

Noninfectious Inflammatory Lung Diseases

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Relevant Disclosures and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Jad Kebbe

I have no relevant financial relationship or affiliation with commercial interests to disclose.

Learning Objectives

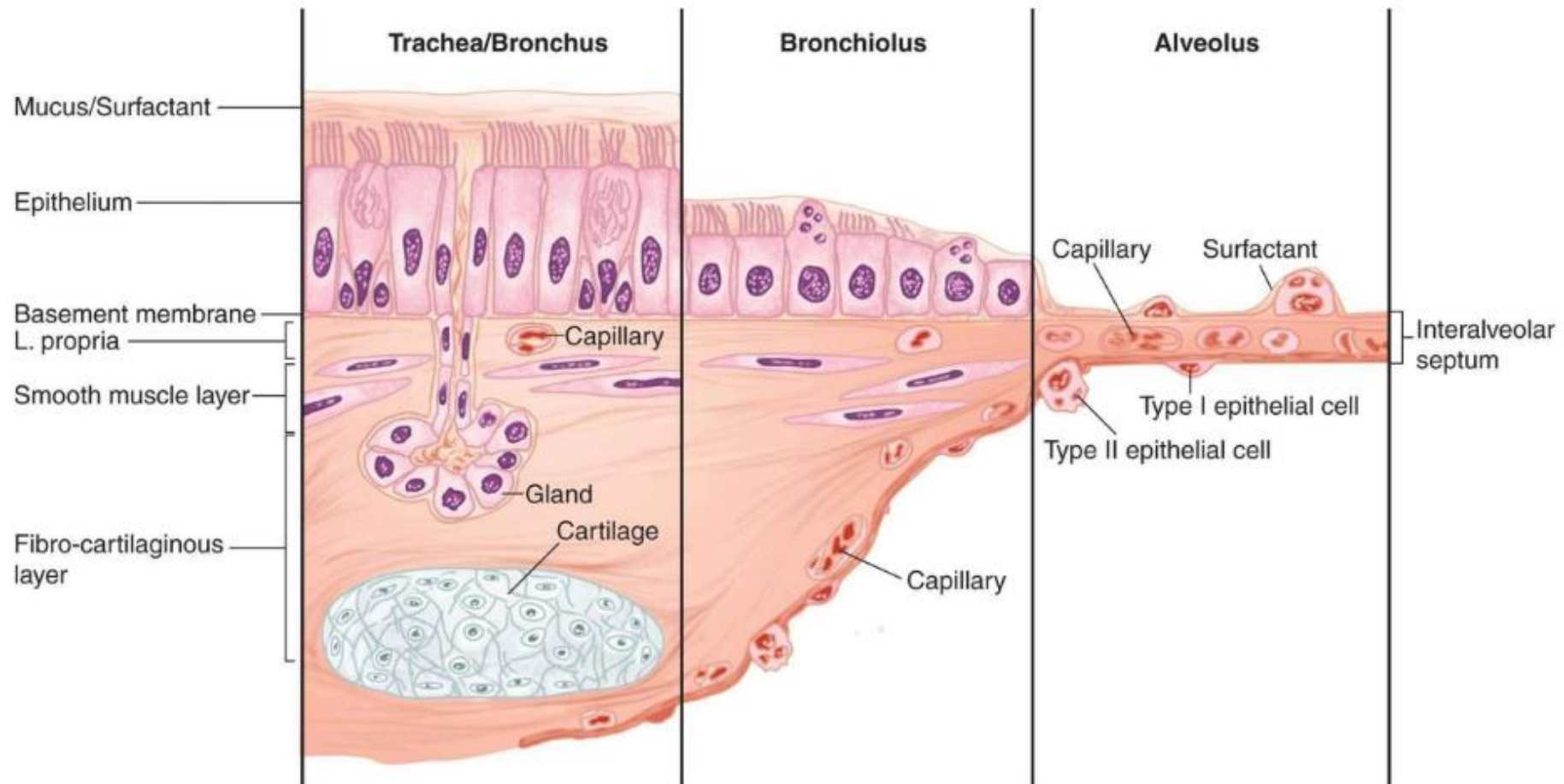
Upon completion of this session, participants will improve their competence and performance by being able to:

1. Appraise the various processes of lung inflammation
2. Differentiate between pathways and etiologies
3. Review examples from different systems
4. Discuss latest data on vaping-related illnesses

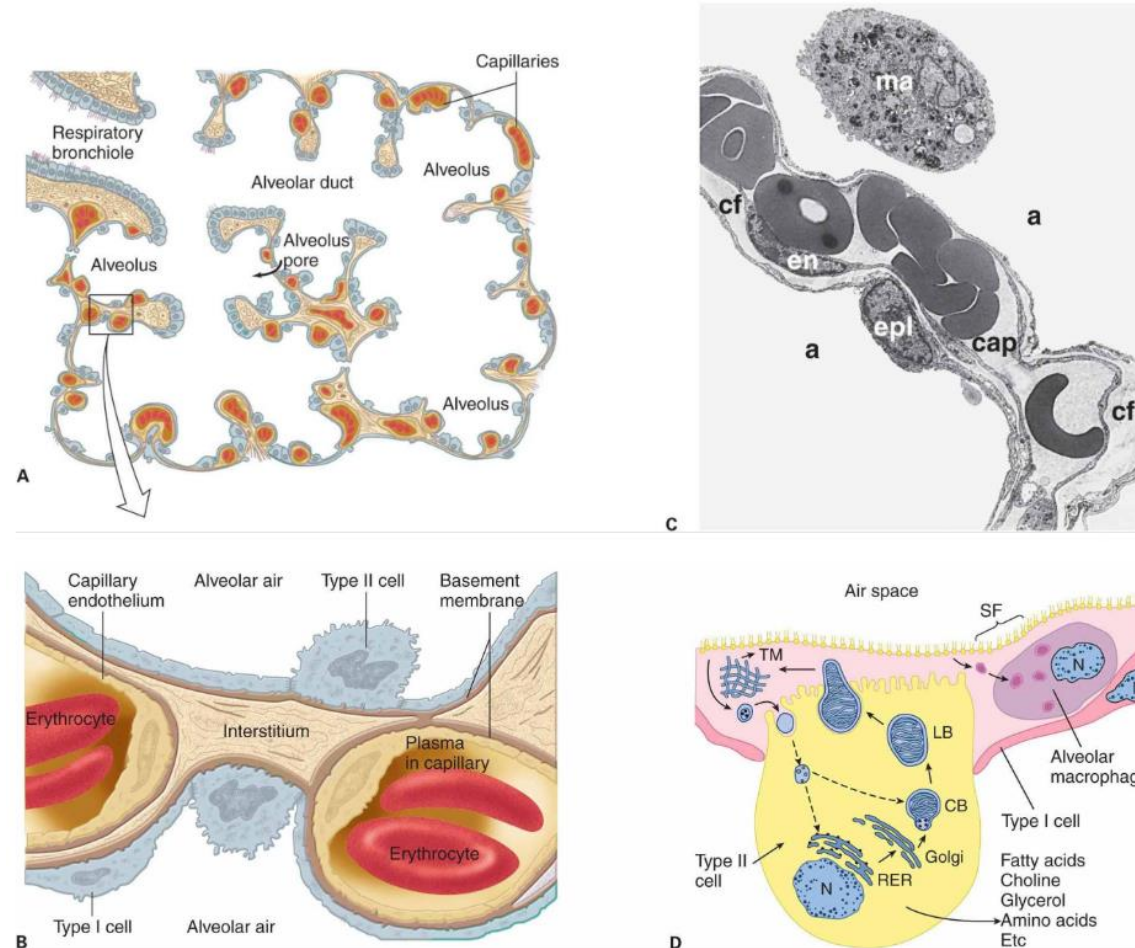
Pulmonary physiology

- Lungs are complex and fascinating
- Primary function: gas exchange
- They are essential to living: you can withhold food or water for a long time, but not breathing!
- Intricate balance and symbiotic relation between air, tissue and blood
- Pulmonary circulation is a mixture of high and low blood flows
- There is a constant interaction between heart and lungs

Airway anatomy and physiology

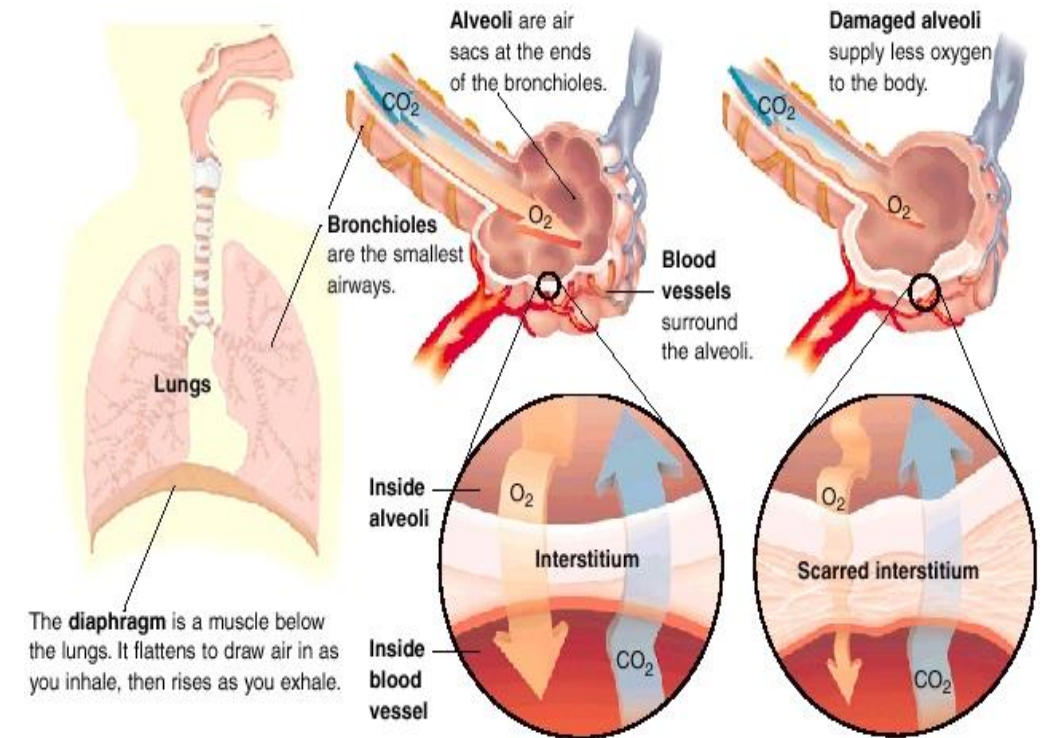


Normal function of pulmonary cells



What in the lungs can become inflamed?

- Airways:
 - Epithelium cells can participate in local cytokine networks
 - They are themselves targets for numerous cytokines
 - Glands
 - Smooth muscle
 - Cartilage
- Interstitial space
- Lymph nodes
- Vessels
- Pleura

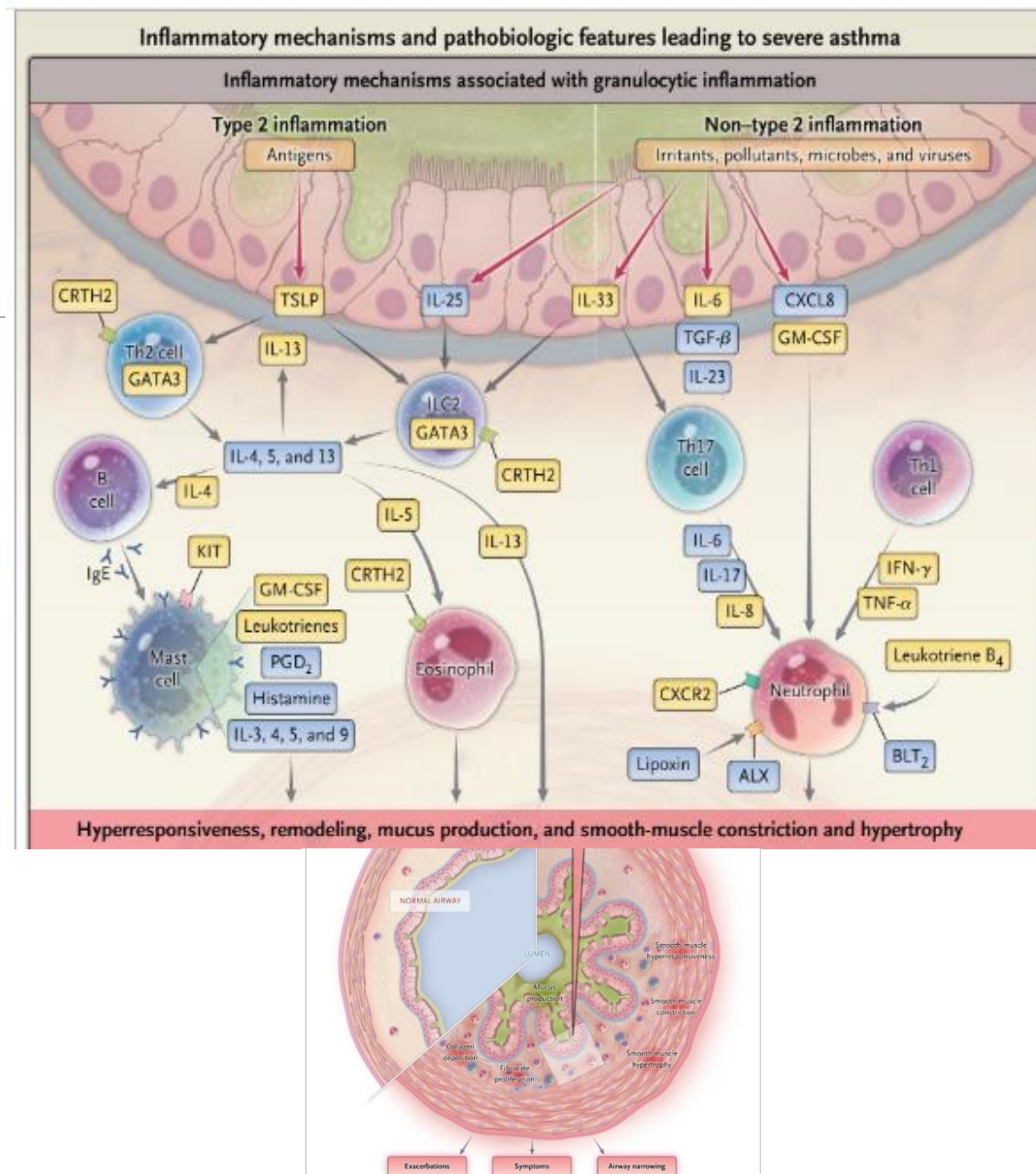


Airway inflammation

- Examples of diseases:
 - Asthma
 - Chronic bronchitis
 - Bronchiectasis
 - Cystic fibrosis
- Asthma & chronic bronchitis affect 25 million persons in the USA
- Inflammation of the conducting airways is a feature of these conditions, characterized by airway obstruction and excessive airway secretions

Mechanisms of airway inflammation

- Several mechanisms of inflammation
 - Chemokines:
 - IL-8 mediates neutrophil chemotaxis in airway disorders
 - IL-8 induces eosinophil and T-lymphocyte chemotaxis, to modulate basophil histamine release
 - Cytokines
 - Growth factors
 - Inflammatory mediators
 - Lipid mediators
- Other mechanisms perpetuate the inflammatory process:
 - Neurogenic inflammation
 - Perpetuation of the acute inflammatory response
 - Cycles of airway epithelial cell-mediated & inflammatory cell-mediated recruitment and activation of inflammatory cells



Pulmonary vascular inflammation

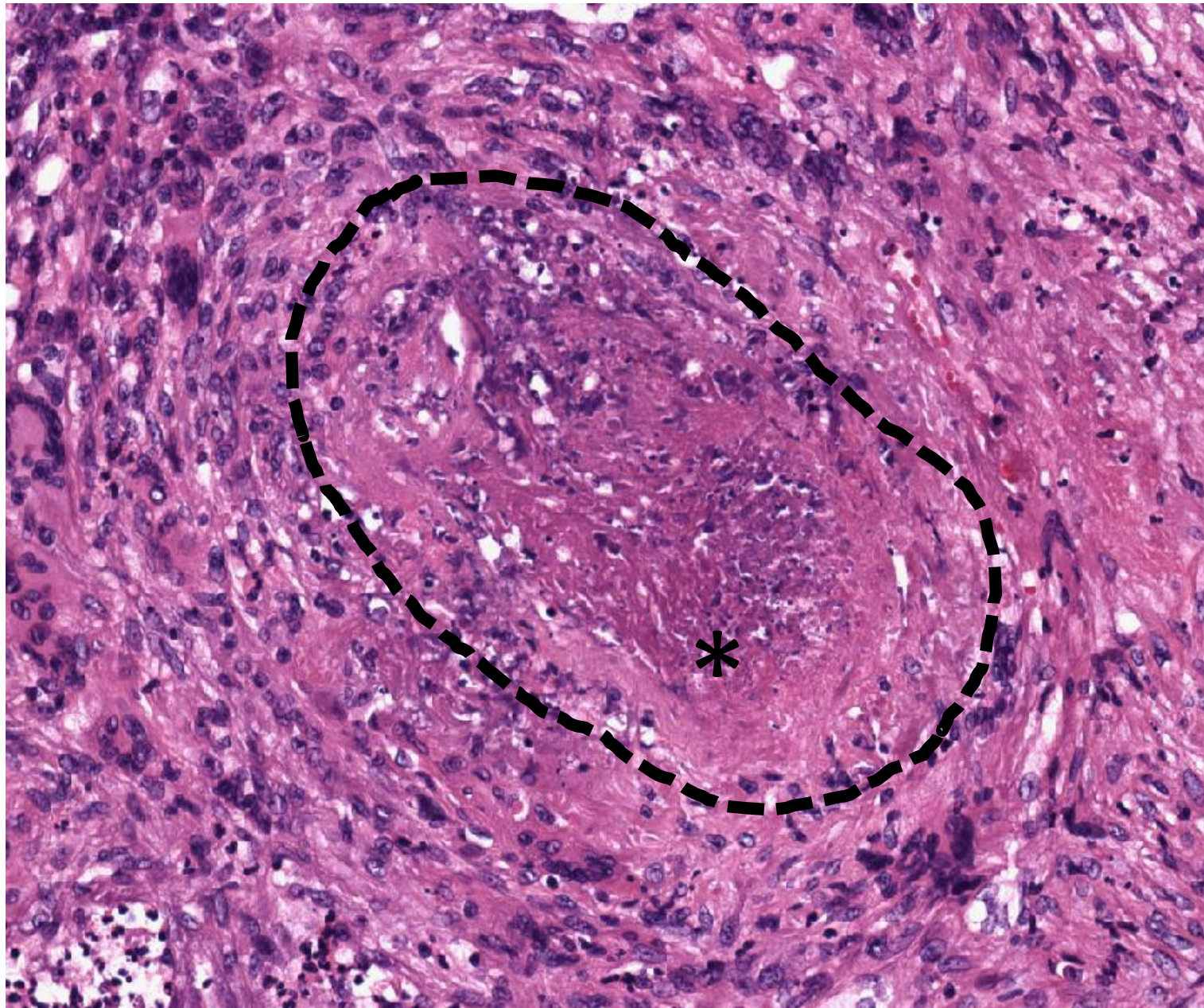
- Vascular circulation in the lungs is unique:
 - Pulmonary circulation: carries **deoxygenated** blood from the right ventricle to the lungs, and returns **oxygenated** blood to the left atrium
 - Bronchial circulation: supplies **oxygenated** blood to pulmonary tissue of larger airways
- Most common pulmonary vasculitides:
 - Granulomatosis with polyangiitis (GPA)
 - Microscopic polyangiitis
- Less common pulmonary vasculitides:
 - Goodpasture
 - Eosinophilic granulomatosis with polyangiitis (previously: Churg Strauss)

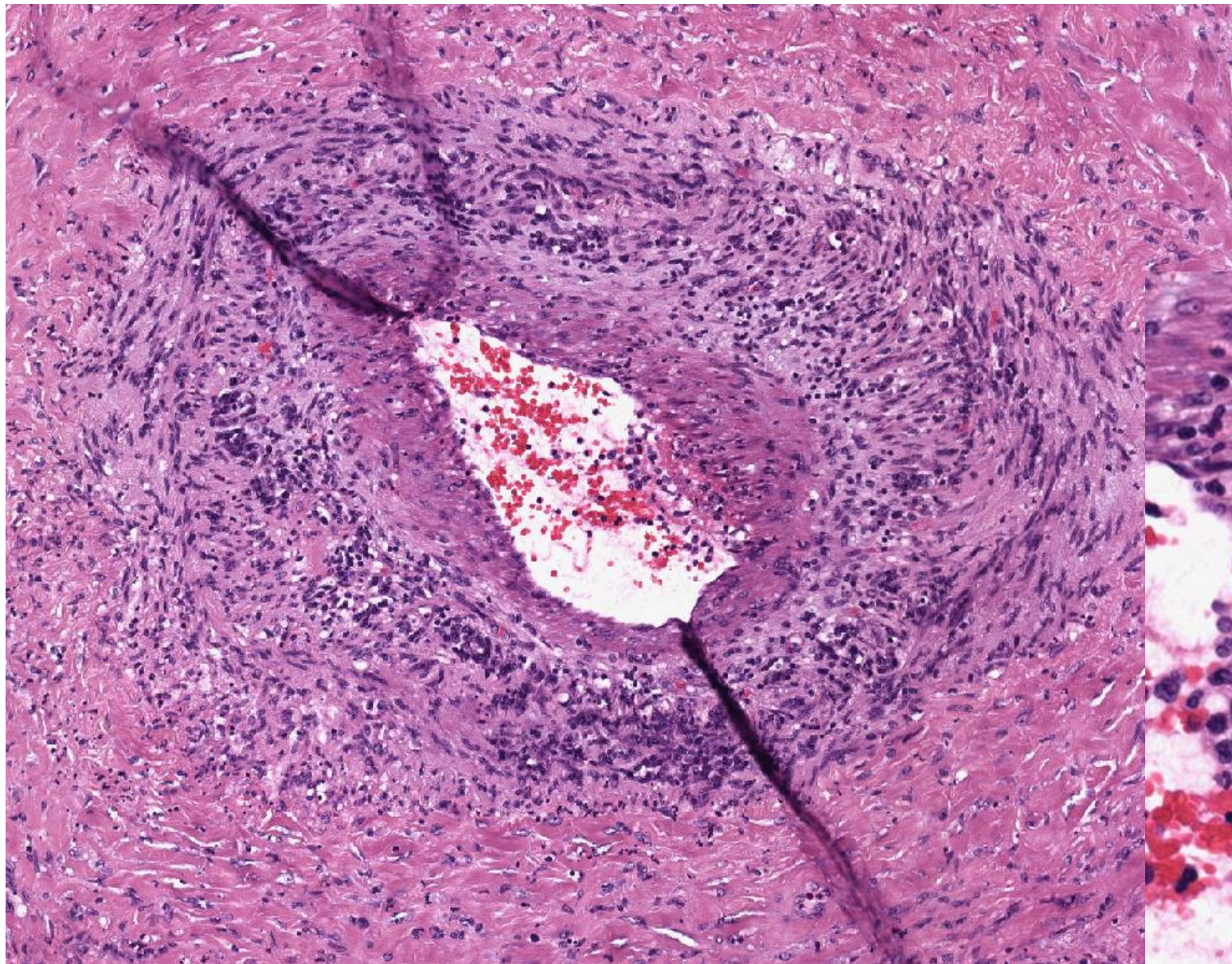
Granulomatosis with Polyangiitis

- GPA can affect arteries, arterioles, capillaries, venules, and veins
- Histopathology:
 - Transmural vascular infiltration with inflammatory cells
 - Neutrophils
 - Lymphocytes
 - Multinucleated giant cells
 - Eosinophils (not abundant)
 - Associated with granulomatous inflammation in the surrounding tissue
- Unique features of granulomatous inflammation: palisading histiocytes oriented with their long axis perpendicular to the necrotic center
- May be ANCA positive (c-ANCA; antiproteinase-3)

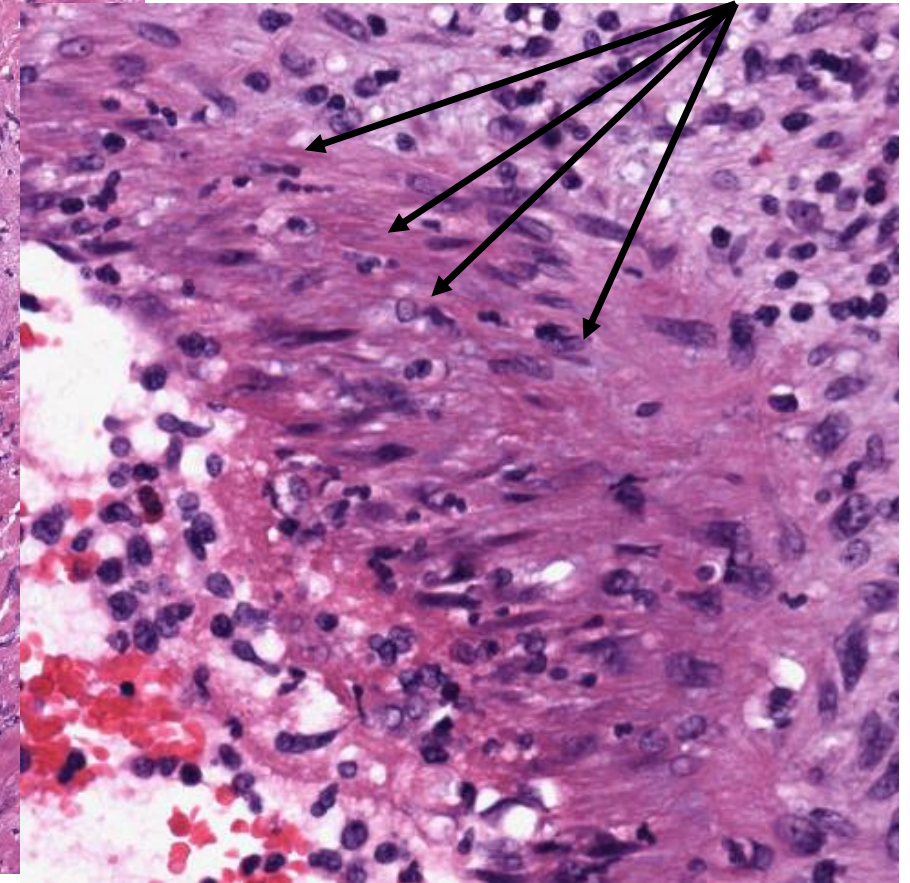
Microscopic polyangiitis

- Unlike GPA, there are no necrotizing granulomas
- Pulmonary presentations can be similar with capillaritis in diffuse alveolar hemorrhage
- Other manifestations:
 - Nodules
 - Interstitial lung diseases
 - Bronchial inflammation and stenosis
- May be ANCA positive (p-ANCA; antineutrophil cytoplasmic autoantibodies)
- Both diseases require immunosuppression



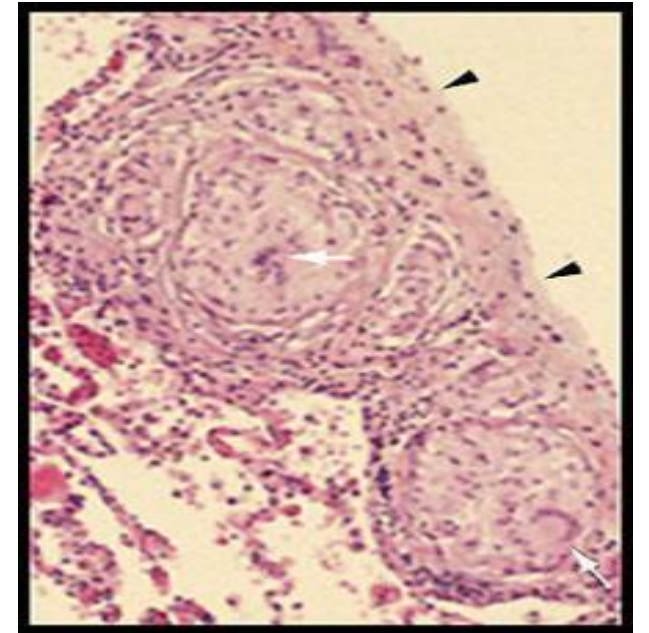


Closer up view:
Neutrophils in
the vessel wall



Sarcoidosis

- Multisystem inflammatory disorder
- May affect airways, interstitium, and lymph nodes
- Mechanism: lymphocytic inflammation that causes non-caseating granulomas
- Important to rule out infections
- May affect several organs:
 - Eyes
 - Brain
 - Kidneys
 - Liver
 - Skin



Pneumonitis

- Can be idiopathic or secondary
- Causes of pneumonitis:
 - Connective tissue diseases e.g. systemic sclerosis, rheumatoid arthritis
 - Inhalational injury e.g. toxic fumes, silica
 - Organic antigens e.g. bird feathers, mushroom spores, mold
 - Respiratory distress
 - Surfactant deficiency
 - Drugs e.g. checkpoint inhibitors, monoclonal antibodies, platinum-based chemotherapy

Mechanisms of pneumonitis

- Lymphocyte mediated (CD8+ T cells): hypersensitivity pneumonitis
- Eosinophil mediated: acute and chronic eosinophilic pneumoniae
- Chemical: aspiration
- Radiation
- Collagen deposition and fibroblast proliferation (osteopontin, surfactant protein D, matrix metalloproteinases, TGF- β): fibrosis
- Organic antigens: avian antigens, mold, mushroom
- Inorganic antigens: coal, silica, asbestos, cobalt

After vaping-related illness, t
year-old's'

Adam Hergenreder's vaping habit alr
more than 450 lung illness associate

The latest weekly tally includes 275 more reports of patients
sickened, in 46 states. There are now 12 deaths linked to

Health department confirms first case of vaping-associated lung injury in Oklahoma

POSTED 10:31 AM, SEPTEMBER 26, 2019, BY [K. BUTCHER](#), UPDATED AT 02:40PM, SEPTEMBER 26, 2019



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A new culprit in pneumonitis: vaping!

- E-cigarettes are battery-operated devices that heat a liquid and deliver an aerosolized product to the user: electronic nicotine delivery system
- 2006 was the year marking the entry of vaping to the US market
- In 2019, there is an ongoing surge in reported cases of acute lung illnesses, including death
- 84% of patients reported having used tetrahydrocannabinol products in e-cigarette devices
- As of September 2019, the CDC has confirmed more than 350 cases in 36 states, which it declared as an “epidemic of severe lung disease”

Vaping: prevalence and popularity

- 2013: 8.5 % of adults report ever having used an e-cigarette/vaping
- 2016: the percentage had increased to 15%
- 2018:

2 % of high school students reported current use of e-cigarettes.

5% of middle school students reported current e-cigarette use.

(esp the “Juul” branded vaping devices).



Juul are cheap, easy to use, and popular

“Starter kit” including device, charging dock, 4 flavor pods runs \$29.99.

Private company based out of San Francisco, 2018 revenue of \$2 billion.

“Juuling” is a term significant with vaping use the Juul device.



Vaping nomenclature

- **Dripping** refers to dripping a few drops directly onto heating element
- **Dabbing** refers to using a device to inhale vapors from “dabs” which are supposed to be concentrated THC in an oil/wax preparation.
 - ❑ **Oil:** oily base extract of marijuana referred as Butane Hash Oil or Honey Oil
 - ❑ **Shatter:** glassy solid concentrate of oil that has been heated in a vacuum oven
 - ❑ **Budder:** solvent extraction of dried marijuana with an oil product that is “whipped”
 - ❑ **Wax:** yellowish cured marijuana that feels waxy



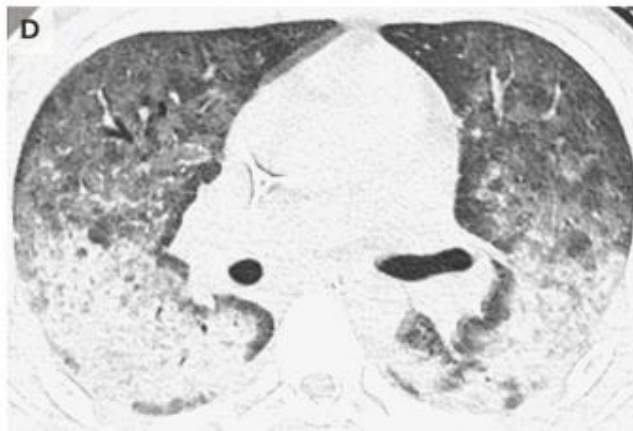
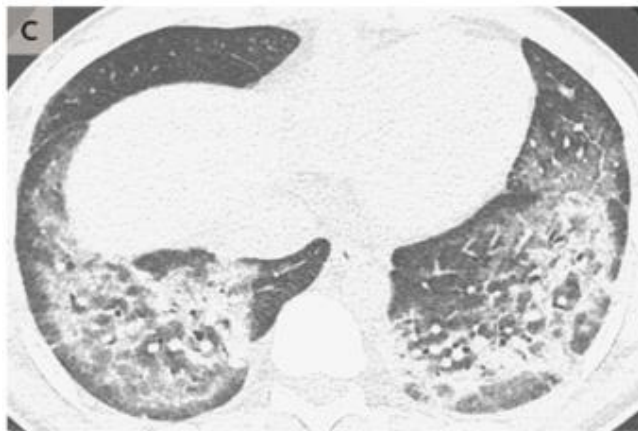
Possible culprits

- Flavorants
 - e.g. diacetyl, a chemical linked to severe lung disease
- Volatile organic compounds
- Heavy metals
 - Nickel
 - Tin
 - Lead
- No one specific liquid or device has been identified as the causative agent
- Illnesses have been reported with the use of nicotine, THC, and CBD

Acute presentation of vaping-related illness

- Nearly 100% of patients have respiratory symptoms
- All patients have bilateral pulmonary infiltrates
- 94% of patients hospitalized
- 32% of patients intubated
- 84% of patients reported using Tetrahydrocannabinol
- Median age: 19 years
- %males: 83%

Acute presentation of vaping-related illness



Cytopathology

- A high level of lipid-laden macrophages with oil red O stain
- Only few biopsies performed
- Identified pathologies and types of pneumonitis:
 - Mild and nonspecific inflammation
 - Acute diffuse alveolar damage and foamy macrophages
 - Interstitial and peribronchiolar granulomatous pneumonitis
 - Chemical pneumonitis
 - Acute eosinophilic pneumonia
 - Acute and subacute hypersensitivity pneumonitis
 - Lipoid pneumonia
 - Metal fume fever
 - Polymer fume fever

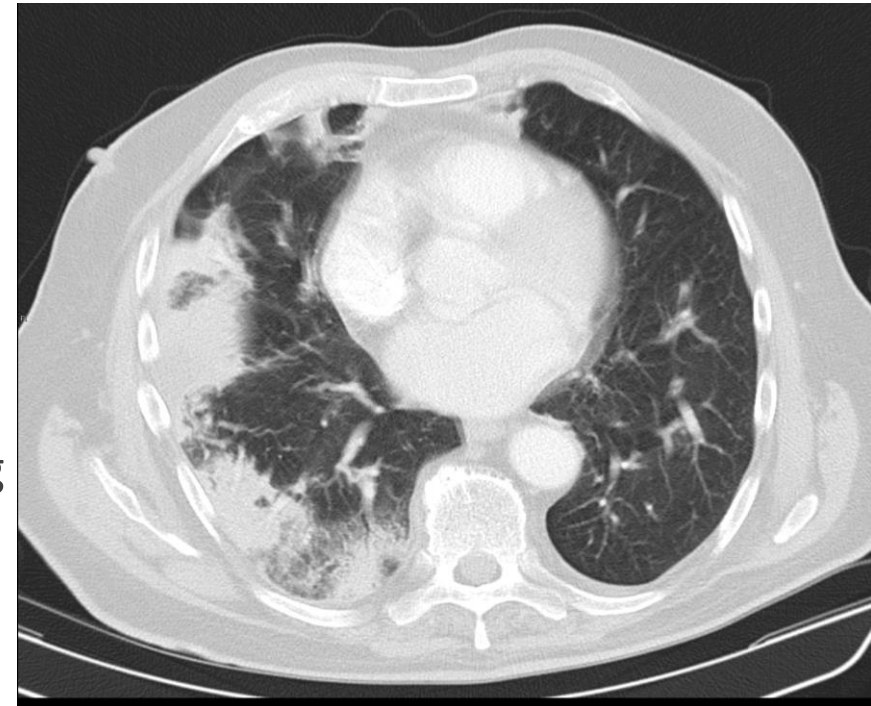
Reporting to the CDC

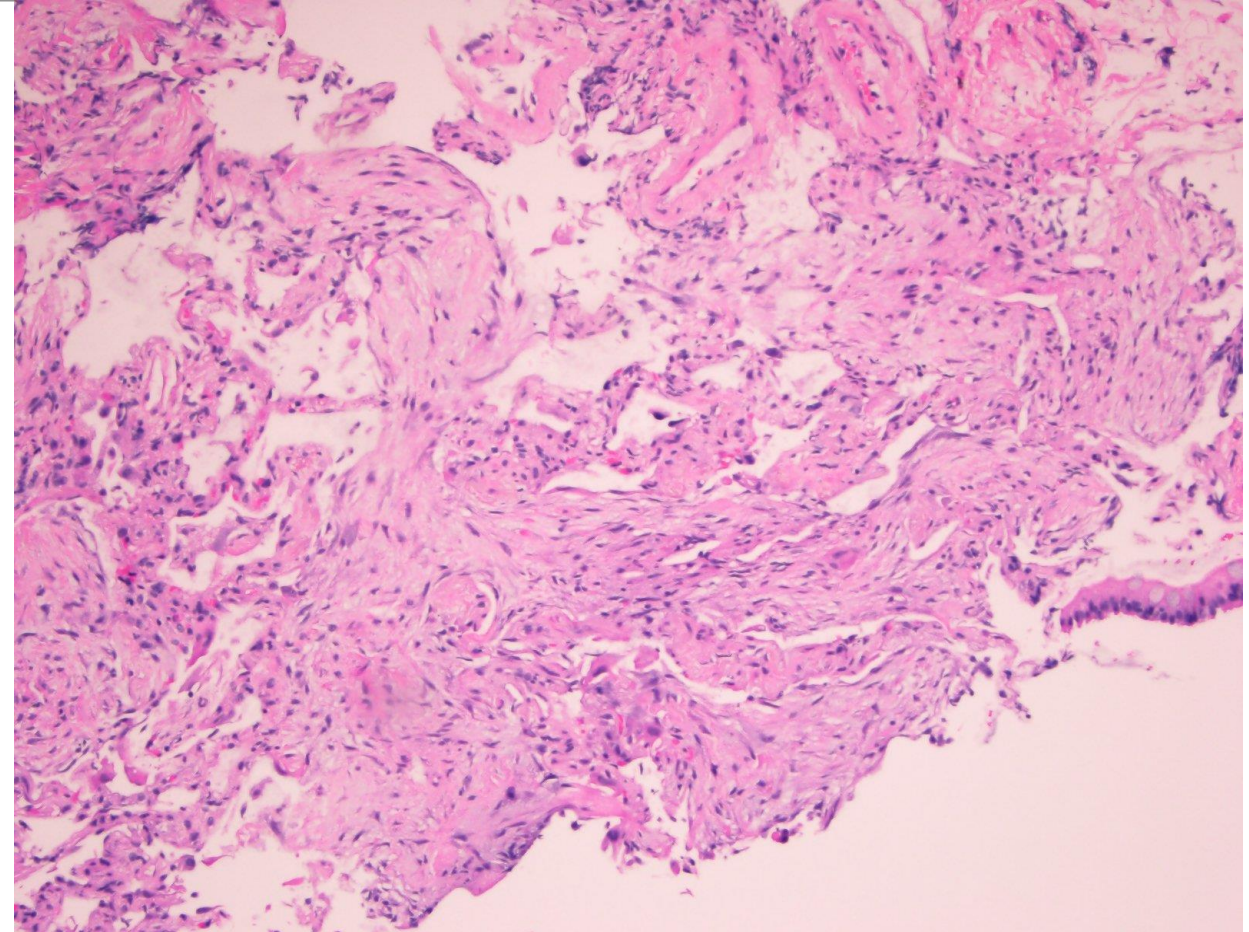
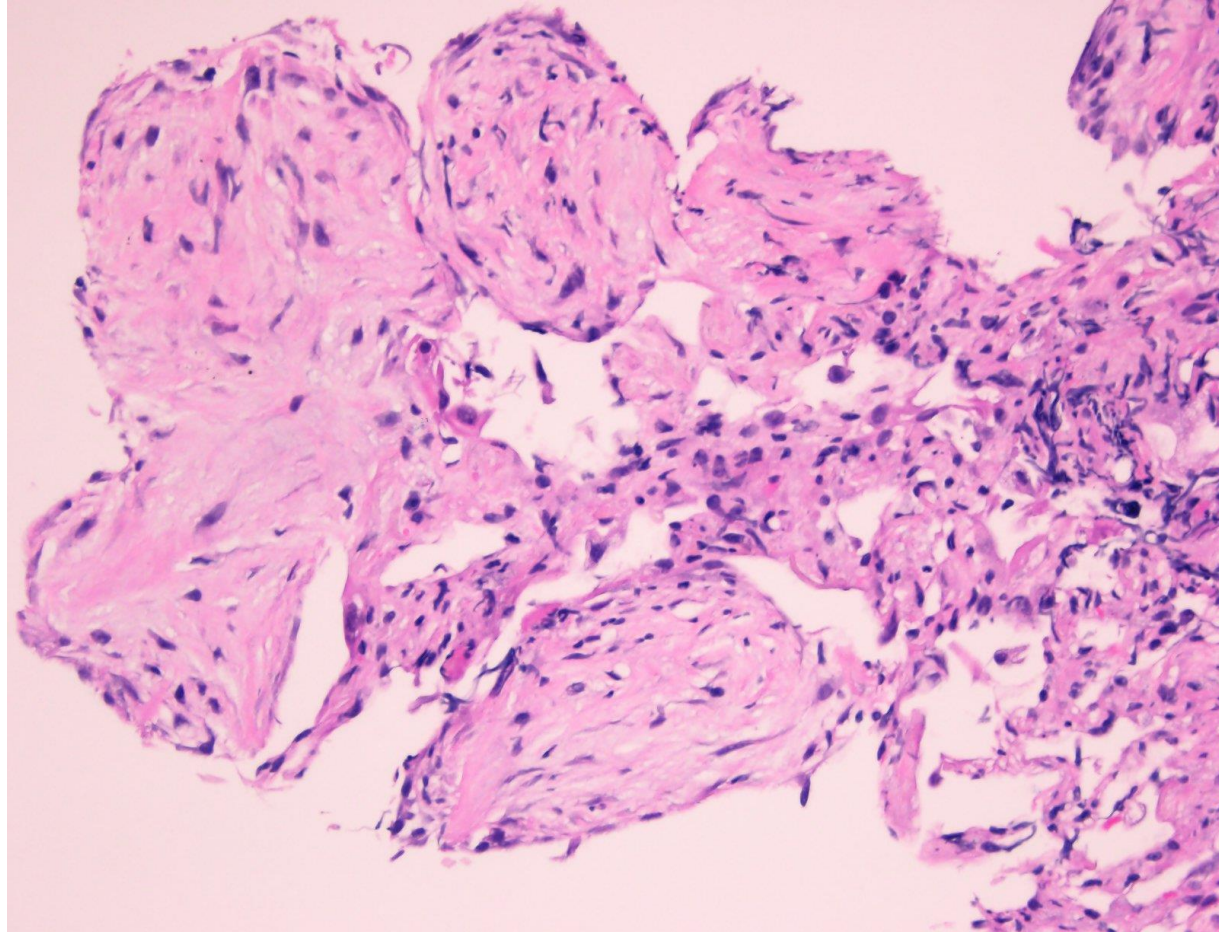
The CDC recommends that clinicians report cases of vaping-related illnesses to their state or local health department, as well as the FDA at <https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=cc7873df-0590-49ec-9d71-ecbf742d34e3> and collect the following information

- ☐ Type of device(s) used (e.g. bottles, cartridges or pods)
- ☐ Specific type(s) of liquid used (e.g. nicotine, THC products, flavored fluids)
- ☐ Were devices, liquids, refill pods and/or cartridges shared with other people?
- ☐ Were old cartridges or pods reused with other homemade or commercial products?
- ☐ Were devices used to inhale drugs that were concentrated by heating prior to vaping (i.e., “dabbing”)?
- ☐ Details of vaping behavior (e.g. cloud volume, frequency of puffs, ‘zero’ or ‘stealth’ vaping, valsalva at end inhalation).

Organizing Pneumonia

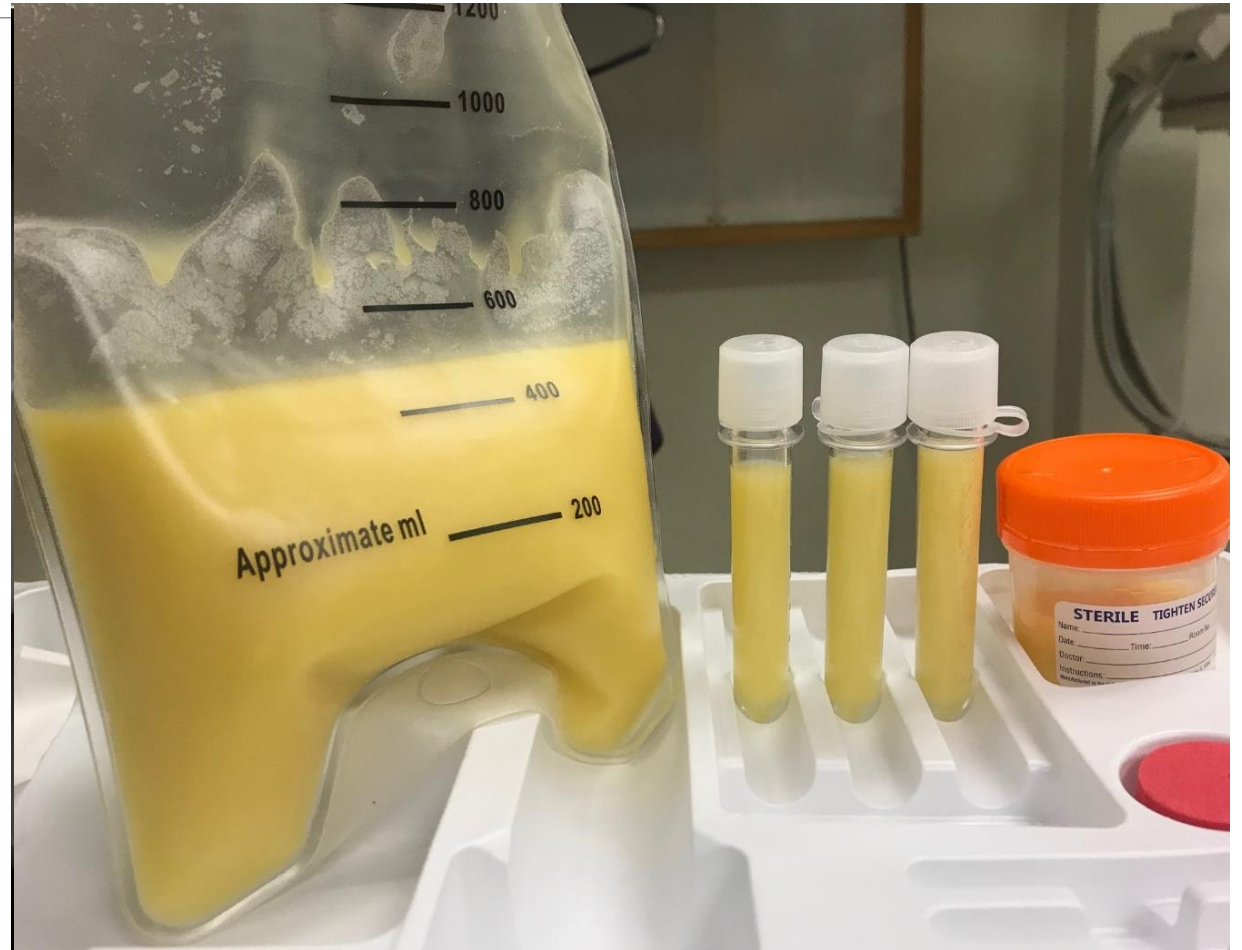
- Can occur without discernible cause (cryptogenic) or associated with connective tissue disorders, drugs, or following an injury
- Usually presents like a typical bacterial pneumonia
 - Fever, cough, malaise, dyspnea
- Patient improves slightly after initiation of antibiotics
- However, condition recurs with similar presentation
- Might be difficult to diagnose
- High lymphocyte count on bronchoscopic lavage
- Chest imaging: peripheral subpleural consolidations with varying locations during different presentations
- Treatment: corticosteroids





Case Study

- 60 y o F with RA presents with mild dyspnea and right pleural effusion
- Pleural pressure turns negative during thora as she develops chest pain
- Fluid analysis:
 - pH: 7.18
 - Glu <10
 - Protein: 4.9
 - LDH: 1681
 - Triglycerides: 21
 - Cholesterol: 388



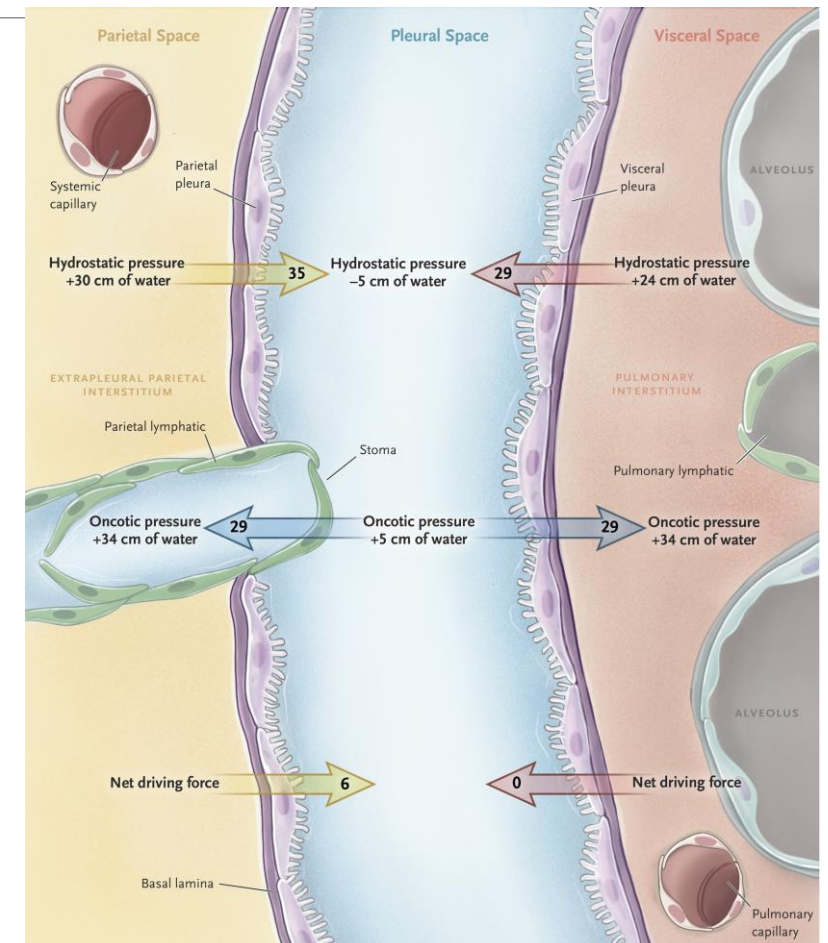
Pleural Effusion

A very common entity

- 1-1.5 million new cases/y in USA
- 80,000-160,000 new cases of malignant effusions/y

Characteristics of pleural space:

- Pressure: -3 to -5 cm H₂O
- Volume: 0.26 mL/kg
- Produced and absorbed by **parietal** surface
- Parietal lymphatic vessels are responsible for resorption
- Resorption rate can increase 20 times in response to increased fluid formation



Non-Malignant Effusions

Broad variety and many causes

Often poorly understood

Hard to classify

Main divisions:

- Transudate vs exudate
- Unilateral vs bilateral
- Infectious vs non-infectious
- Subclinical vs symptomatic

Exudative effusions

Infectious: bacterial, viral, tuberculosis-related, fungal, parasitic

Neoplastic: metastatic disease (e.g., lung cancer, breast cancer, lymphoma, myeloma, ovarian cancer, pancreatic cancer, cholangiocarcinoma), mesothelioma, primary body-cavity lymphoma

Paramalignant effusions: reactive pleuritis due to underlying lung cancer, airway obstruction or atelectasis, radiation-induced pleuritis

Reactive: reactive pleuritis due to underlying pneumonia (i.e., parapneumonic)

Embolic disease: pulmonary embolism

Abdominal disease: pancreatitis, cholecystitis, hepatic or splenic abscess, esophageal perforation after esophageal varix sclerotherapy

Cardiac or pericardial injury, including myocardial infarction (after coronary-artery bypass, cardiac surgery, or cardiac ablation procedures), pulmonary-vein stenosis

Gynecologic: ovarian hyperstimulation, Meigs' syndrome, endometriosis, postpartum complications

Collagen vascular disease: rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, familial Mediterranean fever, eosinophilic granulomatosis, granulomatosis with polyangiitis

Medications: nitrofurantoin, dantrolene, methysergide, dasatinib, amiodarone, interleukin-2, procarbazine, methotrexate, clozapine, phenytoin, β -blockers, ergot drugs

Hemothorax

Chylothorax (most commonly seen after trauma or in patients with lymphoma)

Sarcoidosis

Lymphoplasmacytic lymphoma

Cholesterol effusions (commonly seen in tuberculosis, rheumatoid effusions, and any other chronic pleural effusion)

Miscellaneous: benign asbestos pleural effusion, yellow nail syndrome, uremia, drowning, amyloidosis, electrical burns, iatrogenic effusion, capillary leak syndromes, extramedullary hematopoiesis

Non-Malignant Effusions

Management predominantly focuses on relief of symptoms

Mortality often depends on the underlying cause

They cause substantial morbidity

Adequate treatment relies on identifying an underlying etiology

Transudative effusions

Congestive heart failure

Cirrhosis

Nephrotic syndrome

Glomerulonephritis

Peritoneal dialysis

Hypoalbuminemia (typical serum albumin, <1.5 mg/dl)

Atelectasis

Superior vena cava obstruction

Trapped lung

Sarcoidosis

Peritoneal dialysis

Myxedema

Cerebrospinal fluid leak or ventriculopleural shunt

Urinothorax

Pulmonary arterial hypertension

Pulmonary embolism

Pericardial disease

Extravascular migration of central venous catheter

Common Causes

More than 50 etiologies

Transudative: cardiac (CHF, constriction), renal (nephrotic Sd), or hepatic (cirrhosis, hypoalbuminemia) origin

Exudative: excess inflammation (malignancy, infection, autoimmune, pancreatitis, PE, post-CABG, esophageal rupture...)

The most common cause of a transudate (and effusions as a whole) is [heart failure](#)

Up to 57% of patients with pneumonia develop an effusion

Conclusion and Clinical Pearls

- Inflammation can affect any lung structure
- Certain pulmonary inflammatory conditions are associated with systemic manifestations
- Beware of vaping associated pulmonary inflammation and consult a specialist early

New commandment

Thou shalt not vape!

Thank you!

