers)
  - Modify or add any substances to e-cigarette, or vaping, products that are not recommended by the manufacturer
CDC Public Health Recommendations

- Since the specific cause or causes of lung injury are not yet known, the only way to assure that people are not at risk while the investigation continues is to consider refraining from use of all e-cigarette, or vaping, products
CDC Public Health Recommendations

- E-cigarette, or vaping, products should never be used by youth, young adults, or women who are pregnant
- People who do not currently use tobacco products should not start using e-cigarette, or vaping, products
- Adults using e-cigarettes to quit smoking should not go back to smoking; they should weigh all risks and benefits and consider utilizing FDA-approved nicotine replacement therapies*
- If people continue to use e-cigarette, or vaping, products, they should:
  - Carefully monitor themselves for symptoms
  - See a health care provider immediately if symptoms develop