Pneumonitis
Concerns about smoking and the health effects of using vaping products

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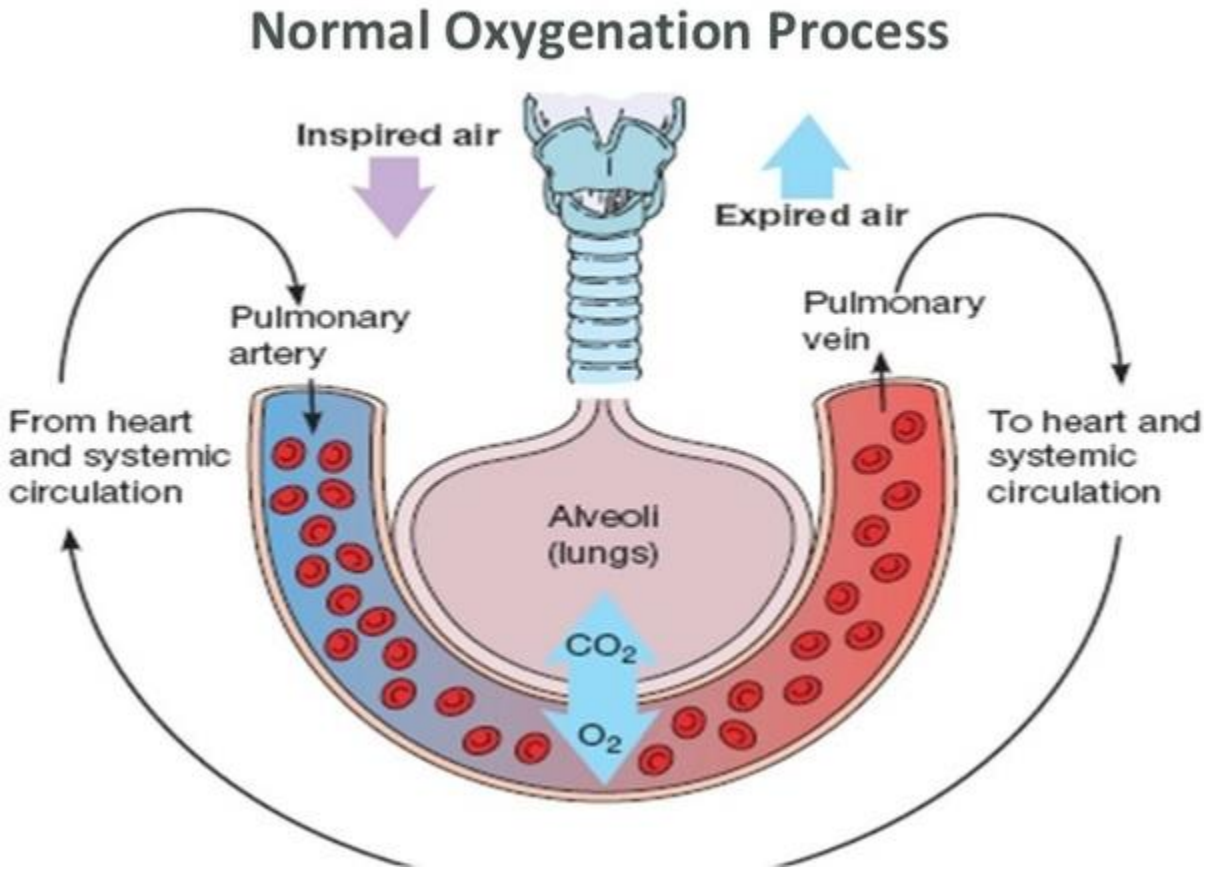
I HAVE NO CONFLICTS

Objectives

- Describe basic respiratory physiology
- Describe the hazards of tobacco marijuana and vaping
- Describe the impact of these products on medical and health expenditures
- Discuss significant pathologic conditions which are related to vaping

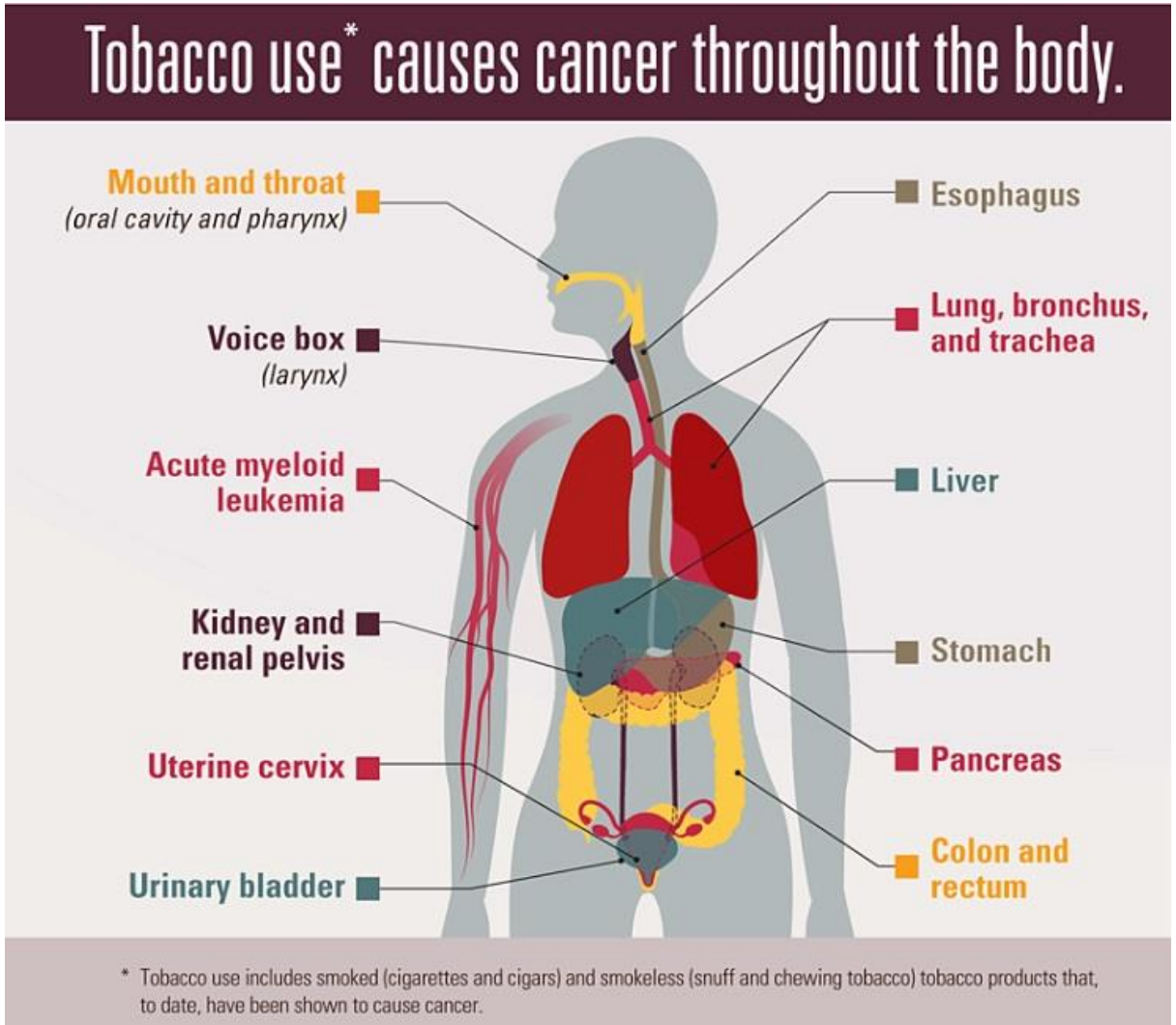
Respiratory Physiology

Normal Physiology



Air Pollution

Tobacco causes <u>A lot of Cancer</u>



Tobacco causes A LOT of Disease

- COPD ILD/IPF
- heart disease - MI CAD
- vascular disease CVA/stokes Aortic aneurysm
- PVD
- Cancer
- Cataracts
- Type 2 DM
- Erectile dysfunction

Cigarettes – over *7000* toxic substances

- Hydrogen cyanide
- Formaldehyde – used to preserve dead bodies
- Lead – in paint which we known is toxic
- Arsenic – rat poison
- Cadmium – main ingredient in batteries
- Ammonia – household cleaning agent
- Radioactive elements, such as uranium
- Benzene – pesticides and gasoline
- Carbon monoxide – exhaust lethal in large quantities
- Nitrosamines
- Polycyclic aromatic hydrocarbons (PAHs)
- Vinyl chloride – main component of plastics

Know History

- USA vs Phillip Morris **1999** - it took 7 years until a decision was made
- Since the 1950's Tob Industry KNEW their product was dangerous
- Took years to convince the public " change attitudes"
- 2006 – The Tobacco industry held accountable for fraudulently covering up the health risks associated with smoking and marketing their products to children.
  - Massive effort 50 yrs and on-going scheme to defraud the public
  - Tobacco settlement ***25 billion***
  - To a cigarette manufacturer – " value of human life" not even worth 10K

Marijuana

- Marijuana is the most commonly used illicit drug in the United States.
- More than 94 million Americans, or 40% of Americans aged **12 years** or older have tried marijuana at least once
- Marijuana smoking may be associated with increased risk of lung cancer.
  - Marijuana smoke contains cannabinoid compounds in addition to many of the same components as tobacco smoke. For instance, benzopyrene, a carcinogenic polycyclic aromatic hydrocarbon, is found in both tobacco and marijuana smoke and has been implicated in mutations related to lung cancer.
  - Although the preponderance of in vitro data supports a biologically plausible association, limited research exists that suggests anticarcinogenic cannabinoid effects.

- physicians should advise patients regarding potential adverse health outcomes until further rigorous studies are performed that permit definitive conclusions.

Vaping and E-cigarettes

Vaping Is Less Harmful Than Smoking - **False**

- E-cigarettes heat nicotine (extracted from tobacco), flavorings and other chemicals to create a water vapor that you inhale.
- Regular tobacco cigarettes contain 7,000 chemicals, many of which are toxic. While we don't know exactly what chemicals are in e-cigarettes, there's almost no doubt that they expose you to fewer toxic chemicals than traditional cigarettes.
- As of December 2019, the Centers for Disease Control and Prevention (CDC) confirmed 54 deaths in patients with e-cigarette, or vaping, product use associated lung injury (EVALI).
- These cases appear to predominantly affect people who modify their vaping devices or use black market modified e-liquids.
  - This is especially true for vaping products containing tetrahydrocannabinol (THC).

Statistics

- 2017 11% High school students used e cigs
- 2019 27% High school students used e cigs
- 2011 only 0.6 % middle schoolers
- 2019 more than 10.5% middle schoolers
- Using e cig inc likelihood to smoke cigarettes
- 2019 National Youth Tob Survey – 12% high school students are current EVERYDAY vaping
- Majority of youth ***DO not know e cig contain nicotine***

Vaping

- Vaping means using an electronic device thought to be smoking “ vapor” – however …. Its not just a gas
- It is actually an aerosol which contain tiny chemical particles from both the liquid and the device ie metals (harmful to lung)
- E Cig uses a battery to heat nicotine liquid (e juice) that turns liquid into a vapor/aerosol
- The liquid comes in flavors – addictive, attractive to youth (watermelon bubble gum etc)
- Misleading you are not just smoking water vapor its ***nicotine***
- ***Concentration of nicotine is not regulated and unknown***
- E cig companies figured out that using nicotine salt formulas allow for much higher levels and more efficient delivery of nicotine and causes much less irritation (compared to older e cigs) ie feels better more smoking more addiction

Vitamin E Acetate

- The CDC has identified **vitamin E acetate** as a chemical of concern among people with EVALI.
- Vitamin E acetate is a thickening agent often used in THC vaping products, and it was found in all lung fluid samples of EVALI patients examined by the CDC.
- Vitamin E acetate and electronic cigarette or vaping product use-associated lung injury (EVALI)
    - factors that lead to accelerated lung function decline, and prognostic differences among patients with acute exacerbation of chronic fibrosing idiopathic interstitial pneumonias (AE-IIPs). NEJM December 20, 2019

Vitamin E acetate was associated with EVALI in a convenience sample of 51 patients in 16 states across the United States.

(Funded by the National Cancer Institute and others.)

Key Facts about Vitamin E Acetate

- Vitamin E acetate is used as an additive, most notably in THC-containing e-cigarette, or vaping, products.
- Vitamin E is a vitamin found in many foods, including vegetable oils, cereals, meat, fruits, and vegetables. It is also available as a dietary supplement and in many cosmetic products, like skin creams.
- Vitamin E acetate usually does not cause harm when ingested as a vitamin supplement or applied to the skin. *However, previous research suggests that when **vitamin E acetate is inhaled**, it may interfere with normal lung functioning*.
- Another potential harmful effect of vitamin E acetate that may contribute to lung injury occurs when it is heated in e-cigarette products. Heating vitamin E acetate in these devices may create ketene by splitting off the acetate group from some or all of the vitamin E acetate.
- **Ketene** is a reactive compound that has the *potential to be a lung irritant*, depending on concentration. The CDC is currently examining ways to quantify ketene and its effects in BAL fluid
- Furthermore, trade websites have reported the addition of various diluents (e.g., vitamin E acetate and medium-chain triglycerides) to THC-containing products to enhance their quality and appearance, provide desirable aroma or taste, and lower product cost.

Table 1. Case Definitions for Patients with EVALI.*

Confirmed Case	Probable Case
Use of e-cigarette ("vaping") or dabbing† during the 90 days before symptom onset *AND*	Use of e-cigarette ("vaping") or dabbing† during the 90 days before symptom onset *AND*
Presence of pulmonary infiltrate, such as opacities, on chest radiography or ground-glass opacities on chest computed tomography *AND*	Presence of pulmonary infiltrate, such as opacities, on chest radiography or ground-glass opacities on chest computed tomography *AND*
A negative respiratory viral panel *AND* A negative influenza PCR or rapid test, if local epidemiology supports influenza testing *AND* Negative results on testing for all other clinically indicated respiratory infectious diseases (e.g., urine antigen for *Streptococcus pneumoniae* and legionella species, sputum culture in the presence of productive cough, bronchoalveolar-lavage culture if performed, blood culture, and HIV-related opportunistic respiratory infections if appropriate) *AND*	Presence of infection identified on culture or PCR, but clinical team determines that this infection is not the sole cause of the underlying lung injury *OR* the minimum criteria to rule out pulmonary infection are not met (or testing not performed) and clinical team determines that this infection is not the sole cause of the underlying lung injury *AND*
No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process)	No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process).

* EVALI denotes electronic-cigarette, or vaping, product use–associated lung injury, HIV human immunodeficiency virus, and PCR polymerase chain reaction.

† This criterion is defined as the use of an electronic device (e.g., electronic nicotine-delivery system, e-cigarette, vaporizer, or other device) or dabbing to inhale substances (e.g., nicotine, marijuana, tetrahydrocannabinol [THC], THC concentrates, cannabidiol, synthetic cannabinoids, flavorings, and other substances).

Table 3. Frequency of Detection of Priority Toxicants in EVALI Case Patients and in Healthy Comparators.*

Toxicant	EVALI Case Patients (N=51)	Healthy Comparators			
		Nonusers (N=52)	E-Cigarette Users (N=18)	Cigarette Smokers (N=29)	All Comparators (N=99)
		number/total number (percent)			
Vitamin E acetate	48/51 (94)	0/52	0/18	0/29	0/99
Medium-chain triglyceride oil	0/49	0/34	0/11	0/18	0/63
Coconut oil	1/48 (2)	0/34	0/11	0/18	0/63
Plant oil	0/49	0/34	0/11	0/17	0/62
Squalane	0/38	0/52	0/17	0/29	0/98
Squalene	0/38	0/52	0/17	0/29	0/98
α-Pinene	0/39	0/52	0/17	0/28	0/97
β-Pinene	0/39	0/52	0/17	0/28	0/97
3-Carene	0/39	0/52	0/17	0/28	0/97
Limonene	1/39 (3)	0/52	0/17	0/28	0/97
Petroleum distillates	0/12	0/52	0/17	0/29	0/98

* The listed toxicants were detected in bronchoalveolar-lavage fluid obtained from 51 patients with EVALI in 16 states from August through December 2019 and in 99 healthy comparators.

Table 4. Exposure History and Clinical Characteristics of Three Patients with Probable Diagnosis of EVALI without Evidence of Vitamin E Acetate in BAL Fluid.*

Variable	Patient 1	Patient 2	Patient 3
Patient-reported exposure history	Reported vaping nicotine products, denied vaping THC products	Reported daily vaping of flavored nicotine products obtained from vape shop starting 1 mo before admission, denied vaping THC products	Incomplete interview with the patient; vaping materials found at the scene by first responders; patient later reported heavy alcohol use immediately before illness
Symptoms	Respiratory, gastrointestinal	Constitutional, respiratory	Constitutional, respiratory
Medical history	Negative for chronic respiratory disease and heart disease	Negative for chronic respiratory disease and heart disease	Negative for chronic respiratory disease and heart disease
Presentation	Found unresponsive; on arrival at emergency department, hemoptysis and cyanosis; was intubated and admitted	Presented to urgent care on day of illness (DOI) 1 and to emergency department on DOI 3 and 5, when he was admitted	Found unresponsive; on arrival at emergency department, severe respiratory failure; was intubated and admitted
Admitted to intensive care unit	Yes	No	Yes
Respiratory support	Mechanical ventilation	None	Mechanical ventilation
Radiologic assessment	Hazy opacities predominantly in left lung on radiography; no CT	Bilateral patchy opacities on radiography; diffuse bilateral nodular opacities with surrounding micronodular and ground-glass opacities on CT	Bilateral infiltrates and opacities on radiography and CT
Infectious diseases workup	Blood cultures negative; methicillin-susceptible *Staphylococcus aureus* (interpreted by clinical team as a contaminant) in BAL fluid	Serologic analysis on admission indeterminate for coccidioides species, follow-up IgM and IgG by immunodiffusion were positive; BAL cell count, 31% eosinophils; negative results on respiratory viral panel, influenza PCR, blood cultures, legionella urinary antigen, *Streptococcus pneumoniae* urinary antigen, *Mycoplasma pneumoniae* PCR, cytomegalovirus PCR, pneumocystis antigen, fungal stain and culture, AFB smear, and mycobacterial culture	Negative results on respiratory viral panel, influenza testing, and blood cultures; methicillin-susceptible *S. aureus* (interpreted by clinical team as a contaminant) in tracheal-aspirate culture
Treatment	Glucocorticoids and antibiotics	Glucocorticoids, antibiotics, and antifungal agents	Glucocorticoids and antibiotics
Disposition	Discharged 3 days after admission	Discharged 3 days after admission	Discharged 13 days after admission
Discharge diagnoses	Unintentional multidrug overdose with benzodiazepines and oxycodone, active nicotinism with vaping, with suspected likely vaping-induced lung injury	Acute eosinophilic pneumonia, initially attributed to EVALI; after discharge, positive results on coccidioides serologic analysis prompted updating of diagnosis to coccidioidomycosis with or without EVALI	Acute hypoxic respiratory failure caused by vaping-associated lung injury, methicillin-susceptible *S. aureus* pneumonia, acute respiratory distress syndrome, distributive shock

* AFB denotes acid-fast bacilli, BAL bronchoalveolar lavage, and CT computed tomography.

Research Suggests Vaping Is Bad for Your Heart and Lungs - **True**

- Nicotine is the primary agent in both regular cigarettes and e-cigarettes, and it is highly addictive.
  - It causes you to crave a smoke and suffer withdrawal symptoms if you ignore the craving.
  - Nicotine is also a toxic substance. It raises your blood pressure and spikes your adrenaline, which increases your heart rate and the likelihood of having a heart attack.
- Is vaping bad for you?
  - There are many unknowns about vaping, including what chemicals make up the vapor and how they affect physical health over the long term.
  - Emerging data suggests links to chronic lung disease and asthma, and associations between dual use of e-cigarettes and smoking with cardiovascular disease. Propylene glycol are humectants that are main component of e cig liquids some use ethylene glycol (Remember your MUDPILES)
  - 7000 flavoring options
  - Metals – tin, lead, nickel, chromium, manganese, and arsenic are found in e cigs

Other Bad effects to be aware of -

- Burn from a Vape Pen – more hazardous reasons not to use them
- Vaping burns are rare, but they can be serious, according to the FDA, especially if the device catches on fire while in the owner’s pocket.
- Popcorn Lung / bronchiolitis obliterans
  - "**Popcorn lung**" is the nickname - condition that damages your **lungs**' smallest airways and makes you cough and feel short of breath. It's sometimes caused by breathing in a chemical used to flavor microwave **popcorn**. But other chemicals vaping associated with this lung disease.

Popcorn Lung

Electronic Cigarettes Are the Best Smoking Cessation Tool – **False** they are not

- Although they've been marketed as an aid to help you quit smoking, e-cigarettes have not received Food and Drug Administration approval as smoking cessation devices.
- A recent study found that most people who intended to use e-cigarettes to kick the nicotine habit ended up continuing to smoke both traditional and e-cigarettes.

A New Generation Is Getting Hooked on Nicotine - True

- Among youth, e-cigarettes are more popular than any traditional tobacco product.
  - In 2015, the U.S. surgeon general reported that e-cigarette use among high school students had increased by 900%
  - 40% of young e-cigarette users had never smoked regular tobacco.
- Three reasons e-cigarettes may be particularly enticing to young people.
  - First, many teens believe that vaping is less harmful than smoking.
  - Second, e-cigarettes have a lower per-use cost than traditional cigarettes.
  - Finally, vape cartridges are often formulated with flavorings such as apple pie and watermelon cotton candy that appeal to younger users.

Diseases related to Vaping

- EVALI - e-cigarette and vaping product use associated lung injury

- **Popcorn lung** – bronchiolitis obliterans smallest airway destroyed and causes cough and SOB
- Asthma COPD

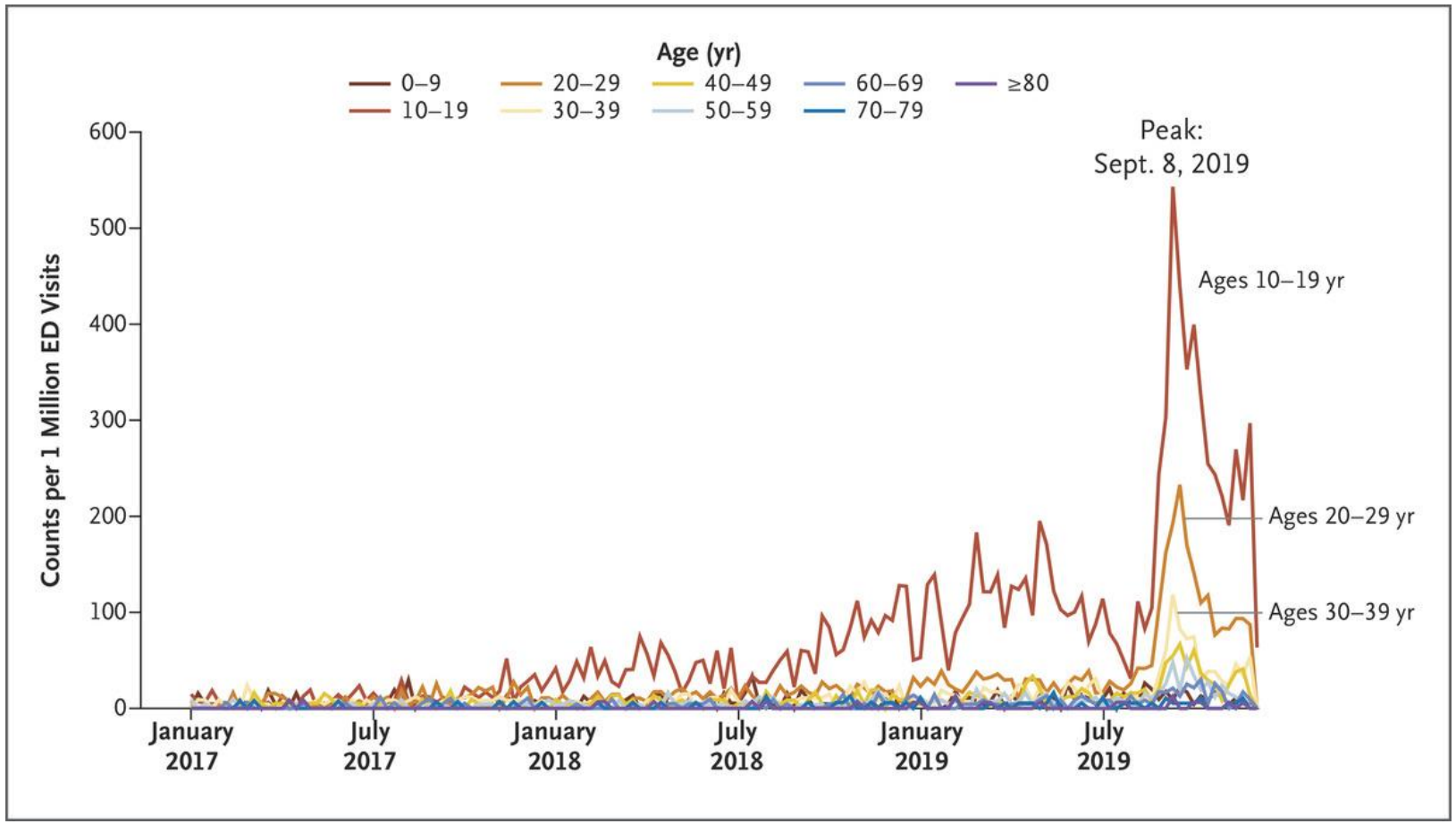
- **Two studies link use of e-cigarettes to asthma, COPD**
- One study, which “looked at a database of more than 705,000 adults, found that “in people who had never smoked regular cigarettes, e-cigarette use was associated with 75% higher odds of COPD.” published in Journal of Preventive Medicine
- In a second study, which involved “400,000 adults who never smoked regular cigarettes,” the study found that “the risk of asthma was 39% higher in current e-cigarette users than in people who had never vaped,” and “the more people vaped, the higher their asthma odds.” published in BMC Pulmonary Medicine.

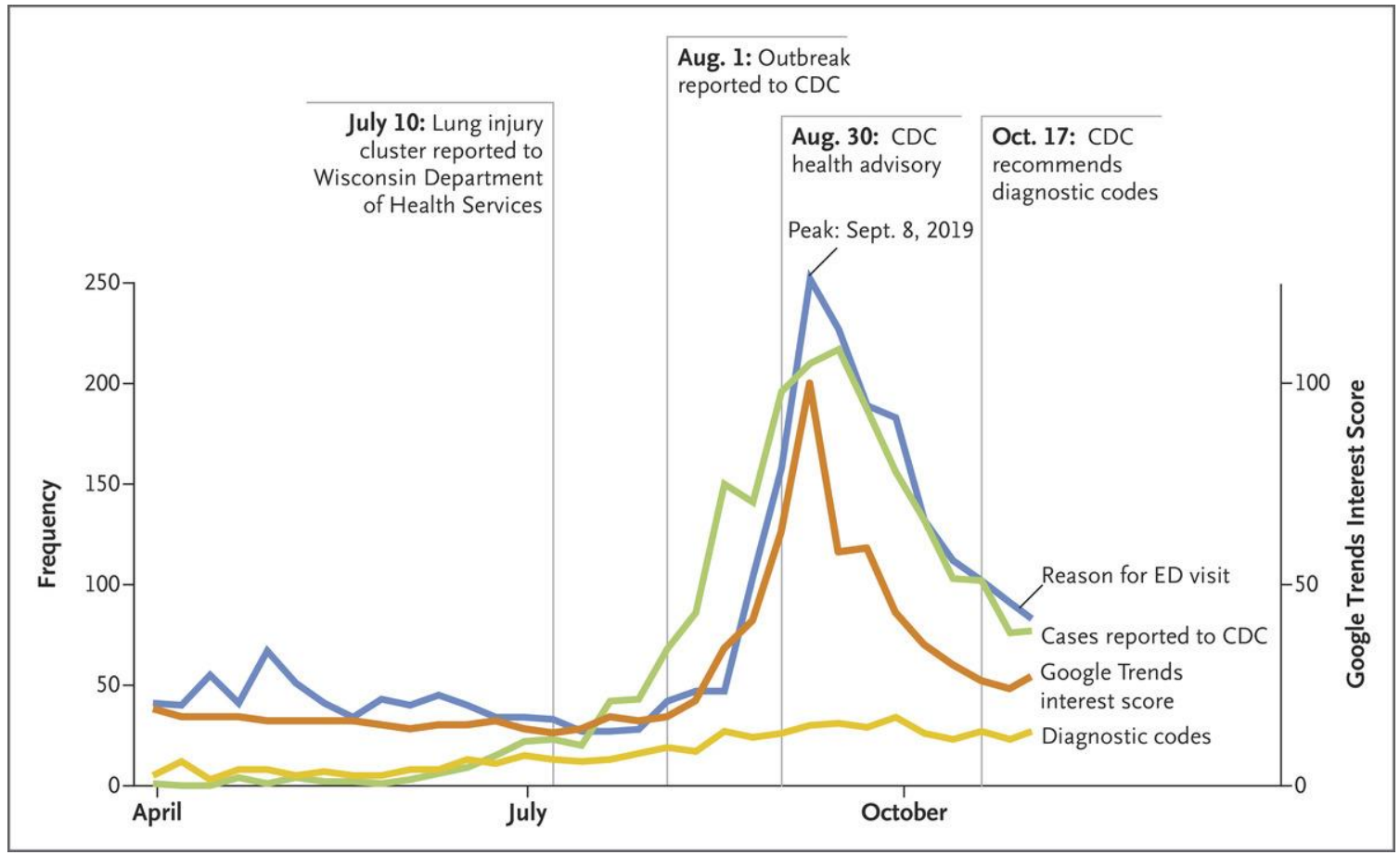
EVALI – CDC reports

- This complex investigation spans all states, involves over 2,500 patients, and a wide variety of brands and substances and e-cigarette, or vaping, products.
- **As of December 3, 2019**, CDC is only reporting hospitalized EVALI cases and EVALI deaths**.**
- **As of January 7, 2020**, a total of 2,602 cases of hospitalized e-cigarette, or vaping, product use-associated lung injury (EVALI) or deaths have been reported to CDC from 50 states, the District of Columbia, and two U.S. territories (Puerto Rico and U.S. Virgin Islands).
- **As of Jan 7, 2020 –** 57 deaths have been confirmed in 27 states and the District of Columbia:
  - Alabama, California, Connecticut, Delaware, District of Columbia, **Florida,** Georgia, Illinois, Indiana, Kansas, Louisiana, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Jersey, New York, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, and Virginia
  - The median age of deceased patients was 51 years and ranged from 15 through 75
  - More deaths are currently under investigation.
- Data suggest the outbreak peaked in September 2019. However, states continue to report new cases, including deaths, to CDC on a weekly basis.

CDC data

- 1,782 hospitalized patients had complete information on substances used in e-cigarette, or vaping, products in the 3 months prior to symptom onset, of whom **(as of December 3, 2019)**: 80% reported using THC-containing products; 35% reported exclusive use of THC-containing products.
- 54% reported using nicotine-containing products; 13% reported exclusive use of nicotine-containing products.
- 12% reported using cannabidiol (CBD)-containing products; 1% reported exclusive use of cannabidiol (CBD)-containing products.
- 40% reported both THC- and nicotine-containing product use.
- 5% reported no THC-, nicotine-, or CBD-containing product use

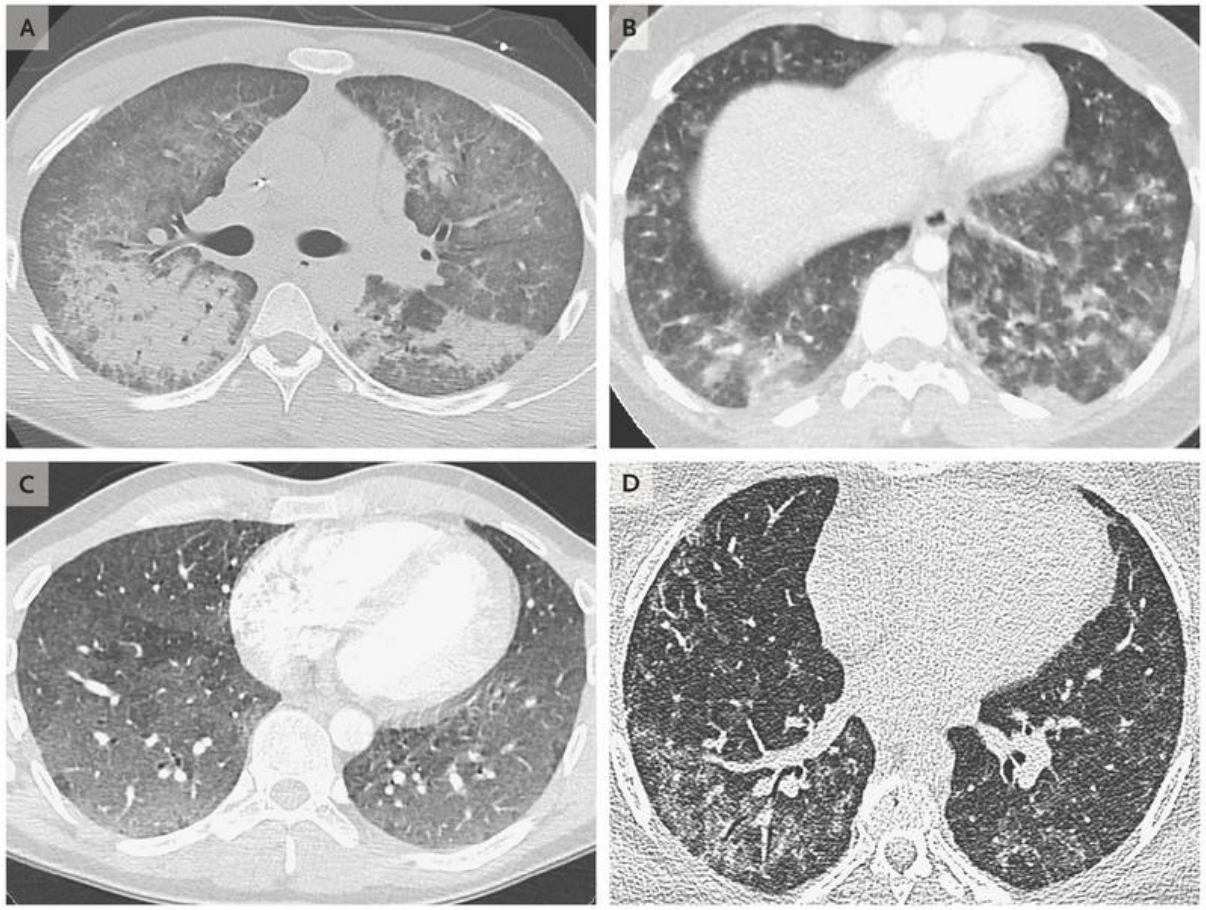

Age (yr)
0–9
10–19
20–29
30–39
40–49
50–59
60–69
70–79
≥80
Counts per 1 Million ED Visits
600
500
400
300
200
100
0
Peak:
Sept. 8, 2019
Ages 10–19 yr
Ages 20–29 yr
Ages 30–39 yr
January 2017
July 2017
January 2018
July 2018
January 2019
July 2019


July 10: Lung injury cluster reported to Wisconsin Department of Health Services
Aug. 1: Outbreak reported to CDC
Aug. 30: CDC health advisory
Oct. 17: CDC recommends diagnostic codes
Peak: Sept. 8, 2019
Frequency
250
200
150
100
50
0
April
July
October
100
50
0
Google Trends Interest Score
Reason for ED visit
Cases reported to CDC
Google Trends interest score
Diagnostic codes

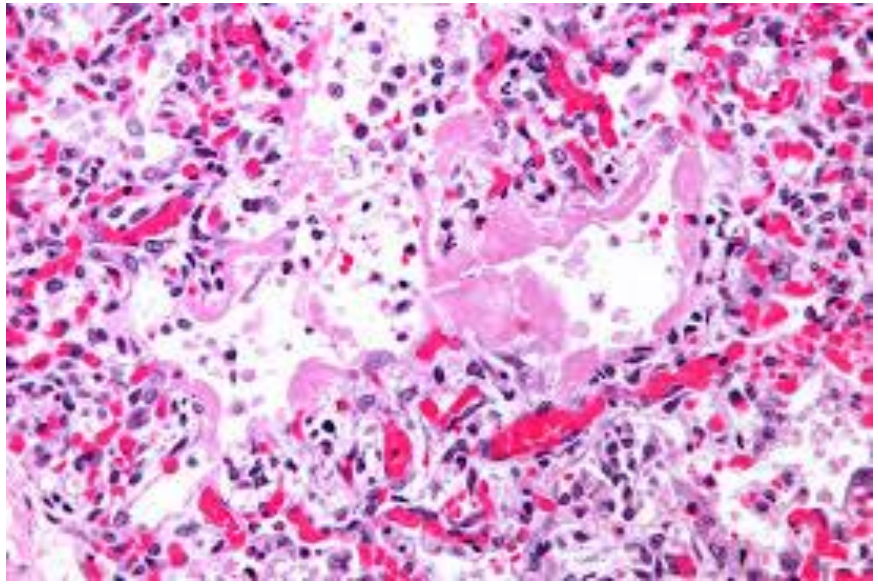
Pathology of Vaping-Associated Lung Injury

- Presence of Tetrahydrocannabinol (THC) e-cigarette cartridges were present.
- In autopsy changes characteristic of acute lung injury were seen, including diffuse alveolar damage.
  - Macrophages containing lipid and granular brown–black refractile foreign material were present in alveoli. Scant neutrophils and eosinophils were present. There was marked type 2 pneumocyte hyperplasia with prominent nucleoli and multinucleation.
- Other pathological findings attributable to vaping, including acute eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia, and lipoid pneumonia
- Predominant patterns - basilar-predominant consolidation and ground-glass opacity, often with areas of lobular or subpleural sparing.
- Rapidly developing acute lung injuries (e.g., acute eosinophilic pneumonia and diffuse alveolar damage) are associated with inhalational injuries and have overlapping pathological and imaging findings, and they have been reported to occur with vaping.
- Hypersensitivity pneumonitis is an immune response to an environmental antigen, but the antigens related to vaping are unknown.
- Lipoid pneumonia is an inflammatory response to the presence of lipids within the alveolar space and typically results from aspiration of hydrocarbons or oil-based products, but it has now been seen with vaping.
- Not all cases are acute; organizing pneumonia often develops subacutely, over a period of days to weeks, and the one case of giant-cell interstitial pneumonia (a rare fibrosing interstitial lung disease) that was correlated with hard metals in ENDS developed over a period of 6 months

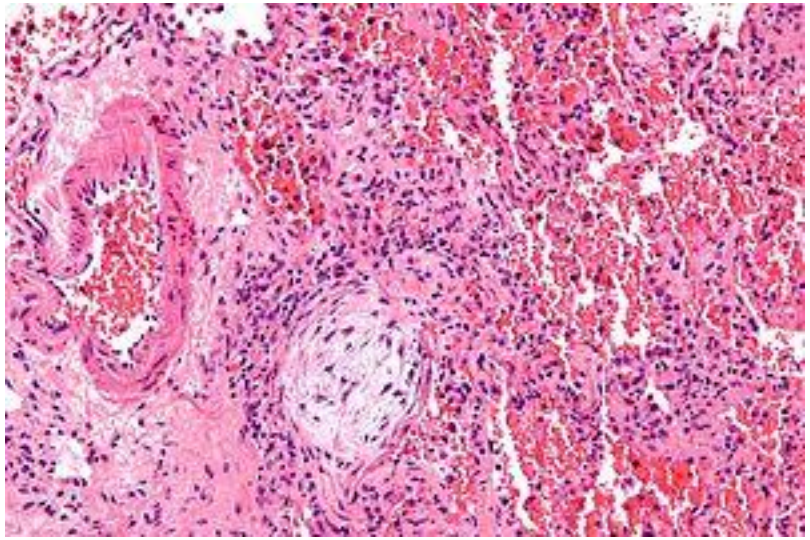
Pneumonitis /ARDS



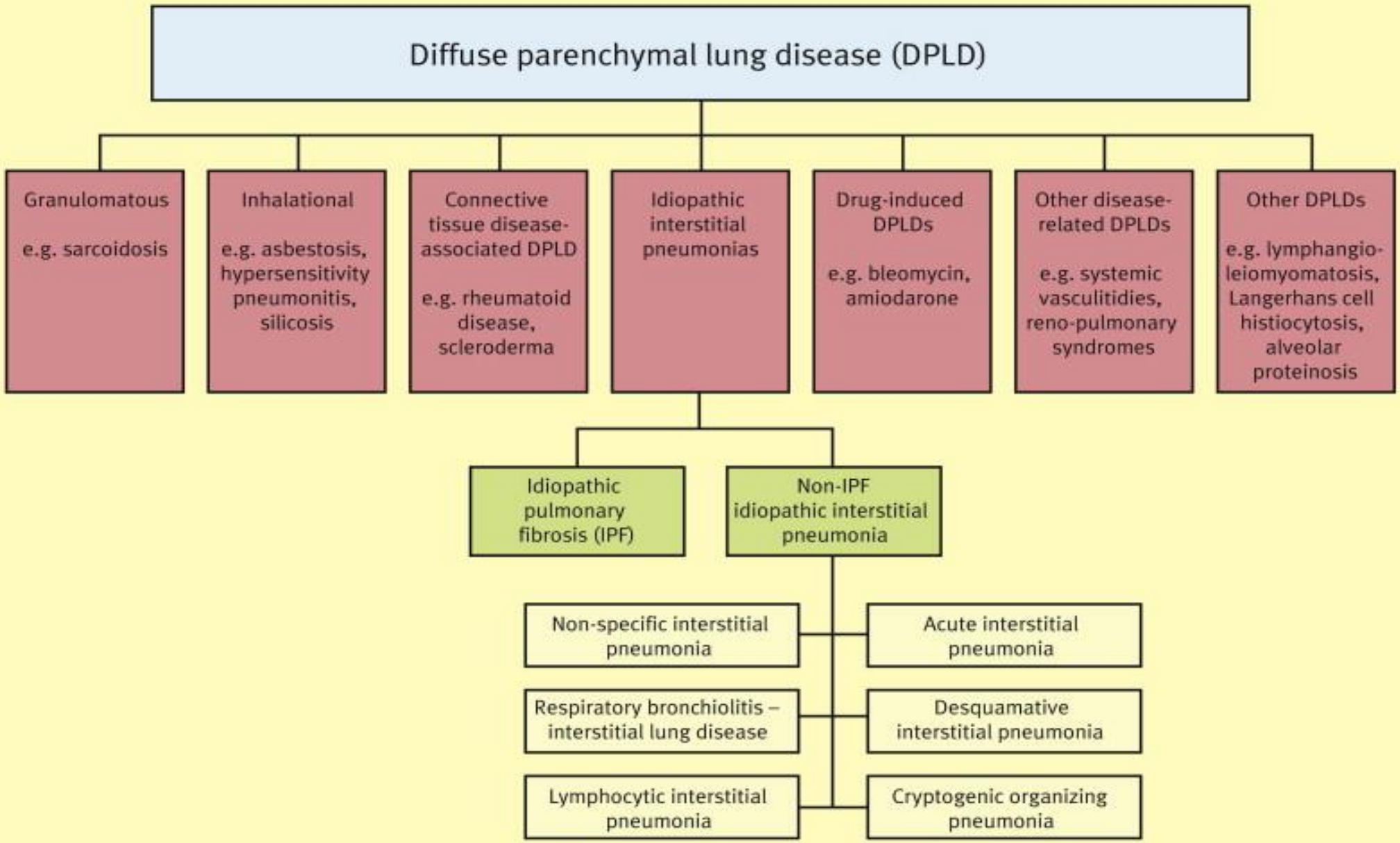
DAD

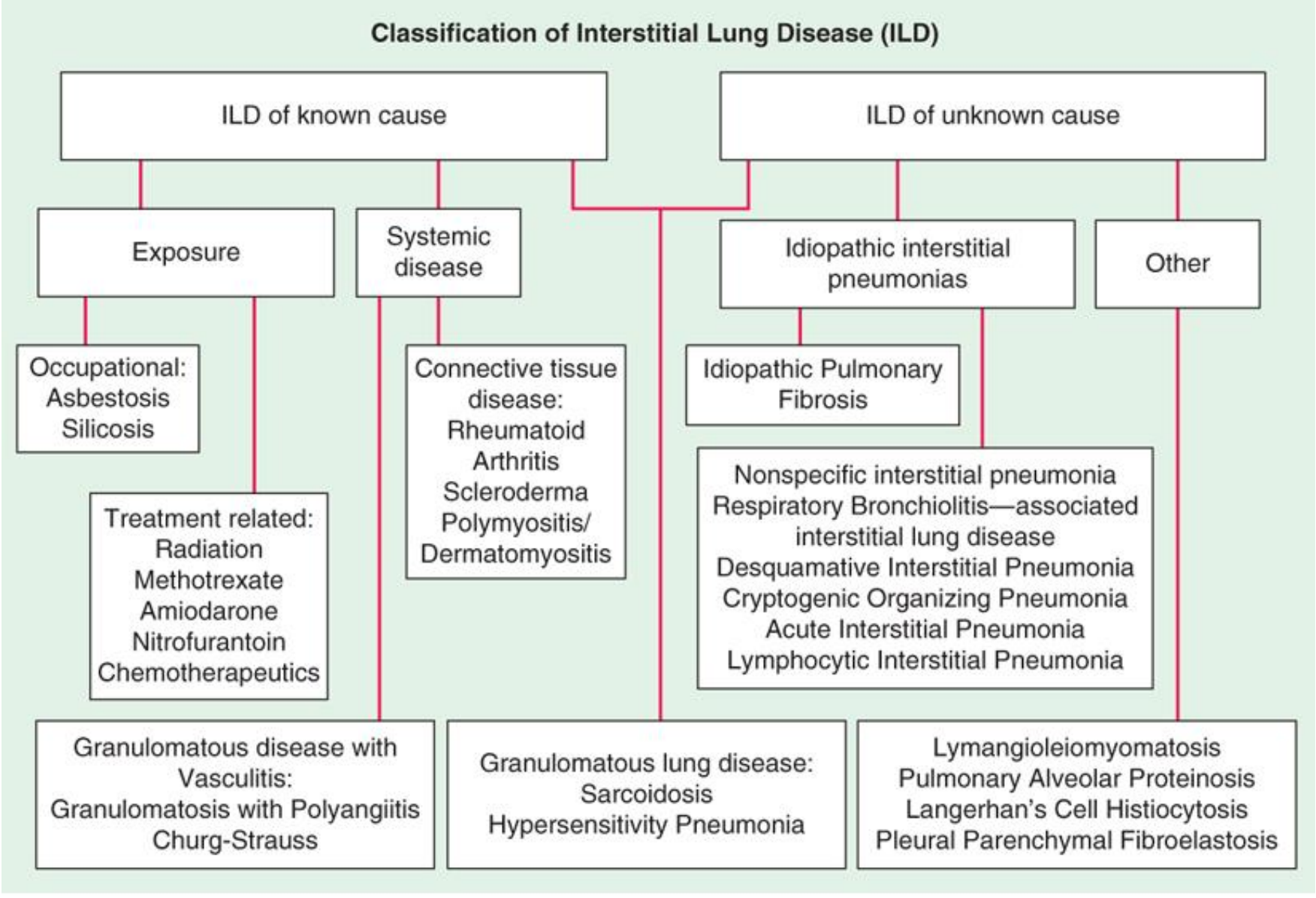


Organizing pneumonia is defined histopathologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue



A schematic for the general classification of the diffuse parenchymal lung diseases





Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Diagnosis

ATS ERS ACCP – definitive diagnosis required surgical biopsy with UIP pattern

1. Exclusion of other known causes **drug toxicity** environmental exposures Coll Vasc disease related ILD,
2. abnormal PFTs +/- abn DLCO impaired oxygenation / gas exchange
3. Imaging c/w ILD
4. Bronch with TBBX - BAL Pattern:
    1. Lymh – sarcoid COP HP
    2. Eos – eos PNA, drug induced ABPA
    3. Neutrophil – infectious CTD AIP ARDS/DAD
5. OLBX -histopathology

Treatment

- Steroids other immunosuppressive agents
- Consider lung transplant
- Palliative care / advanced directives early

- Study Pulmonary Medicine