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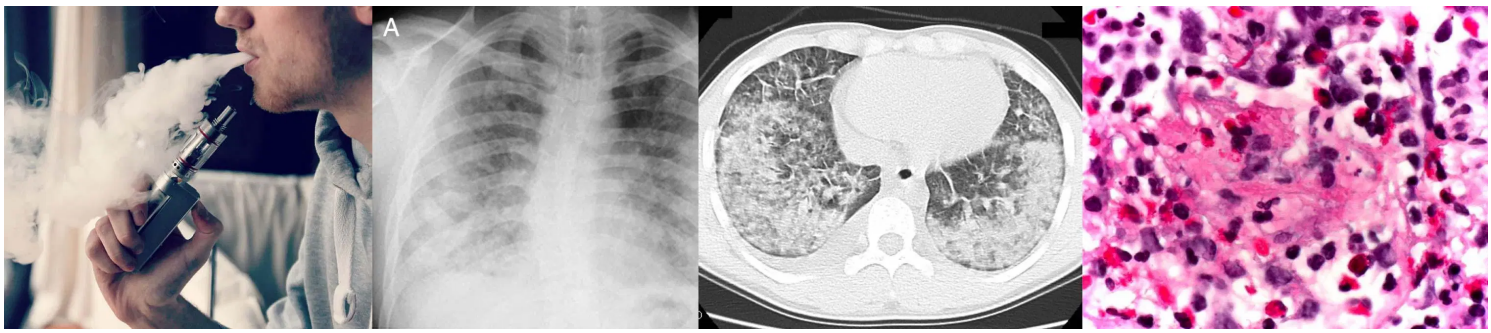
Vaping Associated Pulmonary Injury (VAPI)

August 19, 2019 by Josh Farkas



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introduction & current cluster of VAPI cases

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Currently there is a cluster of cases of VAPI under investigation (https://emergency.cdc.gov/newsletters/coca/081619.htm) 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.

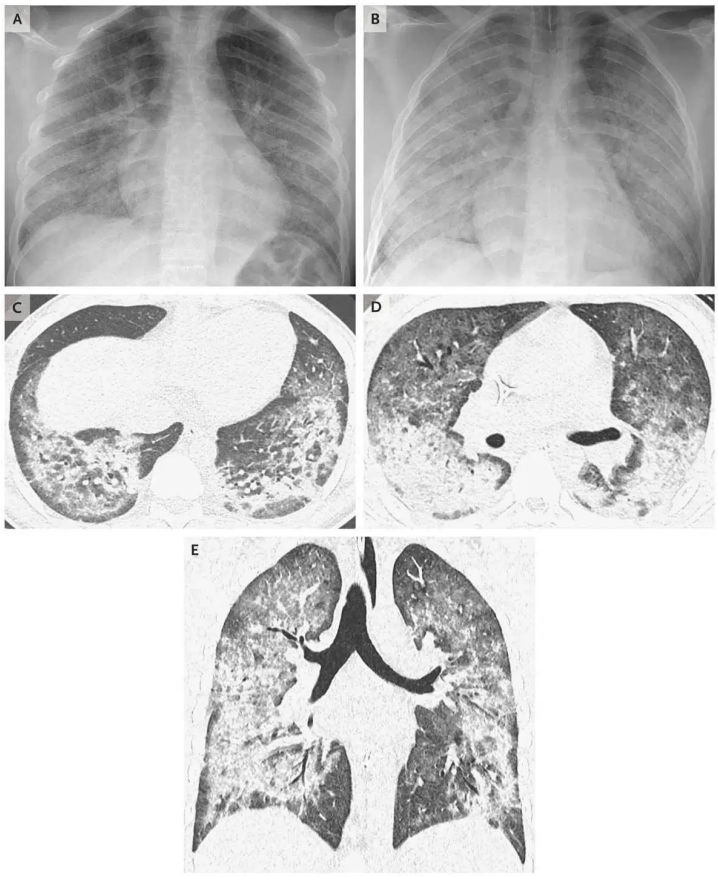
presenting symptoms

- 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

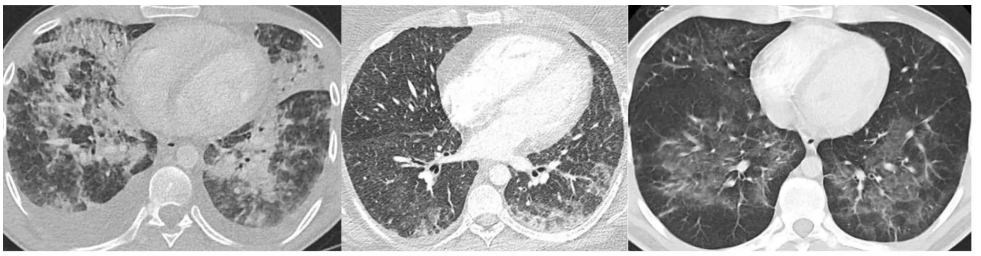
- Temperature >38C was present in 29% of patients.
- Room air oxygen saturation was normal in one third, between 89-94% in a third, and <88% in a third of patients (Layden 2019).

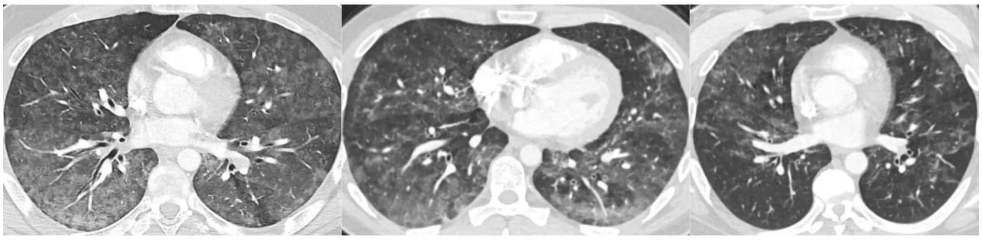
radiographic features



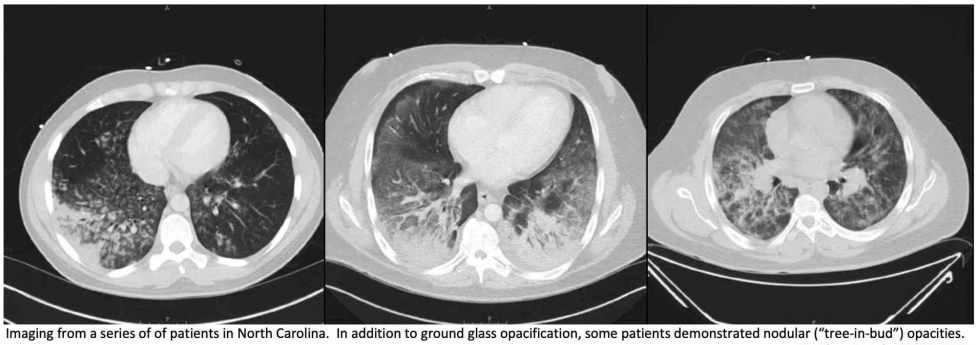
Chest imaging of a patient with VAPI. Admission chest X-ray (A) was mildly abnormal, but this rapidly worsened over 12 hours (B). CT scan shows ground glass opacification with areas of consolidation bilaterally and relative subpleural sparing. -Layden et al 2019 NEJM

- 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.





Imaging from a series of six patients in Utah. Substantial variation between patients is possible. -Maddock SD et al 2019 NEJM



Imaging from a series of of patients in North Carolina. In addition to ground glass opacification, some patients demonstrated nodular ("tree-in-bud") opacities. -Davidson K et al. MMWR 2019

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).
- Brochoalveolar 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.*

Confirmed case

Use of an e-cigarette (vaping) or dabbing in 90 days before symptom onset; and

Pulmonary infiltrate, such as opacities on plain-film radiograph of the chest or ground-glass opacities on chest CT; and

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 *Streptococcus pneumoniae* 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

No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)

Probable case

Using an e-cigarette (vaping) or dabbing in 90 days before symptom onset; and

Pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest CT; and

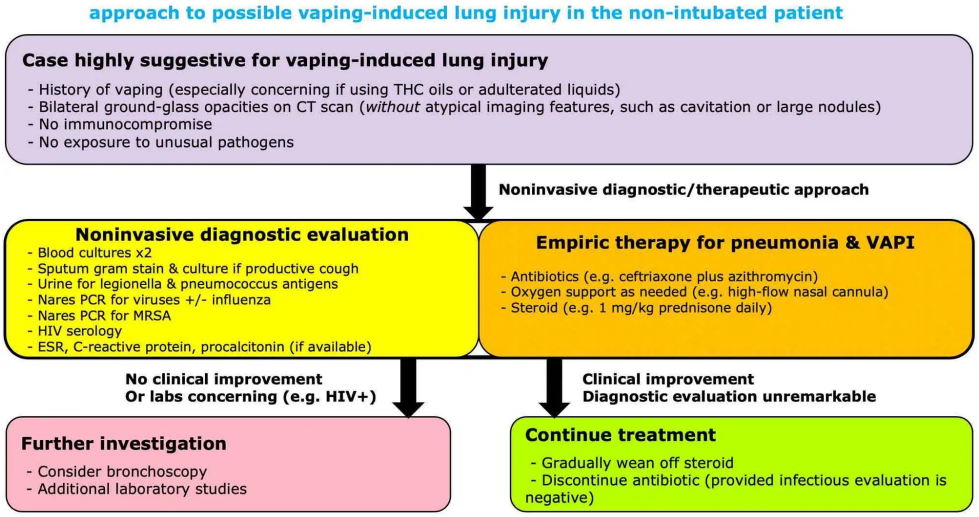
Infection identified by means of culture or PCR, but the clinical team caring for the patient believes that this is not the sole cause of the underlying respiratory disease process; or as the minimum criteria, to rule out pulmonary infection not met (testing not performed) and clinical team caring for the patient believes that this is not the sole cause of the underlying respiratory disease process; and

No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)

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.



Possible strategy for suspected vaping-induced lung injury in a patient who doesn't require intubation. The approach in an intubated patient is similar, but there is generally a lower threshold for bronchoscopy in that context. Please note that this is not based on any high-level evidence (as such evidence doesn't exist). The extent of workup required is controversial and practice patterns will likely evolve as further information becomes available.

-The Internet Book of Critical Care, by @PulmCrit

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.

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general evidence on VAPI

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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.

Age/Sex Comorbidities	Duration of E-cigarette use	Presenting signs & symptoms	Radiology	Other diagnostic data of interest	Diagnosis	Treatment, outcome
18 F Mild asthma Sommerfeld et al.	2-3 weeks	Dyspnea, cough, pleuritic chest pain.	Bilateral dependent opacities. Bilateral effusions. Interlobular septal thickening.	WBC 36,000 with 93% neutrophils. ESR normal, CRP 17 mg/dL. BAL with 22% eosinophils. BAL with lipid-laden macrophages on Oil Red-O stain.	Acute Eosinophilic PNA (also lipoid PNA?)	Intubation Vasopressor support Chest tubes for effusions Methylprednisolone 40 BID Recovery
20 M Thota et al.		Cough, dyspnea, facial flushing beginning an hour after vaping.	Diffuse ground-glass opacities, with upper-lung predominance.	WBC 13,000 with 82% neutrophils. BAL with 74% eosinophils.	Acute Eosinophilic PNA	Hospitalization x5 days Not intubated Prednisone 60 mg/day Recovery
18 F Arter et al.	2 months	Fever (102.4F), cough, dyspnea, pleuritic chest pain.	Diffuse ground-glass opacities, with upper-lung predominance.	WBC 20,000 with 91% neutrophils. BAL with 26% eosinophils.	Acute Eosinophilic PNA	ICU admission but not intubated Methylprednisolone 125 q6hr Recovery
16 M Childhood asthma Aokage et al	2 weeks	Dyspnea, cough beginning after vaping.	Diffuse ground-glass opacities. Interlobular septal thickening.	WBC 28,000 with 98% neutrophils. CRP 32 mg/dL. Tracheal secretions w/ eosinophilia.	Acute Eosinophilic PNA	Intubation, VV ECMO Methylprednisolone pulse (1000 mg daily for three days) Recovery
20 M Kamada et al.	New device & increased usage for two weeks	Fever, dyspnea.	Diffuse ground-glass opacities. Interlobular septal thickening. Right-sided pleural effusion.	WBC 16,000 with 88% neutrophils. CRP 10 mg/dL. BAL with 60% eosinophils.	Acute Eosinophilic PNA	Prednisolone Recovery
40 F Khan et al.	1 month	Dyspnea and pleuritic chest pain worsening for a month.	Diffuse ground-glass opacities, sparing the lung periphery.	Open lung biopsy showed organizing pneumonia.	Organizing pneumonia	Intubation High-dose methylprednisolone Recovery
27 M Mantilla et al.	7 months	Dyspnea, cough, fever, hemoptysis.	CT scan with micronodular pattern initially.	- WBC 17,000; BAL unremarkable. - Transbronchial biopsy with organizing pneumonia.	Organizing pneumonia	Intubation High-dose methylprednisolone Recovery
54 M He et al.	Vaping cannabis oil weekly for years	Dyspnea, hemoptysis.	Extensive airspace opacification in a centrilobular nodular pattern resembling a "tree in bloom."	- Urine positive for cannabinoids. - BAL bloody, suspicious for diffuse alveolar hemorrhage, 61% neutrophils. - Transbronchial bx: organizing PNA	Organizing pneumonia	ICU, high-flow nasal cannula Recovery
42 F Asthma Rheumatoid arthritis McCauley et al.	7 months	7-month history of dyspnea, productive cough, fevers.	Bilateral ground-glass opacities in a crazy-paving pattern.	- WBC 18,000. - BAL with 48% neutrophils, 1% eosinophils, and abundant lipid-laden macrophages.	Lipoid pneumonia	Not very ill. Recovered after d/c exposure
31 F Modi et al.	3 months	Progressive dyspnea and cough.	Diffuse ground-glass opacities in a crazy-paving pattern.	BAL positive for lipid with Oil Red-O stain.	Lipoid pneumonia	Intubated IV steroid Recovery
34 F Viswam et al.	3 years	Insidious onset cough, hemoptysis, dyspnea for three months, fever, night sweats, weight loss.	Diffuse ground-glass infiltrates with reticulation.	- CRP 23 mg/dL. - BAL 68% macrophages, 2% Eos. - Surgical lung biopsy: lipoid pneumonia.	Lipoid pneumonia	Prednisone 40 mg caused some improvement. Continued vaping Persistent illness
46 M Itoh et al.	3 months	Dyspnea for two months, night sweats, fever, weight loss.	Bilateral ground glass opacity greatest in upper lungs.	- WBC 15,000 with 78% neutrophils. - CRP 12 mg/dL. - BAL 58% neutrophils, 19% Eos, abundant lipid-laden macrophages on Oil Red O staining. - Lung bx: Eos & neutrophil infiltration, foci of organization.	Features of both lipoid pneumonia and organizing pneumonia.	- Methylprednisolone pulse (2000 mg daily for three days) followed by prednisone 1mg/kg with taper - Recovery
33 M Diabetes Agustin et al.	2 months, increasing intensity	Dyspnea, hemoptysis.	Diffuse ground glass opacity, in some areas progressing to patchy consolidation.	- ESR, CRP unremarkable. - BAL increasingly bloody, 42% neutrophils, 1% eosinophils. - Surgical lung bx: bland hemorrhage	Diffuse alveolar hemorrhage	Noninvasive ventilation Pulse-dose steroid Recovery
70 M Lung CA, COPD Long et al.	4 weeks heavy use	Dyspnea, cough.	Bilateral diffuse infiltrates.	- BAL increasingly bloody	Diffuse alveolar hemorrhage	Intubation Steroid Died

-Internet Book of Critical Care, by @PulmCrit

(https://emcrit.org/wp-content/uploads/2019/08/vapii.svg) 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 pathological finding (table below). However, in some cases there may be multiple simultaneous injury patterns (e.g. combined features of acute eosinophilic pneumonia and lipoid pneumonia).

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

	Acute Eosinophilic Pneumonia predominant	Organizing Pneumonia predominant	Lipoid Pneumonia predominant	Diffuse Alveolar Hemorrhage predominant
Epidemiology	May begin shortly after initiation of vaping	Usually after longer period of vaping	Usually after longer period of vaping	? Results from intense use
Clinical presentation	- Acute onset - Often requires intubation	- Subacute onset - May require intubation	- Subacute onset - Chronic fever, weight loss - Milder than other forms	- Hemoptysis may be seen
Radiologic clues may include:	- Septal thickening - Pleural effusion(s)	- Micronodular or centrilobular pattern of ground glass opacities - May note peripheral sparing	- Crazy paving	
Findings on bronchoscopy	- Eosinophilia (>~20%)	- Nonspecific	- Macrophages laden with lipid inclusions which stain positive using Oil Red O.	- Increasingly bloody return with sequential lavage.
Treatment	Steroid is essential.	Steroid is essential.	Steroid usually given, but has unclear value.	Unknown

-Internet Book of Critical Care, by @PulmCrit

(https://emcrit.org/wp-content/uploads/2019/08/vapomorphotypes.svg) 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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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.

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

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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

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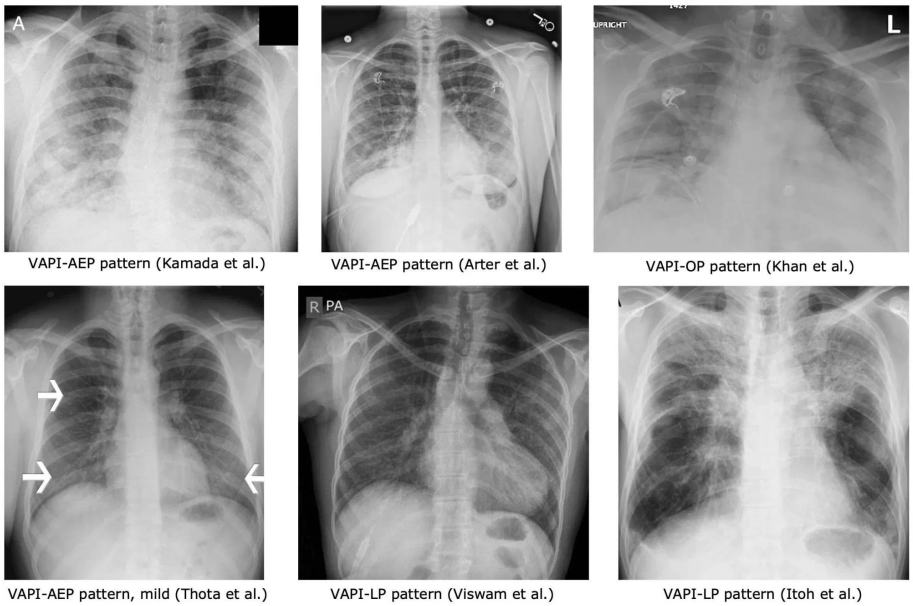
chest X-ray

- 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.

Chest X-ray of patients with various forms of VAPI.
(AEP = acute eosinophilic pneumonia; OP = organizing pneumonia; LP = lipoid pneumonia).



VAPI-AEP pattern (Kamada et al.) | VAPI-AEP pattern (Arter et al.) | VAPI-OP pattern (Khan et al.)

VAPI-AEP pattern, mild (Thota et al.) | VAPI-LP pattern (Viswam et al.) | VAPI-LP pattern (Itoh et al.)

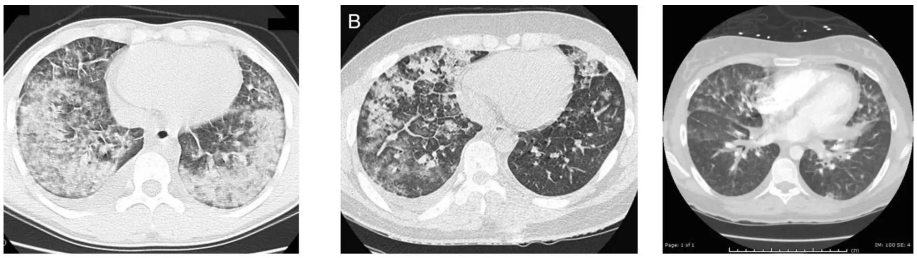
CT scan – basic characteristics of VAPI

- 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

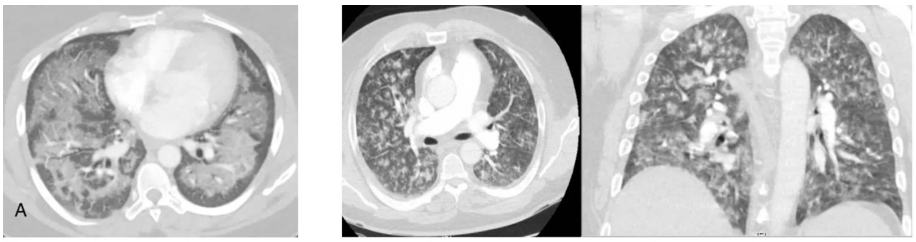
- Bilateral, ground-glass opacities.
- Smooth septal thickening is often seen.
- Pleural effusion(s) may be seen.



Three different patients with VAPI causing acute eosinophilic pneumonia. All show the same pattern of patchy ground glass opacification, Septal thickening, and pleural effusion. (Aokage T. et al, Kamada T. et al, and Arter ZL et al.)

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.



LEFT: VAPI with organizing pneumonia causing a ground glass pattern with peripheral sparing (Khan MS et al.)
RIGHT: VAPI with organizing pneumonia causing centrilobular nodules (He T et al.)

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 un-affected lobules. Septal thickening may accentuate the borders between normal lobules and diseased lobules.

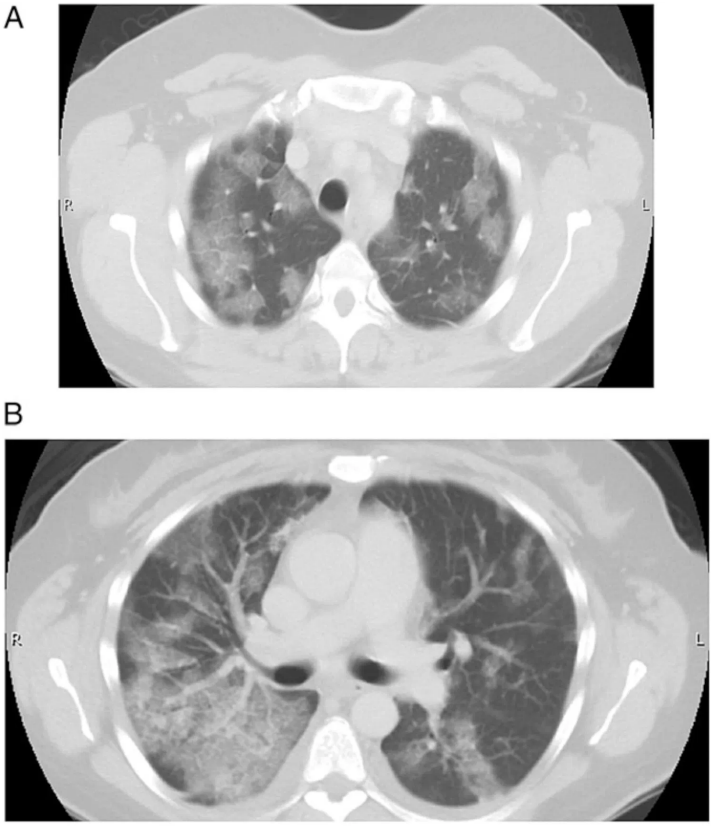


FIGURE 1. Representative CT images show the "crazy paving" pattern of patchy ground glass superimposed on interlobular septal thickening. A, Bilateral upper lobes. B, Bilateral lower lobes.

VAPI with lipoid pneumonia causing a crazy-paving pattern, from McCauley et al. (https://www.ncbi.nlm.nih.gov/pubmed/22474155)

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).

diagnostic/therapeutic pathway

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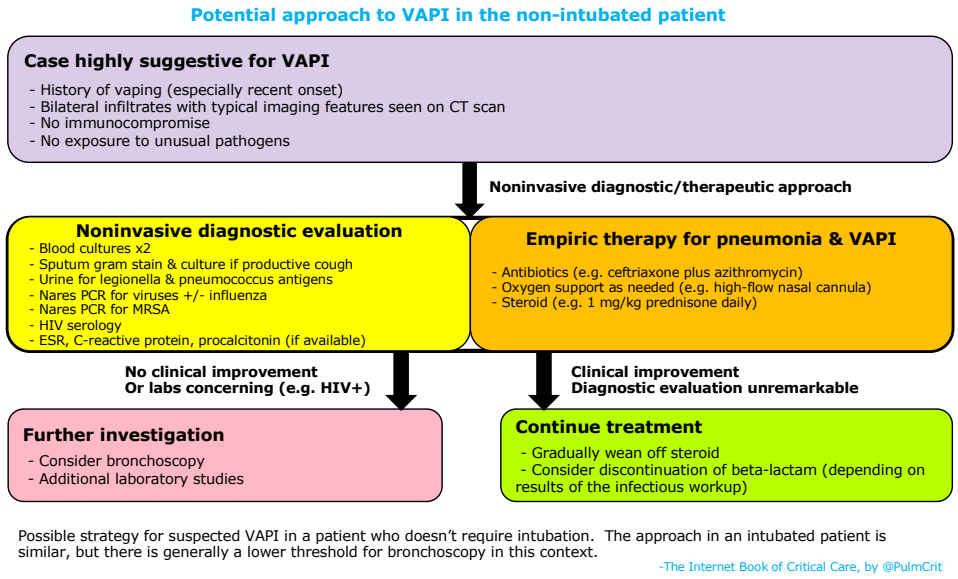
Below is a potential approach to VAPI. Most of these patients are young and previously healthy, which makes evaluation and treatment more straightforward.

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](https://emcrit.org/ibcc/pneumonia/#adjuvant_therapies) for community acquired pneumonia anyway).



Possible strategy for suspected VAPI in a patient who doesn't require intubation. The approach in an intubated patient is similar, but there is generally a lower threshold for bronchoscopy in this context.

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(https://emcrit.org/wp-content/uploads/2019/08/apprvapi.svg)

podcast

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There's no podcast yet – stay tuned.

(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/apps.40518.14127333176902609.7be7b901-15fe-4c27-863c-7c0dbfc26c5c.5c278f58-912b-4af9-88f8-a65fff2da477.jpg)

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questions & discussion

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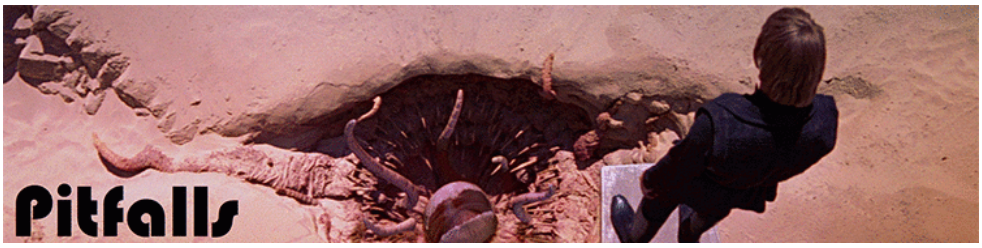
To keep this page small and fast, questions & discussion about this post can be found on another page ***here*** (https://emcrit.org/pulmcrit/vaping-associated-pulmonary-injury/) .



(https://i1.wp.com/emcrit.org/wp-content/uploads/2016/11/pitfalls2.gif)

- 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).

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