Vaping Associated Pulmonary Injury (VAPI)

August 19, 2019 by Josh Farkas

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- Pitfalls

introduction & current cluster of VAPI cases

Currently there is a cluster of cases of VAPI under investigation by the Centers of Disease Control. This situation is rapidly evolving; the information below will be updated as possible (with the understanding that it remains incomplete currently).

epidemiology

- Most patients are young (average age ~20 years old), with a male predominance.
- ~80% of patients report a history of vaping with tetrahydrocannabinol.
- ~94% of patients reported the use of vaping within a week of symptom onset.

presenting symptoms
Severity varies from patients who may have unimpressive symptoms to patients requiring intubation and ECMO. Initial case series will inevitably focus on the more severe end of the spectrum (as these cases are more easily detected). Over time, milder cases will likely be appreciated as well.

**Acuity**
- Onset is usually subacute, with deterioration over a period of days (the median duration of symptoms prior to hospitalization was 6 days).
- About a third of patients are initially diagnosed with a mild pneumonia and discharged home with oral antibiotic (e.g. azithromycin).
- Presenting symptoms (Layden 2019):
  - 98% have respiratory symptoms (dyspnea in 87%; chest pain in 55%; cough in 83%; hemoptysis in 11%)
  - 81% had gastrointestinal symptoms (nausea in 70%; vomiting in 66%; diarrhea in 43%; abdominal pain in 43%). These may initially be a predominant feature of the illness.
  - 100% of patients had some constitutional symptom (fever in 81%; chills in 58%; weight loss in 25%; fatigue/malaise in 45%)
  - 40% had headache.
  - Upper respiratory symptoms (e.g. rhinorrhea, sneezing, or congestion) *don’t* seem to be a component of the illness.

**presenting examination**
- Temperature >38°C was present in 29% of patients.
- Room air oxygen saturation was normal in one third, between 89-94% in a third, and <88% in a third of patients (Layden 2019).

**radiographic features**

- Chest X-ray will generally show bilateral infiltrates (~90% of cases), although these may be absent early in the disease course.
- CT scanning invariably shows bilateral ground-glass opacities. Sub-pleural sparing may also be seen in more “typical” cases.
- However, *various* patterns may be seen. Additional findings which have been noted include pleural effusions, pneumomediastinum, and tree-in-bud opacities.

![Chest imaging of a patient with VAPI. Admission chest X-ray (A) was mildly abnormal, but this rapidly worsened over 12 hours (B). CT scan shows ground glass opacification with areas of consolidation bilaterally and relative subpleural sparing. -Layden et al 2019 NEJM](image-url)
laboratory results

- CBC:
  - WBC count was >11,999/mm3 in 87% of patients. The median WBC count was 16,000 with an interquartile range of 12,000-18,000 (Layden 2019)
  - Differential cell count revealed >80% neutrophils in 94% of patients.
  - No patient had greater than ~2% peripheral eosinophils (Layden 2019).

- Acute phase reactants
  - Erythrocyte sedimentation rate (ESR) of >30 mm/hr was seen in 93% of patients. This may be severely elevated (>100 mm/hr), which may incorrectly raise concern for vasculitis.
  - C-Reactive Protein (CRP) is often elevated in a range of 20-30 mg/dL (Maddock 2019)
  - Procalcitonin was a median of 0.58 ug/L (with an interquartile range of 0.35-1)(Layden 2019).

- Bronchoalveolar lavage results:
  - Often neutrophilic predominance (with a median of 65% neutrophils).
  - Eosinophilia isn't generally a feature (median 0% eosinophils, interquartile range 0-6%)
  - Lipid-laden macrophages are often seen on Oil Red-O stain, but not in all cases (Layden 2019).
Table 1. Outbreak Surveillance Case Definitions of Severe Pulmonary Disease Associated with E-Cigarette Use — August 30, 2019.*

<table>
<thead>
<tr>
<th>Confirmed case</th>
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<tbody>
<tr>
<td>Use of an e-cigarette (vaping) or dabbing in 90 days before symptom onset; and</td>
</tr>
<tr>
<td>Pulmonary infiltrate, such as opacities on plain-film radiograph of the chest or ground-glass opacities on chest CT; and</td>
</tr>
<tr>
<td>Absence of pulmonary infection on initial workup; the minimum criteria include negative respiratory viral panel and influenza PCR or rapid test if local epidemiology supports testing. All other clinically indicated testing for respiratory infectious disease (e.g., urine antigen testing for <em>Streptococcus pneumoniae</em> and legionella, sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, and presence of HIV-related opportunistic respiratory infections if appropriate) must be negative; and</td>
</tr>
<tr>
<td>No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)</td>
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</table>

<table>
<thead>
<tr>
<th>Probable case</th>
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<tbody>
<tr>
<td>Using an e-cigarette (vaping) or dabbing in 90 days before symptom onset; and</td>
</tr>
<tr>
<td>Pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest CT; and</td>
</tr>
<tr>
<td>Infection identified by means of culture or PCR, but the clinical team caring for the patient believes that this is not the sole cause of the underlying respiratory disease process; or as the minimum criteria, to rule out pulmonary infection not met (testing not performed) and clinical team caring for the patient believes that this is not the sole cause of the underlying respiratory disease process; and</td>
</tr>
<tr>
<td>No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)</td>
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Current CDC case definition. Note that this diagnosis does not necessarily require bronchoscopy. This case definition may fail to capture mild or early cases (e.g. prior to development of pulmonary infiltrates). Layden et al 2019 NEJM

case definition & diagnostic process

- The current case definition is shown above.
- VAPI is a diagnosis of exclusion (particularly the exclusion of infection). Most affected patients are young with few other medical problems, which makes this a bit more straightforward.
- Bronchoscopy is not necessary in all cases:
  - Only 45% of the patients in the Layden 2019 series received bronchoscopy.
  - The primary role of bronchoscopy is to exclude alternative diagnoses. In patients with typical imaging features and no competing diagnosis, bronchoscopy may not be needed.
  - In patients with atypical imaging features (e.g. cavitation) or immunocompromise, bronchoscopy would be more important. Clinical features concerning for an alternative diagnosis would also increase the importance of bronchoscopy (e.g. possible vasculitis involving the skin or kidneys).
  - Decisions regarding bronchoscopy may also be colored by how well the patient would likely tolerate this procedure.
therapy & course

- Empiric antibiotics are often provided initially, until pneumonia may be excluded.
- Steroids are usually given.
  - Many reports suggest that this is beneficial (although there is obviously no solid proof that steroid causes benefit).
  - The ideal dose of steroid is unclear. ~ 1 mg/kg methylprednisolone daily generally seems reasonable, although some authors have reported using doses as high as 500 mg methylprednisolone daily (Maddock 2019; Davidson 2019)
- Intubation may be required in about a third of cases (Layden 2019).
- A few deaths have been reported, but the overwhelming majority of patients will recover. Improvement often occurs over a period of days.

pathophysiology and cause ??

- The prevalent theory is that most cases represent lipoid pneumonia, possibly related to vaping of cannabis oils. However, numerous questions remain regarding the exact agent or agent(s) involved. Furthermore, it is unclear whether all patients have the same exact pathology or (more likely) whether there may be some range of different pathophysiologic processes involved (e.g. most patients may have lipoid pneumonia, while some could have other pathologies such as cryptogenic organizing pneumonia).
- Vitamin E (https://www.npr.org/sections/health-shots/2019/09/05/758005409/vitamin-e-suspected-in-serious-lung-problems-among-people-who-vaped-cannabis) has recently been used as a liquid carrier of tetrahydrocannabinol in some forms of vape. Currently this appears to be the most likely culprit chemical. Epidemiologic data shows a spike in cases beginning in June 2019, which could potentially coincide with the timepoint at which a specific chemical entered the vape market (Layden 2019). This remains to be clarified further.

general evidence on VAPI

The remainder of this chapter will discuss VAPI in general (based on data available prior to the current epidemic).

Published evidence consists of case reports, which are summarized below. Although the literature includes only about two dozen case reports, the actual number of cases is probably considerably larger. I’ve seen one patient with probable VAPI, but didn’t submit it for publication (once several cases have been published, there’s little impetus to publish additional case reports). With an increasing recognition of this phenomenon and a rising popularity of vaping, the number of diagnosed cases will increase.
### Vaping Associated Pulmonary Injury (VAPI) - EMCrit Project

**Presentation & Epidemiology**

<table>
<thead>
<tr>
<th>Age/sex Comorbidities</th>
<th>Duration of E-cigarette use</th>
<th>Presenting signs &amp; symptoms</th>
<th>Radiology</th>
<th>Other diagnostic data of interest</th>
<th>Diagnosis</th>
<th>Treatment, outcome</th>
</tr>
</thead>
</table>
| 10 F Hidden smoking    | 2-3 weeks                   | Dyspnea, cough, pleuritic chest pain | Bilateral pulmonary opacities, diffuse effusions, interstitial septal thickening. | CBC 30,000 with 84% neutrophils, ESR 17 mg/dL, CRP 15 mg/L. | Acute respiratory distress syndrome (ARDS) | Intubation Vts |}

**Resuscitation**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical presentation</th>
<th>Radiologic clues may include</th>
<th>Findings on bronchoscopy</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAPI</td>
<td>- Acute onset</td>
<td>- Septal inflammation</td>
<td>- Endobronchial foreign body (EFB)</td>
<td>Steroid is essential. Steroid is essential. Steroid usually given, but has unclear value.</td>
</tr>
</tbody>
</table>

**General description of various patterns of Vaping-Associated Lung Injury (VAPI)**

1. **Acute Eosinophilic Predominant**
   - **Epidemiology:** May begin shortly after initiation of vaping
   - **Clinical presentation:** Usual after longer period of vaping
   - **Radiologic clues may include:** Septal inflammation
   - **Findings on bronchoscopy:** Eosinophilia (>25%) - Non-specific
   - **Treatment:** Steroid is essential. Steroid is essential. Steroid usually given, but has unclear value.

2. **Organizing Pneumonic Predominant**
   - **Epidemiology:** May begin shortly after initiation of vaping
   - **Clinical presentation:** Subacute onset, May require intubation
   - **Radiologic clues may include:** Non-nodular or centrilobular pattern of ground glass opacities
   - **Findings on bronchoscopy:** Non-specific
   - **Treatment:** Steroid is essential. Steroid is essential. Steroid usually given, but has unclear value.

3. **Lymphocytic Predominant**
   - **Epidemiology:** May begin shortly after initiation of vaping
   - **Clinical presentation:** Subacute onset
   - **Radiologic clues may include:** Non-nodular or centrilobular pattern of ground glass opacities
   - **Findings on bronchoscopy:** Non-specific
   - **Treatment:** Steroid is essential. Steroid is essential. Steroid usually given, but has unclear value.

4. **Diffuse Alveolar Hemorrhage**
   - **Epidemiology:** May begin shortly after initiation of vaping
   - **Clinical presentation:** Subacute onset
   - **Radiologic clues may include:** Non-nodular or centrilobular pattern of ground glass opacities
   - **Findings on bronchoscopy:** Non-specific
   - **Treatment:** Steroid is essential. Steroid is essential. Steroid usually given, but has unclear value.

**Internet Book of Critical Care, by @PulmDn**

VAPI will often masquerade as pneumonia. However, pleuritic chest pain may also raise concerns for acute pulmonary embolism. Occasional patients may present with hemoptysis as a primary complaint.


Overall, vaping seems to be capable of causing a variety of injury patterns in the lung. This reflects the large number of different chemicals involved, which may have variable pathologic effects. Cases may be roughly grouped based on the predominant pathologic finding (table below). However, in some cases there may be multiple simultaneous injury patterns (e.g. combined features of acute eosinophilic pneumonia and lipid pneumonia).


This evidence is obviously very incomplete. The omnipresent challenge to resuscitationists is to manage patients on the basis of incomplete information. Please employ information in this chapter cautiously, with the recognition that this is a rapidly evolving topic.

The probable role of publication bias bears specific mention here. Published cases are probably more dramatic and more thoroughly investigated than unpublished cases. For example, a patient with moderate VAPI who improves with steroid and doesn’t undergo bronchoscopy is unlikely to merit publication. Thus, it’s probable that published cases may over-estimate the severity of VAPI.

**clinical presentation**

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**core clinical features**

- Dyspnea
- Hypoxemia
- Vaping history (often with a recent initiation, increased frequency, or different product)

**additional features which may be seen**

- Cough (may be productive, possibly with hemoptysis)
- Pleuritic chest pain
- Fever
- Night sweats and weight loss

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**laboratory evaluation**

Laboratory evaluation is useful primarily to exclude other possible disorders.

**typical results may include:**

- Complete blood count may show leukocytosis (up to ~40,000), generally with a neutrophilic predominance.
  - Eosinophilia is generally absent on admission – even in patients with acute eosinophilic pneumonia.
- Erythrocyte sedimentation rate is usually normal in published cases, but can be elevated (see tweet below by Dr. Aberegg).
- C-reactive protein (CRP) may be moderately elevated (e.g. 10-40 mg/dL).

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**radiographic evaluation**

**chest X-ray**

- Should show bilateral infiltrates.
- Infiltrates typically reflect alveolar filling (“fluffy,” poorly-defined infiltrates). However, reticular infiltrates are also possible.
- Chest x-ray is useful as a screening test, but it doesn't provide definitive characterization of infiltrates.
CT scan – basic characteristics of VAPI

- Core features
  - Bilateral, ground-glass opacities
  - Features which shouldn't be seen (if present, may argue against VAPI)
    - Dense lobar consolidation
    - Dense nodules
    - Cavitation or necrosis of lung tissue

Some specific types of VAPI may be associated with signature findings on chest CT scan. Although this isn't reliable, it may serve as a useful clue.

VAPI with an acute eosinophilic pneumonia predominant pattern

- Bilateral, ground-glass opacities.
- Smooth septal thickening is often seen.
- Pleural effusion(s) may be seen.

VAPI with an organizing pneumonia predominant pattern

- Bilateral, ground-glass opacities.
- Organizing pneumonia can generate diverse findings on CT chest, which makes it challenging to define a stereotypical pattern. The following patterns have been reported:
  - (a) Sparing of the lung periphery (this pattern may be seen with various types of inhalation lung injury).
  - (b) Multiple ground-glass nodules distributed in a centrilobular pattern.
VAPI with lipoid pneumonia predominant pattern

- Bilateral, ground-glass opacities.
- Crazy-paving may be seen. This refers to patchy involvement of some lobules, which are adjacent to unaffected lobules. Septal thickening may accentuate the borders between normal lobules and diseased lobules.

**Figure 1.** Representative CT images show the “crazy paving” pattern of patchy ground glass superimposed on interlobular septal thickening. A. Bilateral upper lobes. B. Bilateral lower lobes.

**VAPI with lipoid pneumonia causing a crazy-paving pattern, from McCauley et al.**

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**bronchoscopy?**
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The main role of bronchoscopy is to exclude infection. Bronchoscopy can help diagnose various forms of VAPI (e.g. acute eosinophilic pneumonia or lipoid pneumonia). However, this generally won't affect clinical management, because all forms of VAPI are treated with supportive care and steroid.

Most patients with suspected VAPI probably don't require bronchoscopy. Potential indications for bronchoscopy might include the following:

- Significant immunocompromise.
Clinical features (e.g. CT scan findings or exposure history) suggest the possibility of unusual infectious diseases, such as fungal pneumonia.

- Patient is intubated for another reason (bronchoscopy may be increasingly easy and safe in this context).

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### diagnostic/therapeutic pathway

Below is a potential approach to VAPI. Most of these patients are young and previously healthy, which makes evaluation and treatment more straightforward.

VAPI is a diagnosis of exclusion. Therefore, due diligence should always be invested to consider alternative diagnostic possibilities. However, an invasive workup is often not necessary. In younger patients without other medical problems, the differential diagnosis will generally boil down to pneumonia vs. VAPI. A reasonable approach is empiric therapy with antibiotic and steroid (especially given that steroid is often beneficial for community acquired pneumonia anyway).

#### Potential approach to VAPI in the non-intubated patient

**Case highly suggestive for VAPI**
- History of vaping (especially recent onset)
- Bilateral infiltrates with typical imaging features seen on CT scan
- No immunocompromise
- No exposure to unusual pathogens

**Noninvasive diagnostic evaluation**
- Blood cultures x2
- Sputum gram stain & culture if productive cough
- Urine for legionella & pneumococcal antigen
- Nares PCR for viruses +/- influenza
- Nares PCR for M. pneumoniae
- HIV serology
- ESR, C-reactive protein, procalcitonin (if available)

**Empiric therapy for pneumonia & VAPI**
- Antibiotics (e.g. ceftriaxone plus azithromycin)
- Oxygen support as needed (e.g. high-flow nasal cannula)
- Steroid (e.g. 1 mg/kg prednisone daily)

**Further investigation**
- Consider bronchoscopy
- Additional laboratory studies

**Nonclinical improvement or labs concerning (e.g. HIV+)**

**Empiric diagnostic evaluation unremarkable**

**Clinical improvement**

- Gradually wean off steroid
- Consider discontinuation of beta-lactam (depending on results of the infectious workup)

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### podcast

There's no podcast yet – stay tuned.

[Listen](https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/apps.40518.14127333176902609.7be7b901-15fe-4c27-863c-7cd0dbfc26c5c.5c278f58-912b-4af0-8818-a65ff2da477.jpg)


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### questions & discussion

To keep this page small and fast, questions & discussion about this post can be found on another page [here](https://emcrit.org/pulmcrit/vaping-associated-pulmonary-injury/).
• Failure to obtain a history regarding vaping and to consider this as a potential cause of respiratory failure. Ideally this history should also include whether the patient is adulterating their own vaping liquid (which might increase the risk of VAPI).

• The assumption that every patient with possible vaping-induced pulmonary injury requires an invasive evaluation (bronchoscopy and potentially surgical lung biopsy).

References


• Maddock SD et al. Pulmonary lipid-laden macrophages and vaping. NEJM September 2019; E-publication ahead of print.


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.