LUNG INFECTIONS

Kenneth Alonso, MD, FACP

Pneumonia

- Sixth leading cause of death in US
- Signs and symptoms
- Fever and productive cough
- Elderly often have no fever
- Malaise
- Shortness of breath
- Late inspiratory crackles
- Increased tactile fremitus with consolidation
- (Pleuritic) chest pain
- Usually with effusion
- May have friction rub (if fibrinous pleuritis)

Pneumonia

- Egophony, if present, increases likelihood of pneumonia (LR+, 8.6).
- Dullness to percussion diagnostic of pleural effusion (LR+, 18.6; LR-, 0.04)
- Neither a normal chest examination nor a normal chest x-ray excludes the diagnosis of pneumonia.
- Elderly may be dehydrated
- Insufficient circulating volume to manifest inflammatory changes on chest x-ray
- Elderly may not present with an elevated white blood cell count
- BUT show shift to the left with many band forms

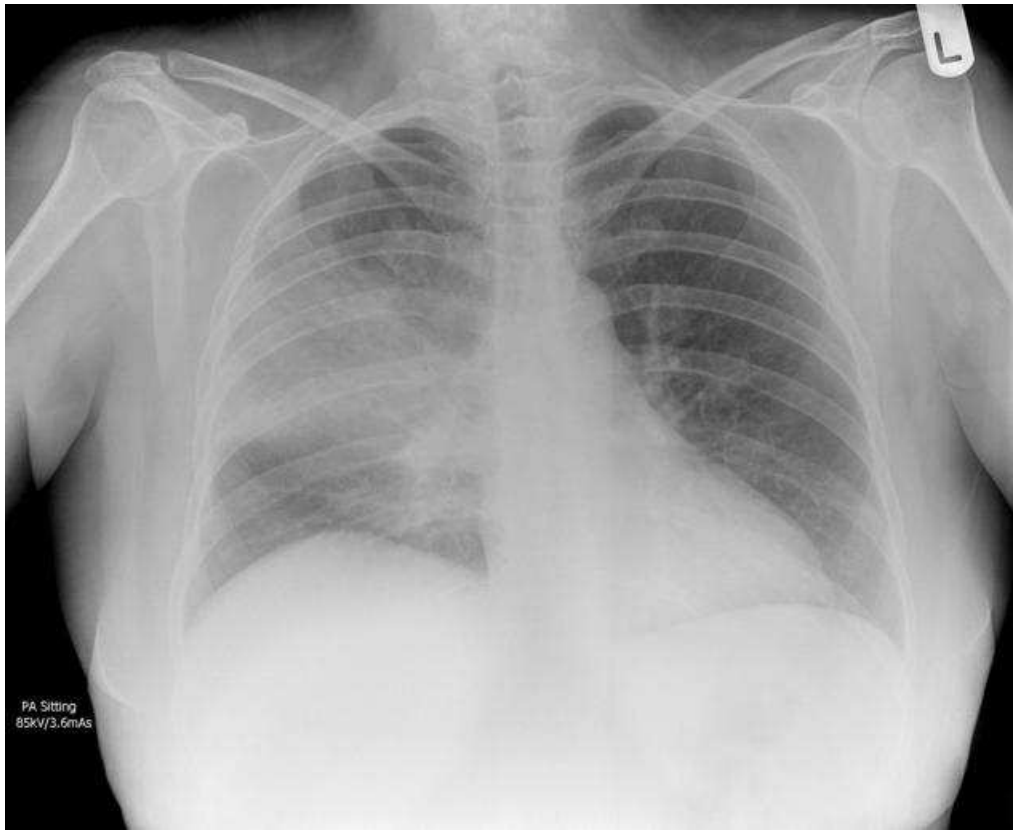
Bronchopneumonia

- Centered on bronchi
- Neutrophils in bronchi, bronchioles and adjacent alveolar spaces
- If lipid laden microphages, it is called lipid pneumonia
- One or more lobes of lung
- Right middle lobe or lower lobe
- Patchy distribution of neutrophilic infiltrate and bacterial organisms (microabscesses) in one or many lobes
- May progress to lobar pneumonia

Lobar pneumonia

- May be due to extension of existing bronchiolitis or bronchitis
- Confined to one lobe of lung
- Congestion with bacteria and few neutrophils
- Followed by massive congestion with many neutrophils, fibrin, and red cells (red hepatization)
- Gray hepatization (fibrinosuppurative exudate as red cells have broken down)
- Resolution with resorption of exudate
- OR organization (fibrosis)

Lobar pneumonia



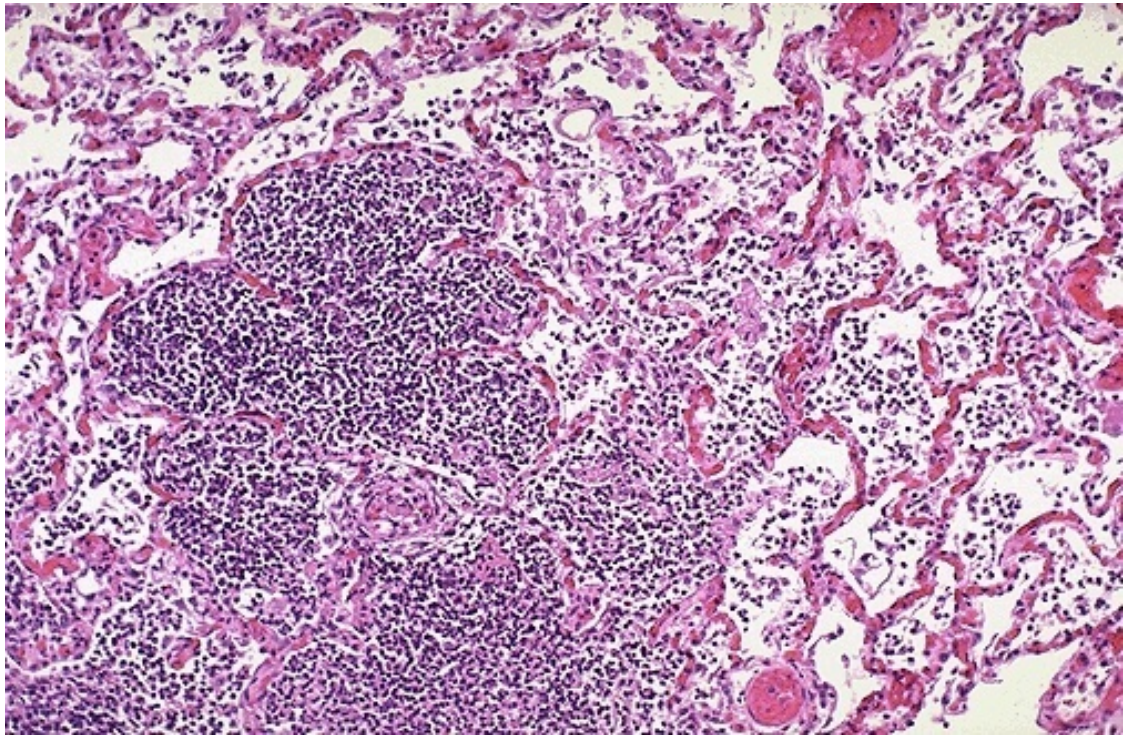
Relative sparing of bronchi (air bronchogram).

Infection spreads across segmental boundaries.

Spread facilitated by pores of Kohn and canals of Lambert.

https://radiopaedia.org/articles/lobar-pneumonia
Accessed 12/10/2019

Pneumonia

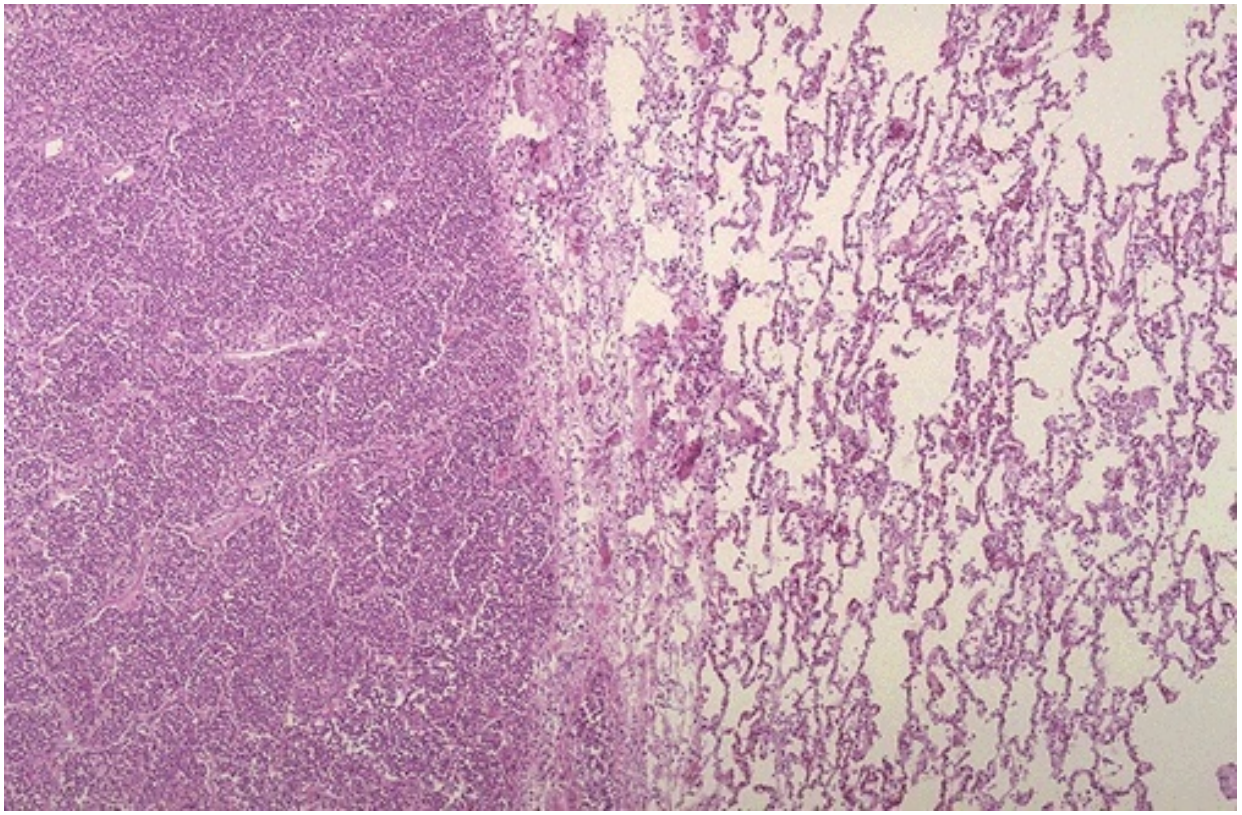


Patchy distribution of neutrophils in alveolar spaces. The initial stage.

Other alveolar structures are intact, permitting preservation of function following resorption of infiltrate.

https://webpath.med.utah.edu/LUNGHTML/LUNG022.html Accessed 12/10/2019

Pneumonia

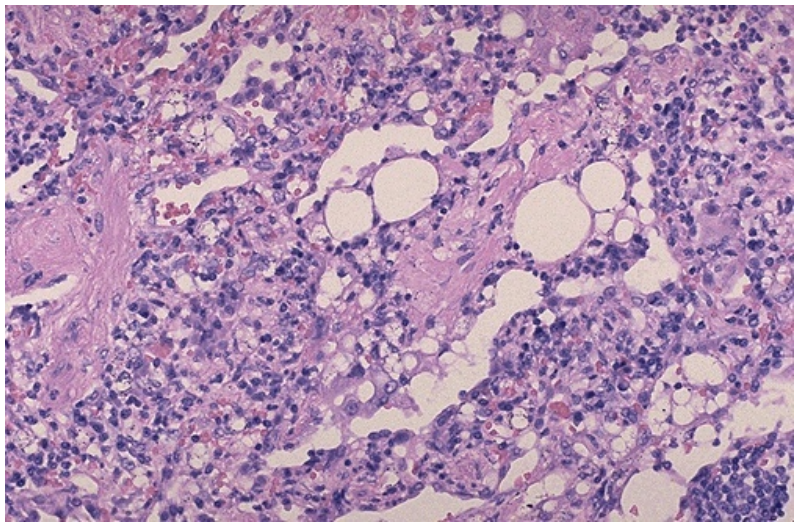


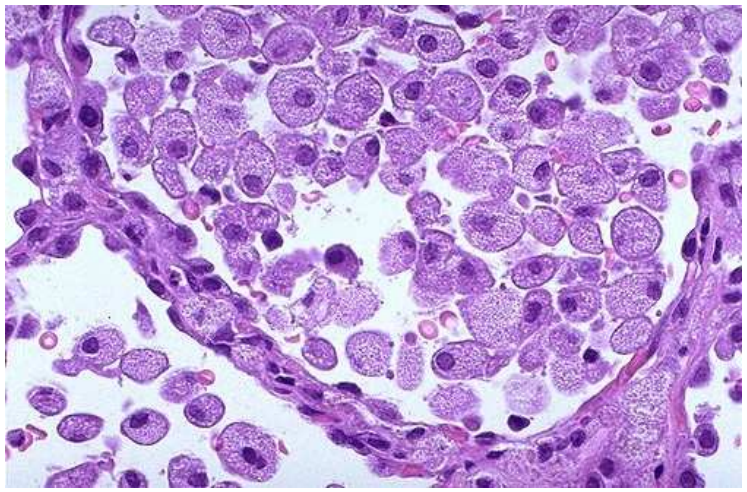
Consolidation on left. Red hepatization.

Lung parenchyma preserved on right.

https://webpath.med.utah.edu/LUNGHTML/LUNG022.html
Accessed 12/10/2019

Lipid pneumonia

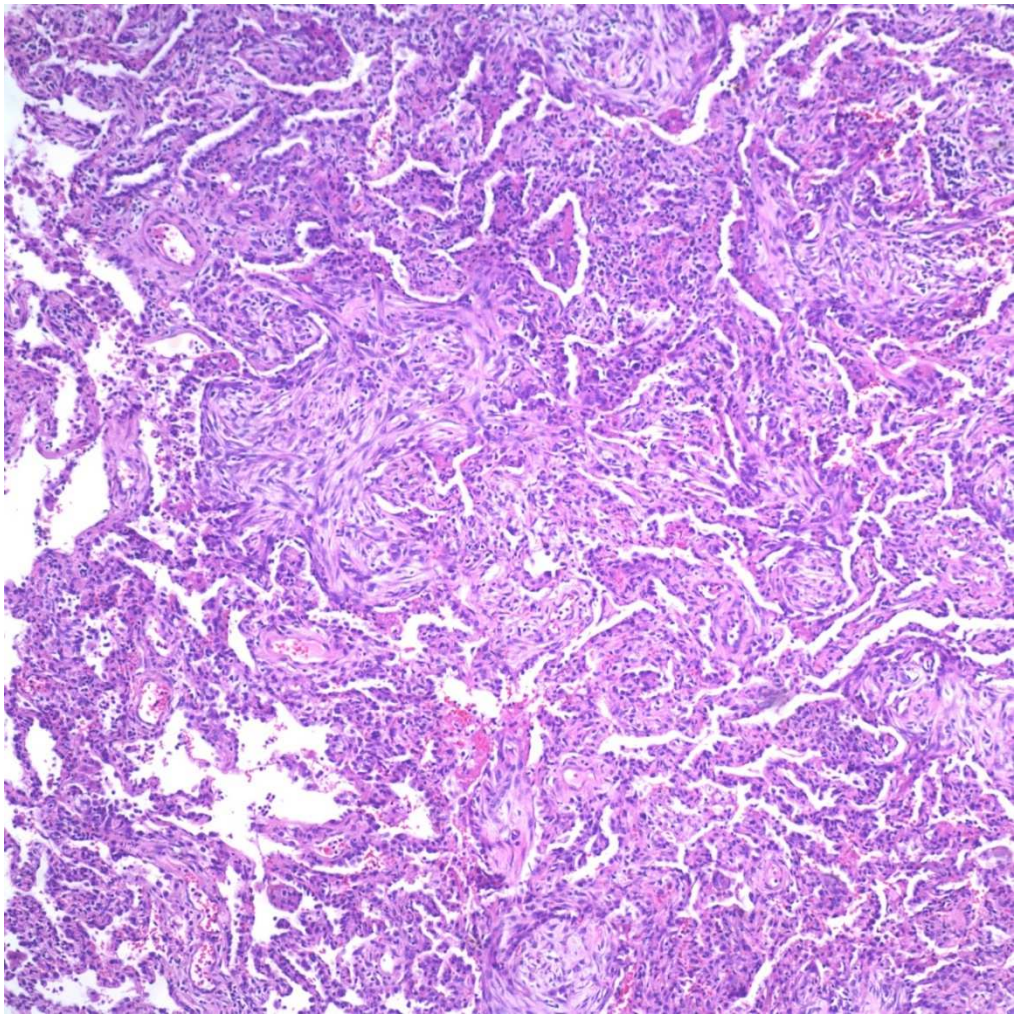




The lung may appear golden brown in the area of injury and repair.
Left is the microscopic appearance of an exogenous lipid pneumonia in which lipid vacuoles appear, mainly along airways, accompanied by an inflammatory response that can contain foreign body giant cells. Vaping, smoke inhalation, oil ingestion as causes.
Right are lipid laden macrophages in an alveolar space. They have ingested lung breakdown products. Often found distal to an obstruction. Are endogenous.

https://webpath.med.utah.edu/LUNGHTML/LUNG 027 and 125.html
Accessed 01/20/2020

Organizing pneumonia



https://media.clinicaladvisor.com/images/dsm/ch4359.fig5.jpg
Accessed 12/04/2019

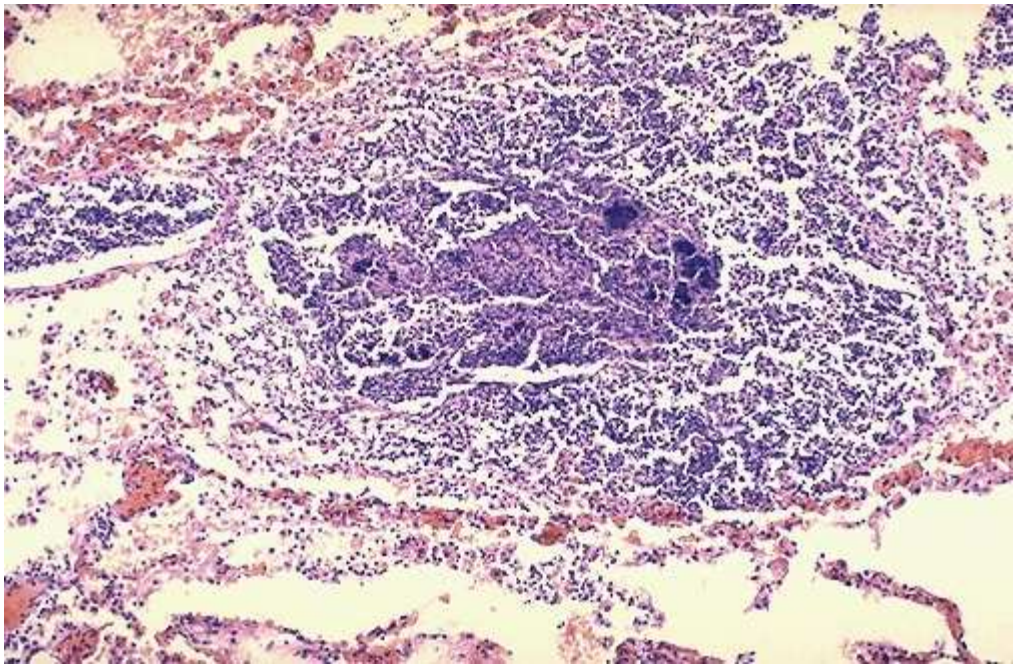
Empyema

- In addition to lobar consolidation, inflammatory material can extend into pleural cavity (empyema).
- Usually Escherichia coli
- Aspiration may lead to bronchial obstruction with inflammation and air trapping distal to the obstruction
- More common on right side as right sided bronchus is more vertical
- Usually single
- Air fluid level present if there is communication with air passages
- May lead to abscess formation
- May extend into pleural cavity as well

Aspiration pneumonia

- Presents with fever, cough
- Foul spelling sputum
- Usual causes
- Sinus and bronchial infections
- Dental sepsis
- Hematogenous spread
- Common agents
- Staph. Aureus
- Strep. Pyogenes
- Klebsiella pneumoniae
- Bacteroides
- Fusobacterium

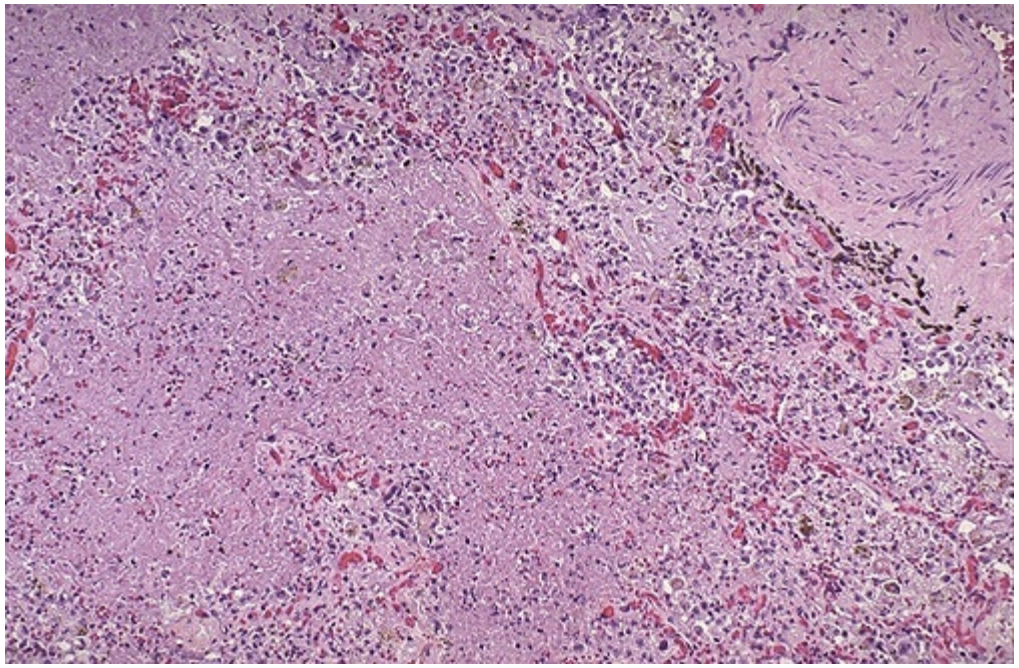
Aspiration pneumonia



Focal abscess with neutrophil exudate. Bacteria at center of abscess.

https://webpath.med.utah.edu/LUNGHTML/LUNG022.html
Accessed 12/10/2019

Abscess



Necrotic tissue on the left, bordered by inflammatory infiltrate and capillary proliferation

https://webpath.med.utah.edu/LUNGHTML/LUNG022.html
Accessed 12/10/2019

Empyema

The pleural surface left demonstrates thick yellow-tan purulent exudate and the pleural cavity is filled with purulent exudate.

The lobe is consolidated.

https://webpath.med.utah.edu/LUNGHTML/LUNG022.html
Accessed 12/10/2019

Bronchiectasis

- Permanent dilatation of bronchi
- Follows bronchial obstruction or infection with inflammation and destruction of bronchi
- Recurrent infections because of the stasis in these airways.
- Copious purulent sputum production with cough is typical.

Bronchiectasis

Dilated bronchi are present
in the mid lower portion of the lung

https://webpath.med.utah.edu/LUNGHTML/LUNG052.html
Accessed 12/10/2019

Pathophysiology

- Pneumonia is due to impairment of normal defense mechanisms or lowered host resistance
- Pathogen inhaled for infected individual
- OR aspirated from nasopharyngeal flora while asleep
- Normal defense mechanisms
- Nasal clearance (sneezing, blowing, swallowing)
- Tracheobronchial clearance (mucociliary action)
- Alveolar (macrophage) clearance

Pathophysiology

- Impairment
- Primary or acquired immunosuppression
- Those who lack a spleen lack the capacity to phagocytose encapsulated bacteria
- Suppression of cough reflex
- Drugs, virus, coma, anesthesia
- Injury to mucociliary apparatus
- Smoking, virus, Kartegener's syndrome
- Macrophage injury
- Tobacco, alcohol, anoxia
- Pulmonary congestion or edema
- Accumulation of secretions (cystic fibrosis)

Causes of pneumonia

- NEONATES (0-4 weeks of age)
- Group B Streptococcus
- E. Coli

- Viral pneumonia may lead to lobar pneumonia

- CHILDREN AND ADULTS
- Streptococcus pneumoniae
- Respiratory syncytial virus (RSV)
- Parainfluenza
- Mycoplasma pneumoniae
- Chlamydophilia pneumoniae

Epidemiology

- Community acquired
- Usually Streptococcus pneumoniae
- Hemophilus influenzae
- Moraxella catarrhalis
- COPD
- Staph. Aureus
- Usually following viral pneumonia
- Intravenous drug users
- Klebsiella pneumoniae
- Debilitated
- Chronic alcoholics
- Mycoplasma pneumoniae
- Influenza A
- RSV, adenovirus

Epidemiology

- Special cases of community acquired disease:
- Pseudomonas aeruginosa
- Cystic Fibrosis
- Legionella pneumophilia
- Multiorgan involvement
- Aspiration of contaminated water

- Hospital acquired
- Pseudomonas aeruginosa (respirator source)
- MRSA
- Enterobacter species
- Clostridium dificile (antibiotic use)

Epidemiology

- Immunocompromised
- Diffuse lung infiltrates
- Cytomegalovirus
- Mononucleosis-like presentation
- Infected cell enlarged with prominent basophilic intranuclear inclusion ("owl's eye")
- Pneumocystis jiroveci
- Insidious onset
- Fever and cough

Epidemiology

- Focal lung infiltrates
- Gram negative bacteria
- Staph. Aureus
- Aspergillus fumigatus
- Candida species

Antibiotic selection based on Gram-stain pending culture results

Prevention of first opportunistic infection (CDC)

- All patients should receive
- Influenza A and B immunization
- Varicella Zoster Virus immunization

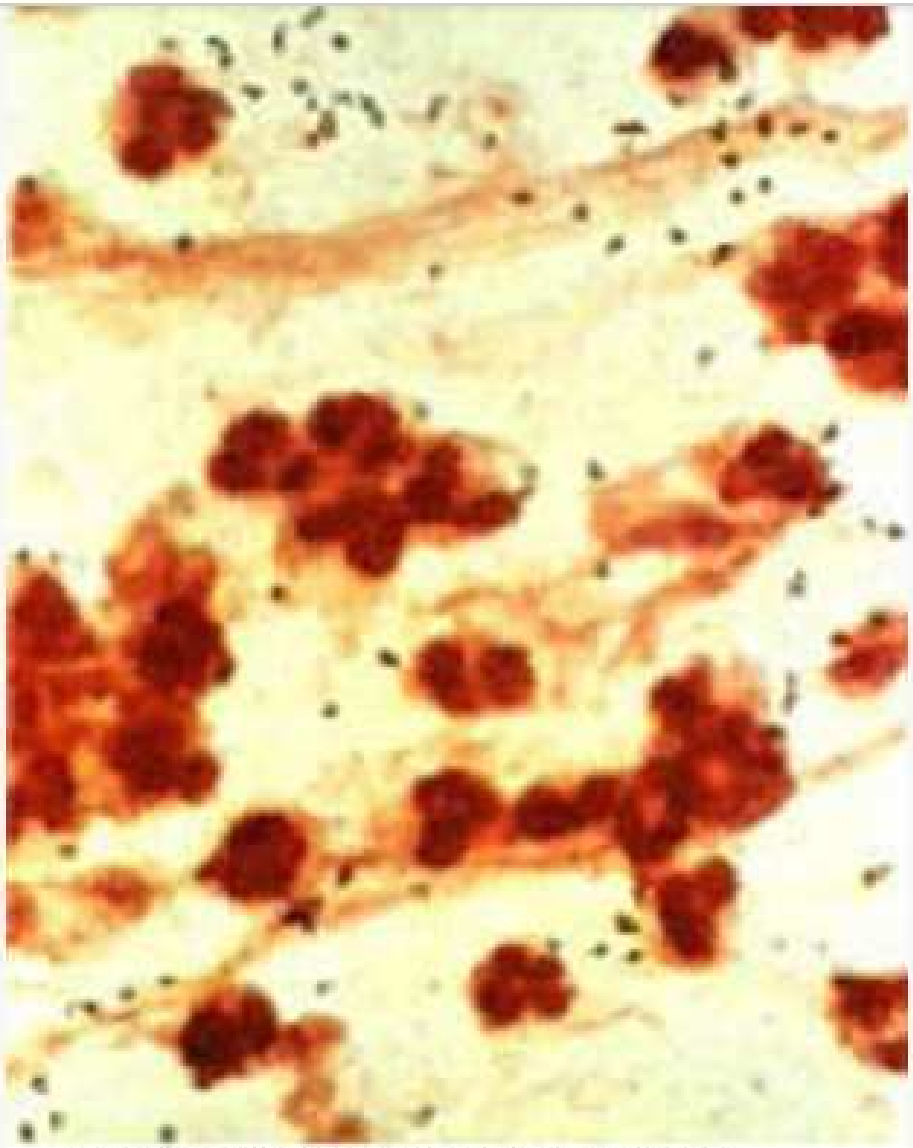
- CD4 >350 cells/ul
- HAV immunization
- HBV immunization
- HPV immunization

Prevention of first opportunistic infection

- CD4 <200 cells/ul
- Fluconazole (If Coccidiodes endemic area)
- Itraconazole (If Histoplasma endemic area)
- Trimethoprim-Sulfamethoxazole (P. jiroveci)
- CD4 <100 cells/ul
- Trimethoprim-Sulfamethoxazole (Toxoplasma gondii)
- Itraconazole (If Talaromyces endemic area)
- CD4 <50 cells/ul
- Azithromycin or Clarithromycin (MAC)

Bacterial pneumonia

- Usually Streptococcus pneumoniae.
- Acute onset of fever and chills, with productive cough
- Consolidation of lobe usual
- Half the patients may also have an effusion with pleuritic pain.
- Rusty sputum is characteristic.
- Other causes:
- Escherichia coli
- Hemophilus influenza (may follow viral infection)
- Staphylococcus aureus (may follow viral infection)



Source: Maxine A. Papadakis, Stephen J. McPhee, Michael W. Rabow:
Current Medical Diagnosis and Treatment 2021

Hemophilus influenzae

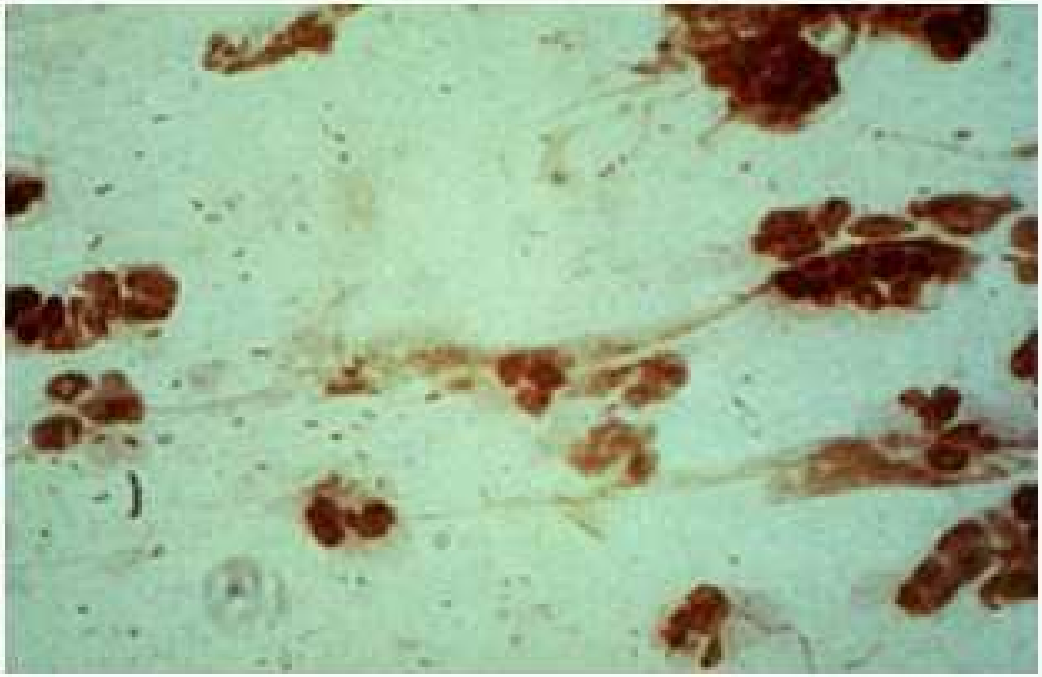
- Pneumonia may follow a viral infection
- Wheezing often the presenting sign
- Descending laryngeo-tracheobronchitis may lead to vocal cord swelling
- Usual cause of right middle lobe pneumonia and lobar consolidation
- Increased density along right heart border on PA chest x-ray with loss of lucency of lower thoracic spine on lateral chest x-ray
- 10-42% mortality rate

Right middle lobe pneumonia

- The usual organism is Hemophilus influenza (Hib)
- In adults over 40 years of age, is associated with:
- COPD
- Alcohol abuse
- Klebsiella pneumoniae
- Thick mucoid sputum characteristic
- May be seen with aspiration
- And later abscess formation as airway impacted
- Also associated with COPD and alcohol abuse
- Moraxella catarrhalis is second most common agent exacerbating COPD

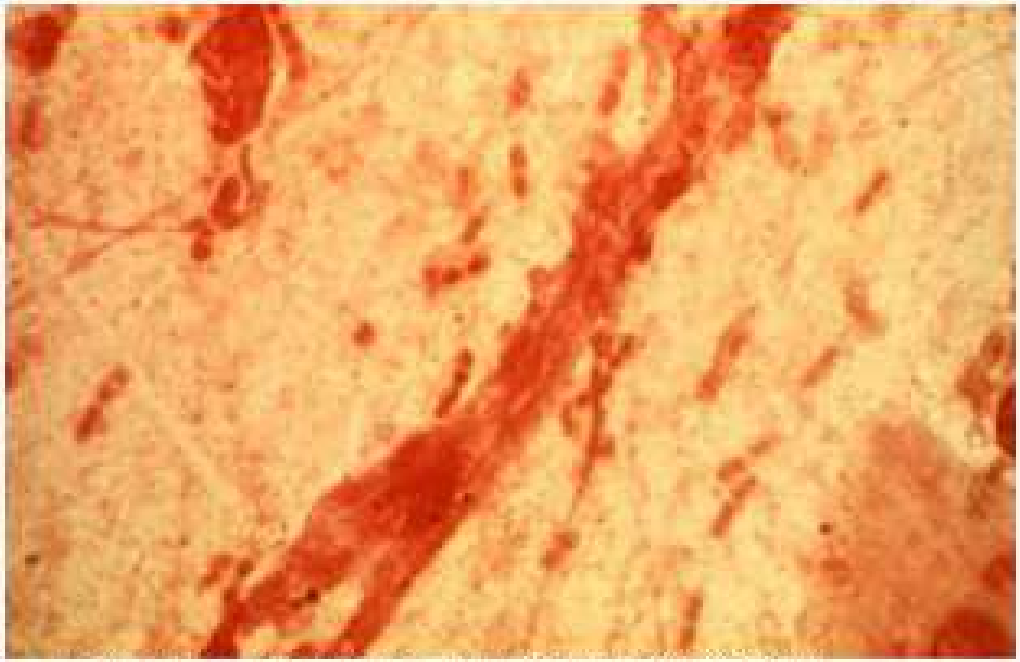
EFIGURE 9–9.

Haemophilus influenzae.

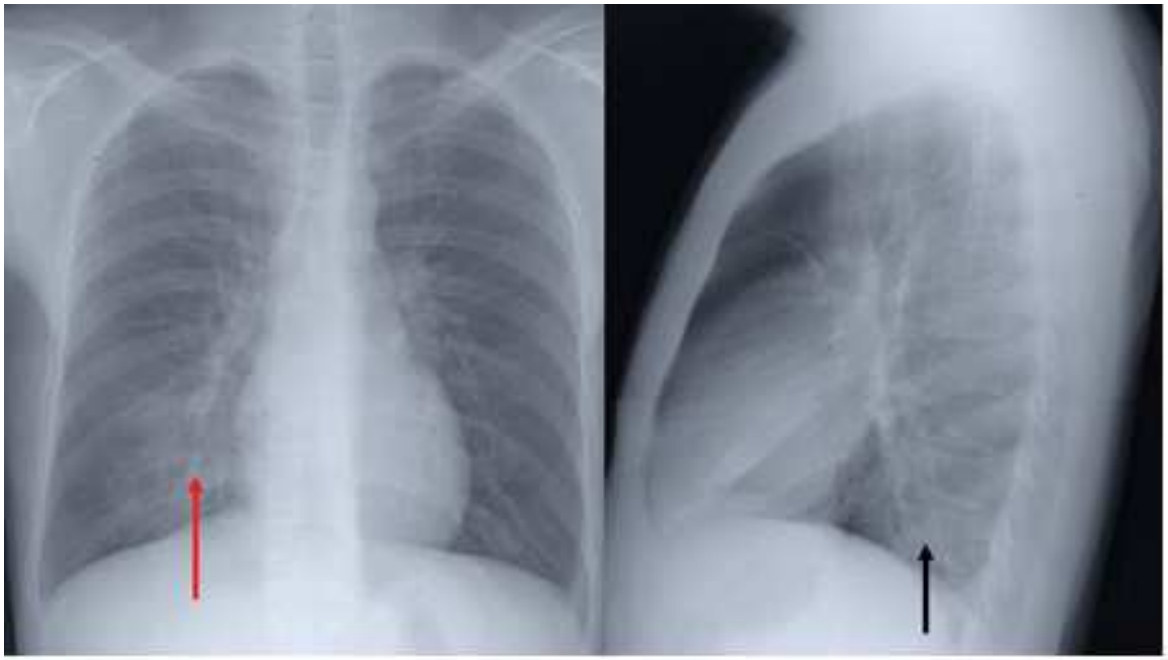


EFIGURE 9–10.

Klebsiella pneumoniae.



Right middle lobe pneumonia



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Subtle opacity on PA film (red arrow), while the lateral film illustrates the "spine sign" (black arrow) where the lower spine does not become more lucent.

Fig. e24-26 Accessed 03/17/2010

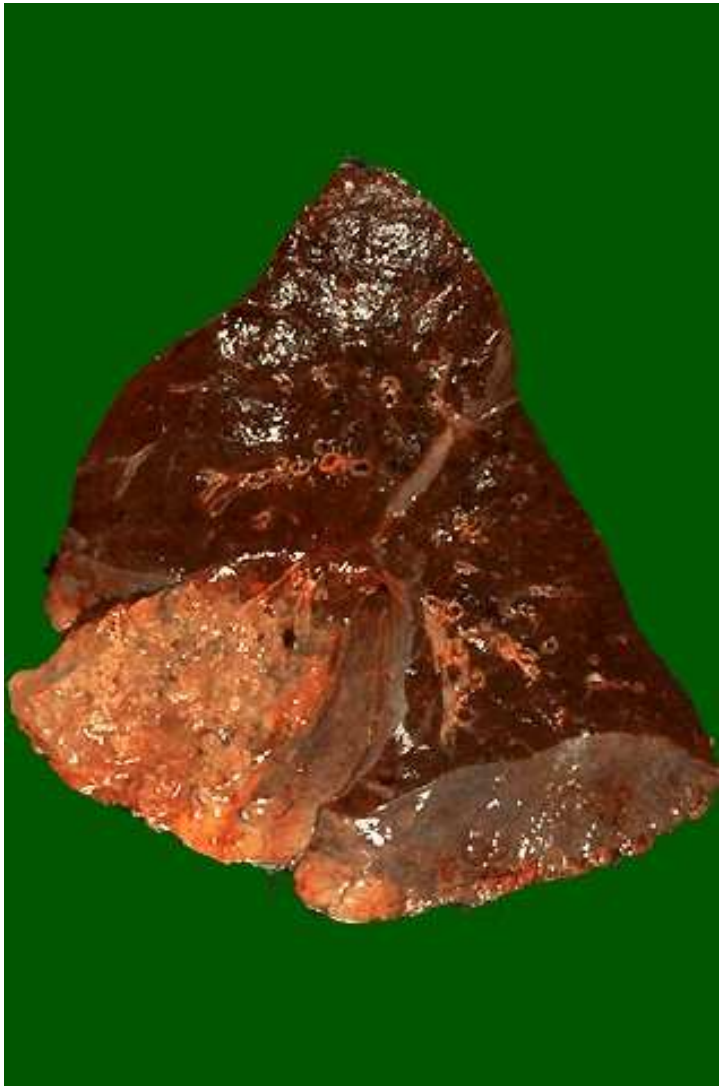
Lung abscess

- Generally due to aspiration of material from the oropharynx
- Obtunded
- Dental caries
- Anaerobes common
- 10-15% secondary to airway obstruction by cancer
- Spiking fever, productive cough (foul smelling)
- May see cavitation n x-ray
- Right side usual site of aspiration

Source: Maxine A. Papadakis, Stephen J. McPhee, Michael W. Rabow:
Current Medical Diagnosis and Treatment 2021

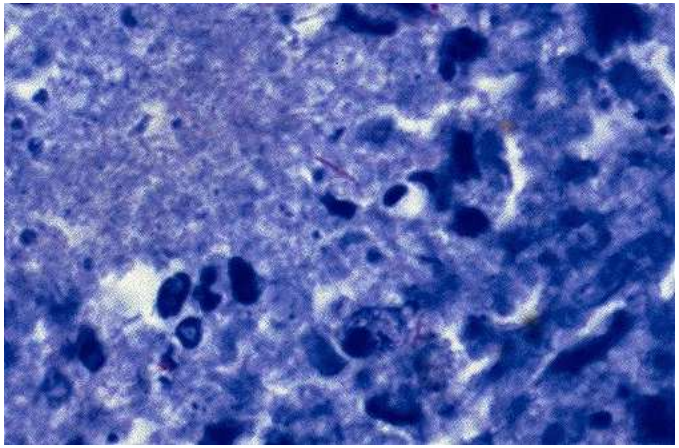
Lung abscesses usually occur in the posterior segments of the upper lobes or superior segments of the lower lobes since these are the most frequent locations for aspiration.

Right middle lobe pneumonia with abscess formation.



Firm, tan middle lobe with chronic abscess formation.

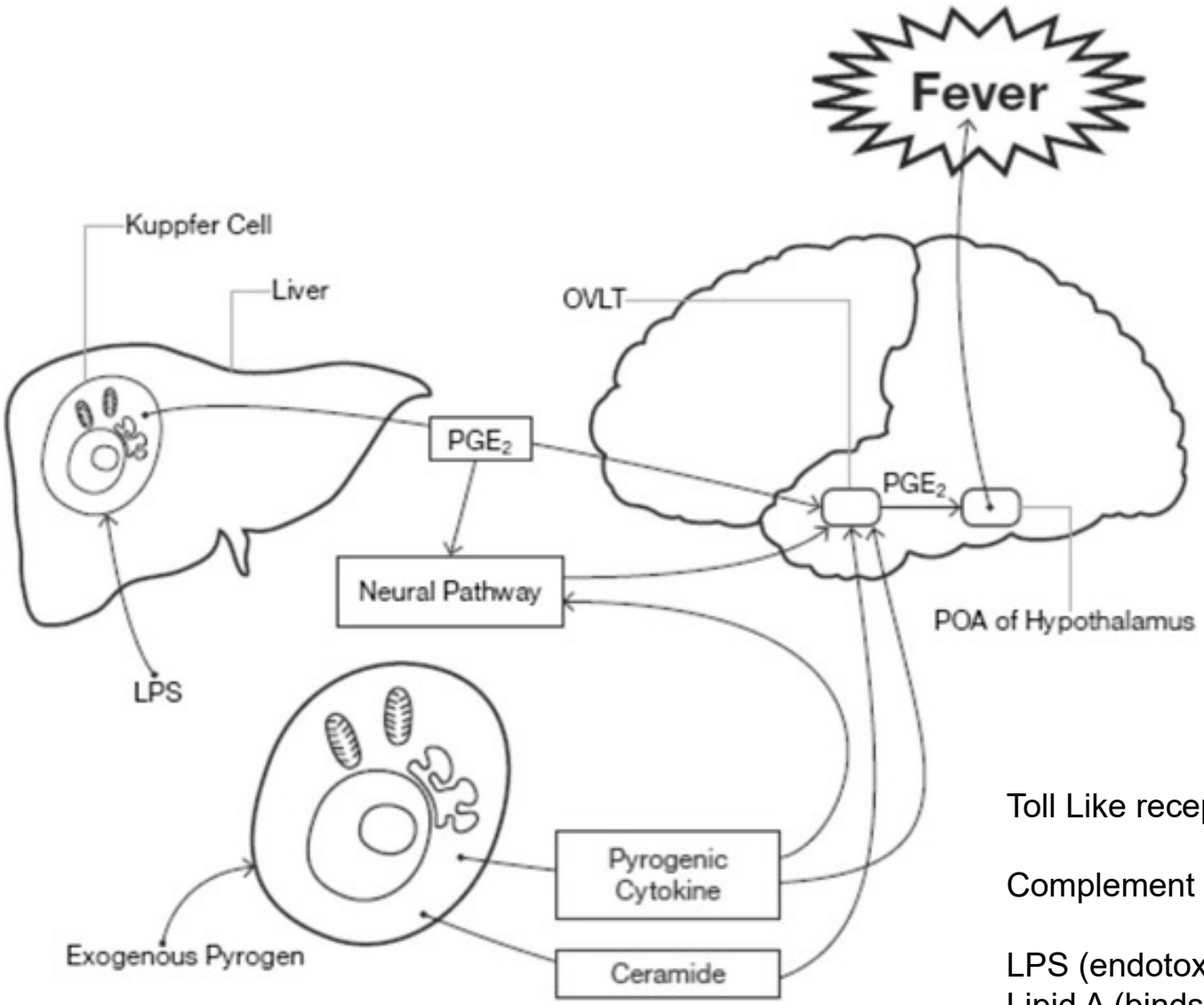
Nocardia as cause.



https://webpath.med.utah.edu/LUNGHTML/LUNG022.html
Accessed 12/10/2019

Fever

- Sepsis accounts for up to 74 % of fever in hospitalized patients
- Fever is a core temperature of 38.3°C (101ºF) or higher
- Normothermia: 37±1ºC (98.6±1.8ºF)
- Hyperthermia: >40ºC (>104ºF)
- The NF-κβ protein family is activated
- Results in a mass release of pro-inflammatory cytokines including TNF-α, IL-1, IL-12, and HIF-1α



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4944485/

Toll Like receptors activated

Complement cascade activated

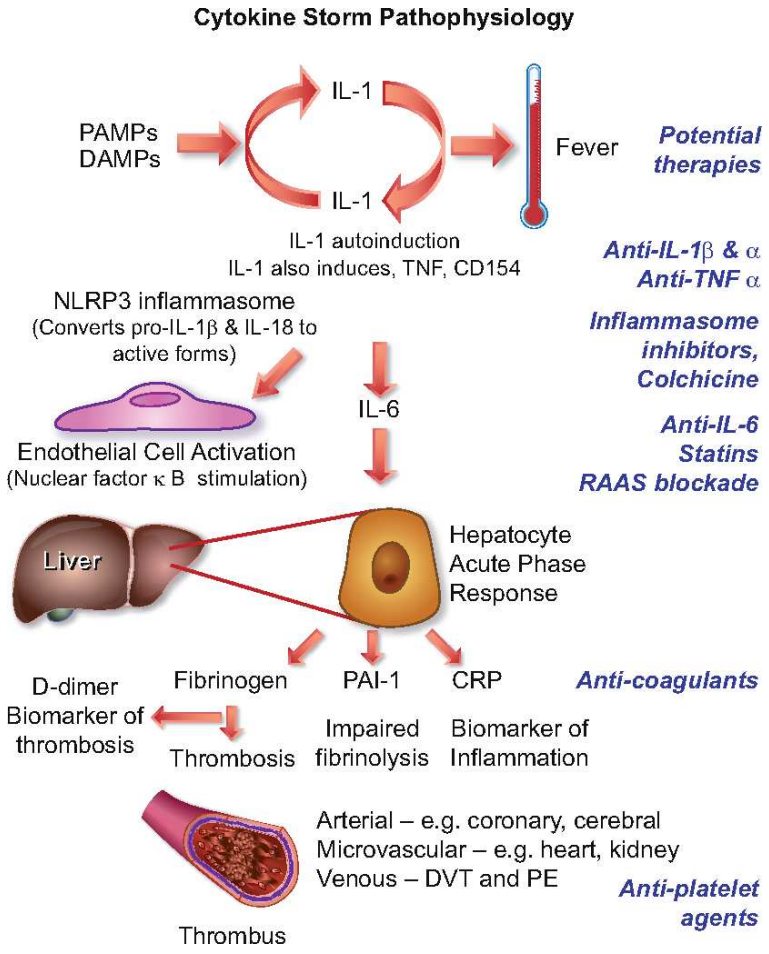
LPS (endotoxin) degrades to Lipid A (binds to monocytes

Ceramide is a bioactive lipid derivative

Fever

- A temperature between 37.5 °C and 39.4 °C is associated with improved outcomes compared with normothermia or hyperthermia.
- In elderly patients with community-acquired pneumonia, the observed mortality rate was significantly higher in patients who lacked fever (29 %) when compared with patients who developed a febrile response (4 %)
- A temperature greater than 38.2 °C has also been found to have a protective role against invasive fungal infections.

Figure 2 Cytokine storm. Proinflammatory cytokines such as IL-1 and TNF-α induce each other's gene expression, ...



Eur Heart J, Volume 41, Issue 32, 21 August 2020, Pages 3038–3044, https://doi.org/10.1093/eurheartj/ehaa623

SIRS

- Cytokine production responsible for the maintenance of fever.
- IL-1, IL-6, TNF-α
- Dysregulation of these mechanisms leads to the sepsis immune response syndrome (SIRS)
- Fever >38C OR <36C
- Heart rate >90/min
- Respiratory rate >20/min
- pCO_2 <37 mmHg
- WBC >12,000 /fL OR <4,000 /fL with 10% bands
- May lead to multi-organ failure

Compensatory anti-inflammatory response syndrome (CARS)

- Restoration of homeostasis
- Release of IL-4 and IL-10, cytokines responsible for decreasing the production of TNF-α, IL-1, IL-6, and IL-8.
- Normally a major characteristic of the CARS response is a Th1 to Th2 switch to restore hemostasis
- In some patients there is a complete down regulation of both Th1 and Th2 responses rather than a shift to an anti-inflammatory response.

Cavitary disease

- Persistent productive cough with fever and chills
- Night sweats
- Loss of appetite and weight loss.
- With blood vessel invasion, patients may have hemoptysis.
- With extensive involvement of the lung, patients may have dyspnea on exertion.
- Cavitation in upper lobe on chest x-ray
- Usually Mycobacterium tuberculosis
- Miliary form of TB is associated with generalized small nodules throughout lung fields
- Mediastinal adenopathy
- Demonstration of organism is diagnostic.

Cavitary disease

- Dimorphic fungi
- Histoplasma capsulatum
- Soil contaminated with bird or bat droppings
- Endemic in the Ohio and Mississippi Valleys as well as the Caribbean
- Often identified as radiolucent nodule on chest x-ray
- Lung apices
- May present with fever, cough, night sweats
- May see military disease
- May see extrapulmonary spread
- Small thin-walled yeasts in macrophages in caseating granulomas

Cavitary disease

- Blastomyces dermatiditis
- Soil inhabiting
- Pulmonary form presents with fever and productive cough
- May have headache, chest pain, night sweats, abdominal pain, anorexia
- Upper lobes usually involved
- Suppurative granulomas in lung
- Small round yeast cell that divides by broad based budding
- Thick double contoured cell wall
- Nuclei visible
- Self-resolving but may progress
- If skin or larynx involved, may lead to epithelial proliferation mimicking carcinoma

Cavitary disease

- Coccidiodes immitis
- Endemic in Sonoran life zone
- 10% symptomatic
- San Joaquin Valley fever complex
- Fever, cough, pleuritic pain with
- Erythema nodosum or Erythema multiforme
- Thick walled nonbudding spherules within giant cells or macrophages of granuloma
- Actinomycetes (fruiting body with septate filaments)
- Nocardia (beaded branching filaments)
- Aspiration pneumonia

Tuberculosis

Left upper lobe scarring with hilar retraction with scarring in right upper lobe as well.

Fig. e24-5 Accessed 03/17/2010

Tuberculosis

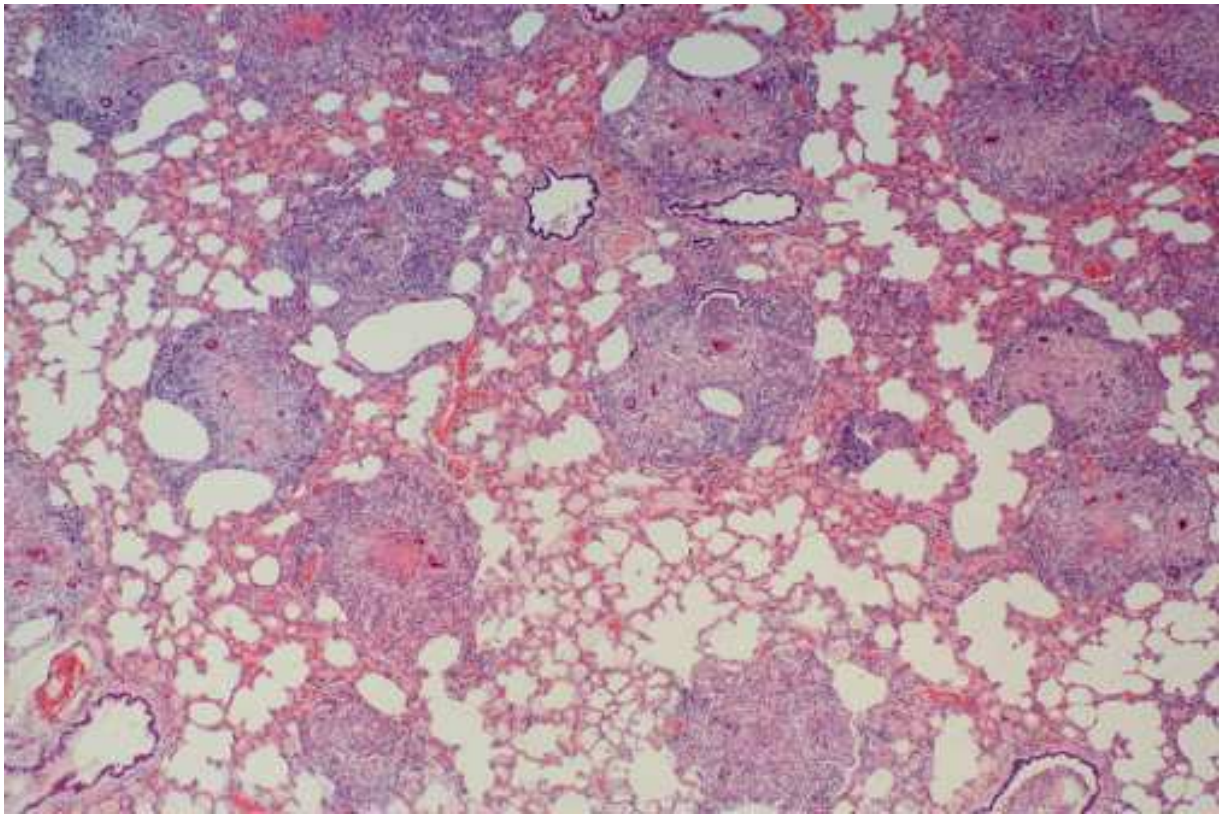
Miliary Tuberculosis

Nodules 1-3mm in diameter scattered throughout lung fields.

This is hematogenous spread and carries a poor prognosis.

https://radiopaedia.org/articles/miliary-tuberculosis?lang=us Accessed 12/10/2019

Tuberculosis

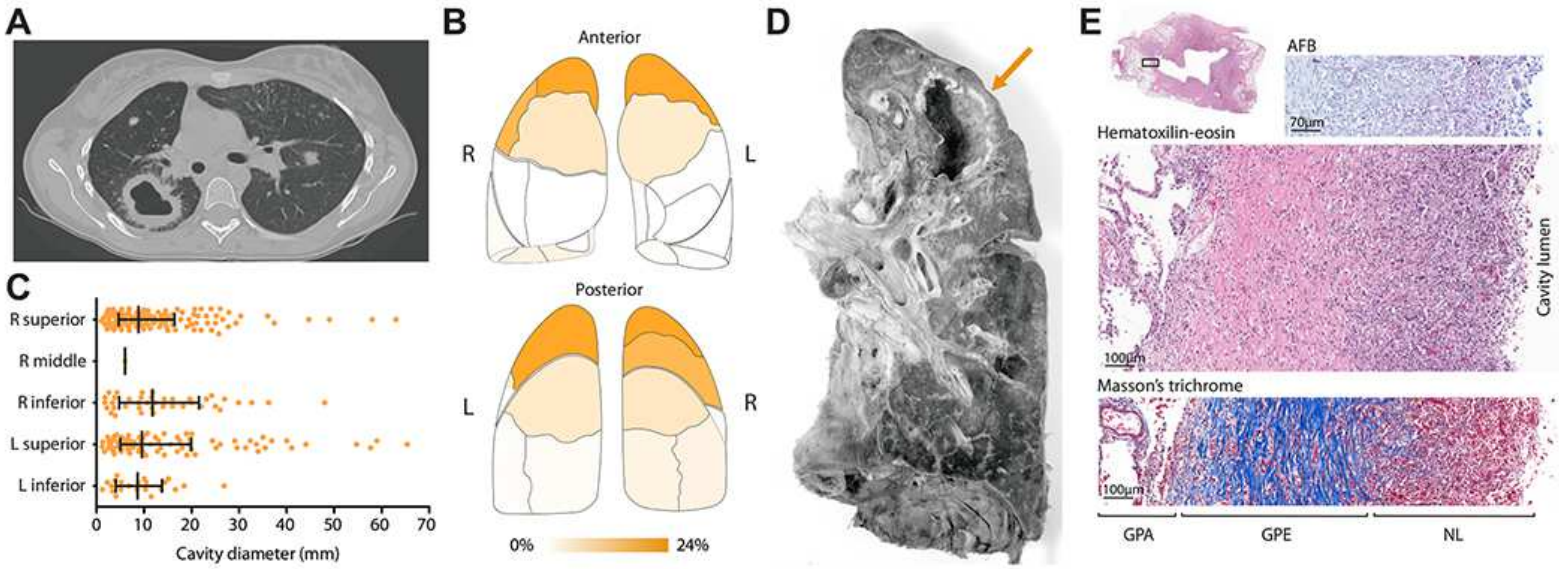


Pale pink central caseous necrosis, dark blue lymphocytes, elongated epithelioid cells, and multinucleated Langhan's giant cells.

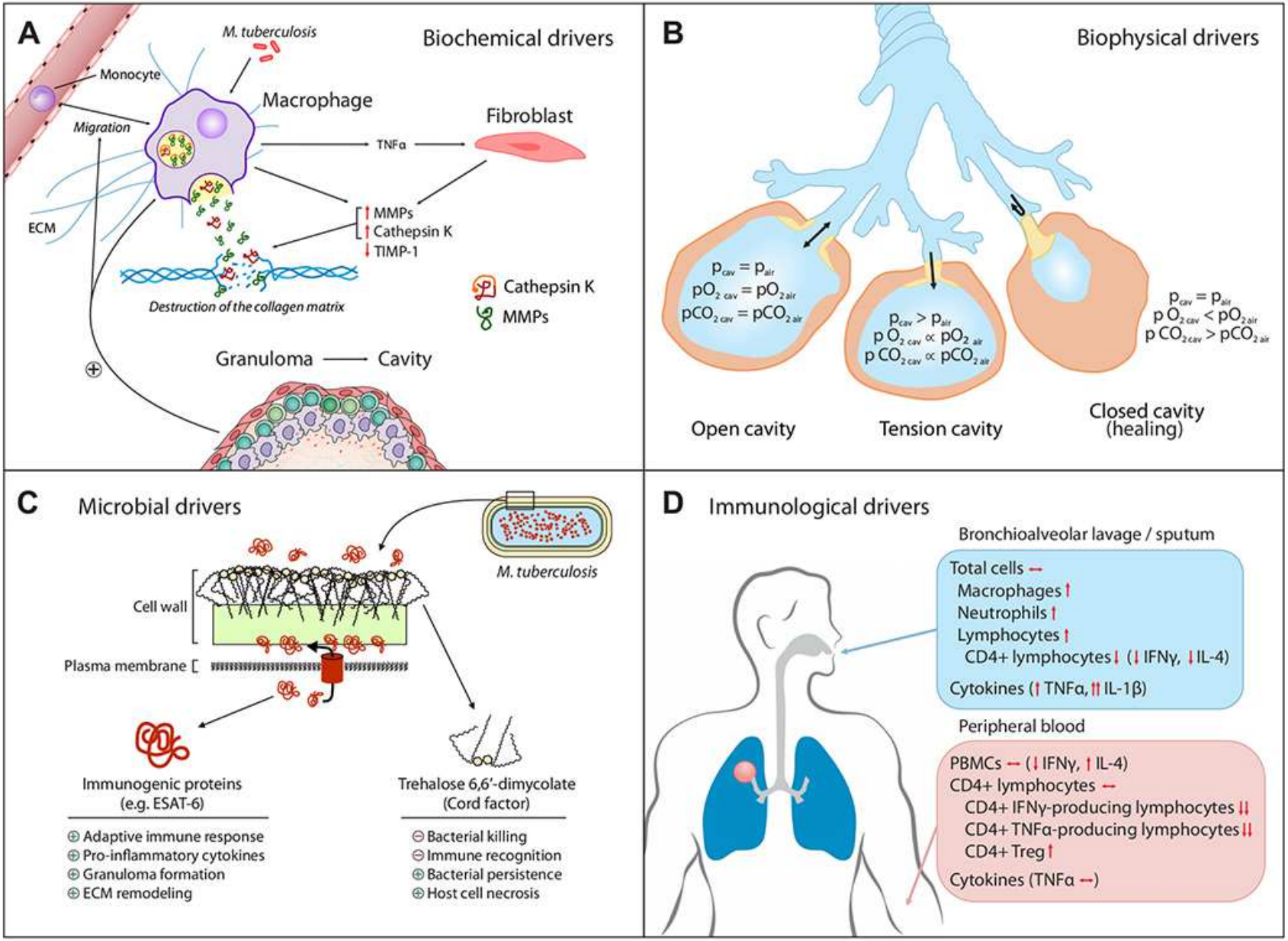
https://webpath.med.utah.edu/LUNGHTML/LUNG036.html Accessed 12/10/2019

Cavitary disease: Tuberculosis

Cavitary disease

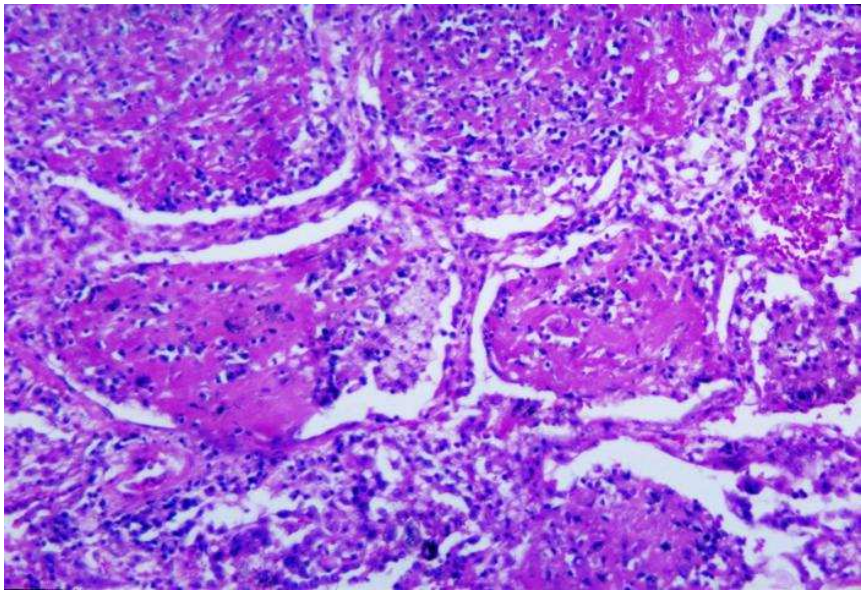


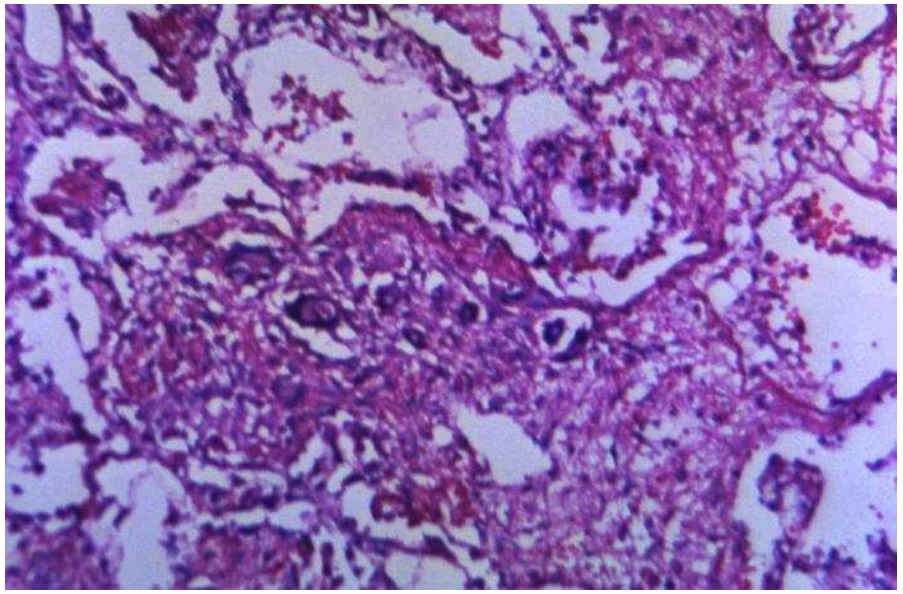
doi: 10.1016/S1473-3099(20)30148-1



doi: 10.1016/S1473-3099(20)30148-1

Fungal disease



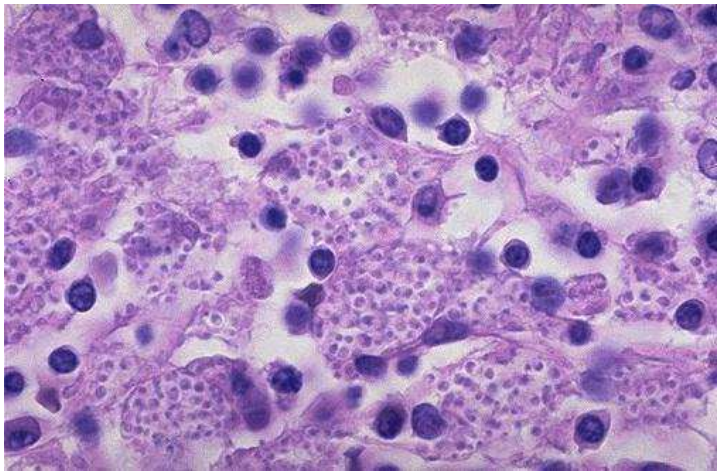


Hematoxylin-eosin (H&E)-stained lung tissue specimens, revealed the presence of cytoarchitectural changes indicative of a fungal infection. Note that large portions of the lung tissue had been replaced by inflammatory cells, fibrin, and necrotic debris, with only a few remnants of the alveoli still visible. On the left, Histoplasma capsulatum; on the right, Blastomyces dermatidis.

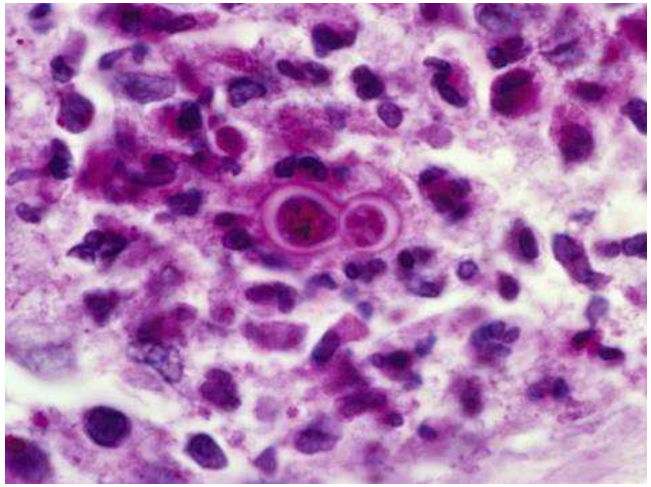
Centers for Disease Control and Prevention's Public Health Image Library #3941 and 22827 Accessed 01/24/2020

Dimorphic fungi

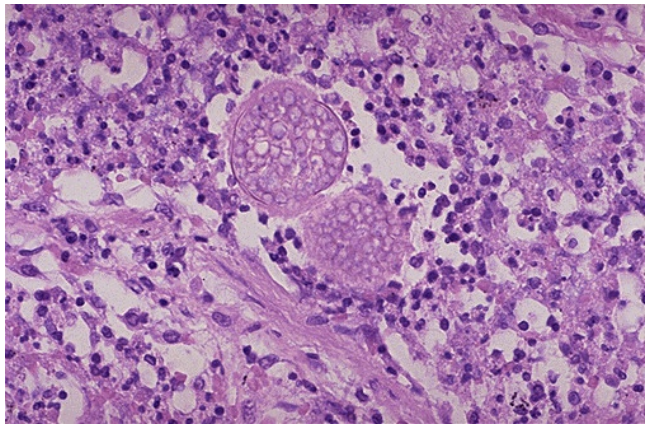
H. capsulatum



B. dermatiditis



C. immitis



https://classconnection.s3.amazonaws.com/665/flashcards/523665/jpg/ Histoplasma
http://imgc.allpostersimages.com/images/P-473-488-90/64/6471/T7RH100Z/posters/gladden-willis-budding-yeast-of-blastomyces-dermatitidis-fungus.jpg
Blastomyces
https://webpath.med.utah.edu/jpeg2/AIDS050.jpg Coccidioides
Accessed 01/20/2020aids0641333549206304.jpg

Atypical pneumonia

- Signs and symptoms
- Insidious onset
- Low grade fever
- Non-productive cough.
- Chest x-ray demonstrates a reticulo-nodular pattern (interstitial) throughout lung fields.
- Flattened diaphragms
- Hyperlucency at apices.

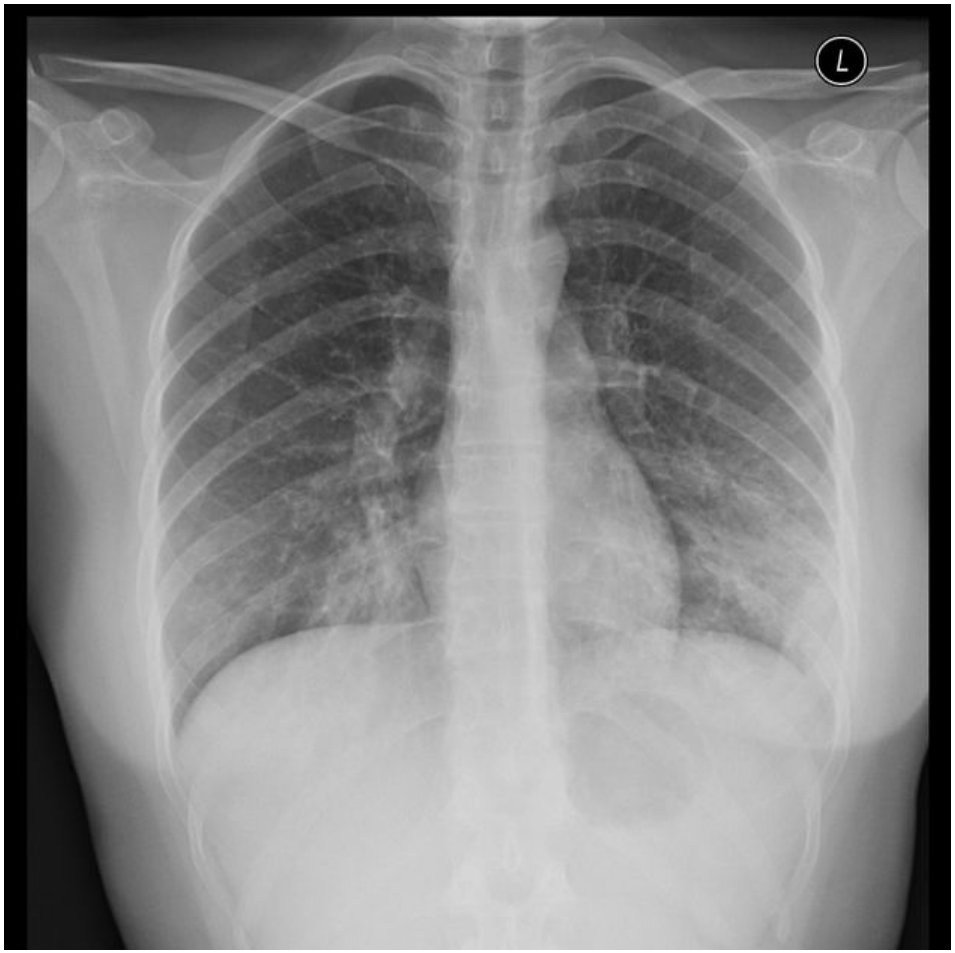
Atypical pneumonia

- Major causes:
- 1. Mycoplasma pneumoniae
- Presents with coryza
- Human pathogen
- Community acquired respiratory distress syndrome (CARDS) toxin permits surface epithelial colonization
- Frequently with cold agglutinins
- May lead to Guillan-Barré or Lambert-Eaton syndromes
- 2. Chlamydophilia pneumoniae
- Presents with coryza

Atypical pneumonia

- Major Causes:
- 3. Legionella pneumophiliae
- Fever, myalgia, and cough
- Gastrointestinal symptoms
- Clinical or x-ray evidence of pneumonia
- 10-25% mortality rate
- There is a milder form, Pontiac fever.
- No pneumonia
- Gram stain of sputum guides all pneumonia therapy until cultures available.
- Transbronchial biopsy or bronchial washings may be needed to recover offending organism

Atypical pneumonia



https://radiopaedia.org/articles/atypical-pneumonia Accessed 12/10/2019

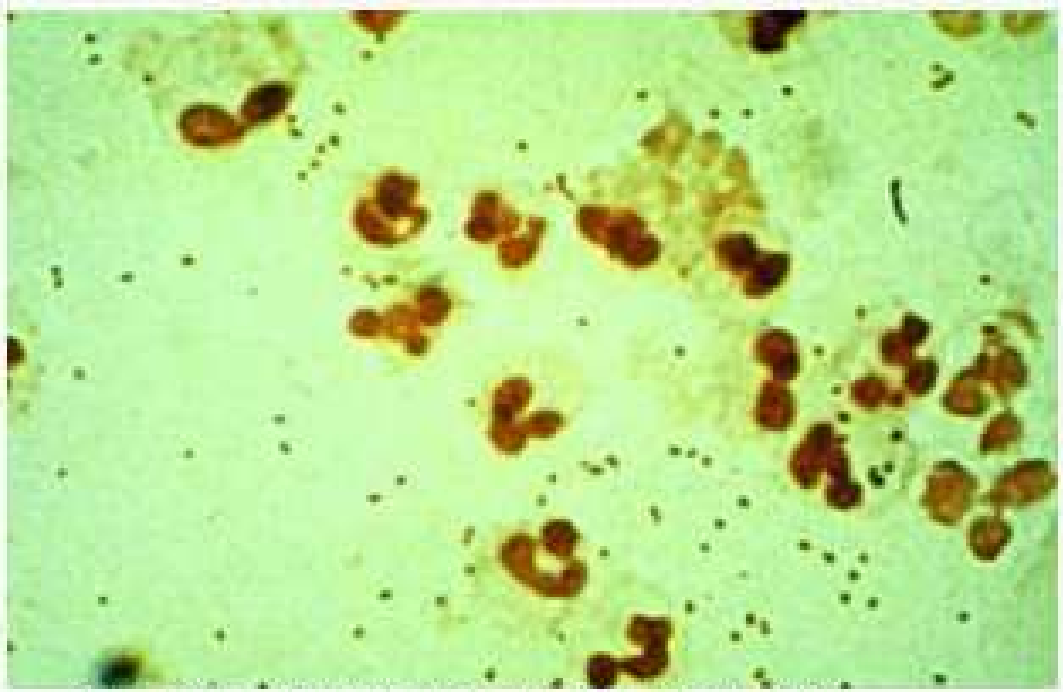
Patchy reticular or reticulonodular opacities.

Prominent in perihilar lung.

May have accompanying atelectasis.

EFIGURE 9–11.

Moraxella catarrhalis.



Cryptococcus pneumonia

- Cryptoccous neoformans causes pneumonia in immunocompromised
- C. gatti in immunocompetent
- Often fatal even if treated
- Fever, dry cough, headache, blurred vision, even confusion (if meningeal spread)
- Subacute presentation over several weeks
- Fibrocaseous nodules with granulomas in lung

Cryptococcus pneumonia

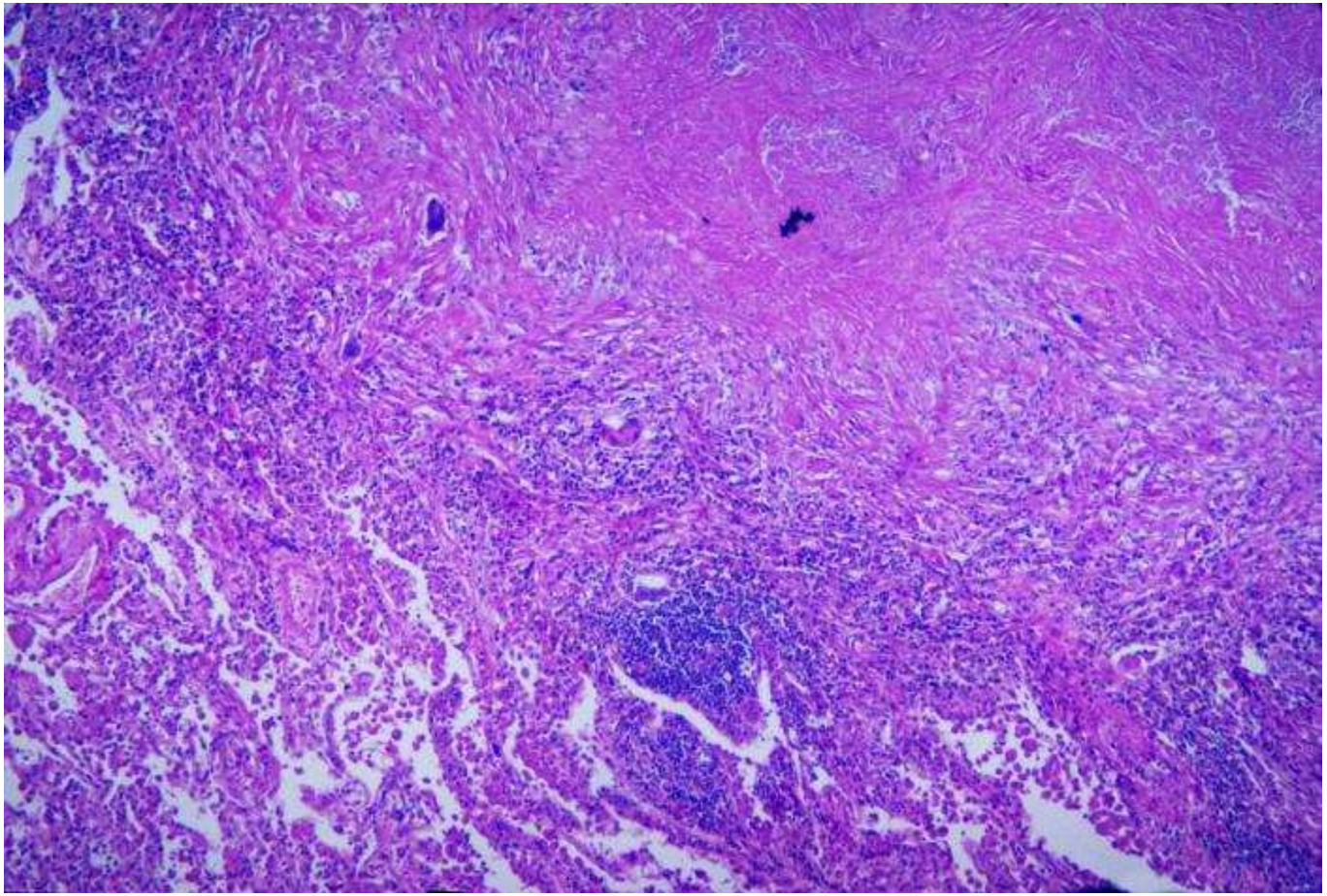
- Best diagnosed by presence of cryptococcal antigen in body fluid
- India ink preparation may miss 15-20% of cases
- Immune reconstitution inflammatory syndrome (IRIS)
- Immunologic reaction in recovering patients that leads to recrudescence of meningeal symptoms, and, possibly, death

Cryptococcus neoformans

India Ink preparation showing double walled yeast.

http://faculty.ccbcmd.edu/courses/bio141/labmanua/lab9/crypto.html
Accessed 01/20/2020

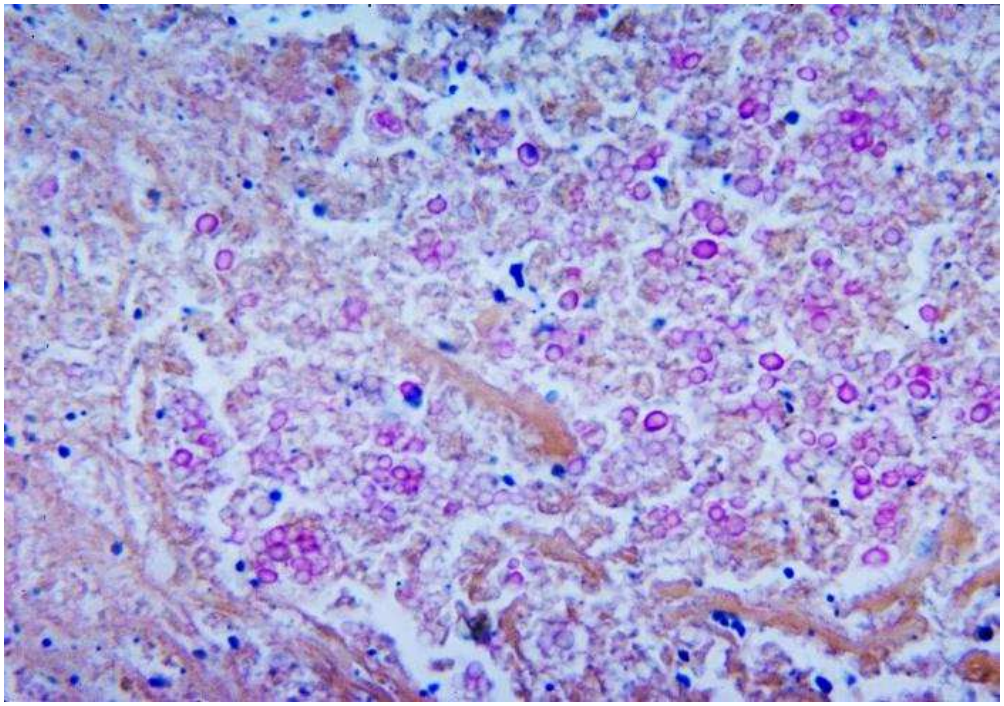
Cryptococcus neoformans



Present in fibrocaseous nodule is C. neoformans. Below is organizing pneumonia.

Centers for Disease Control and Prevention's Public Health Image Library **#3139 Accessed 01/24/2020**

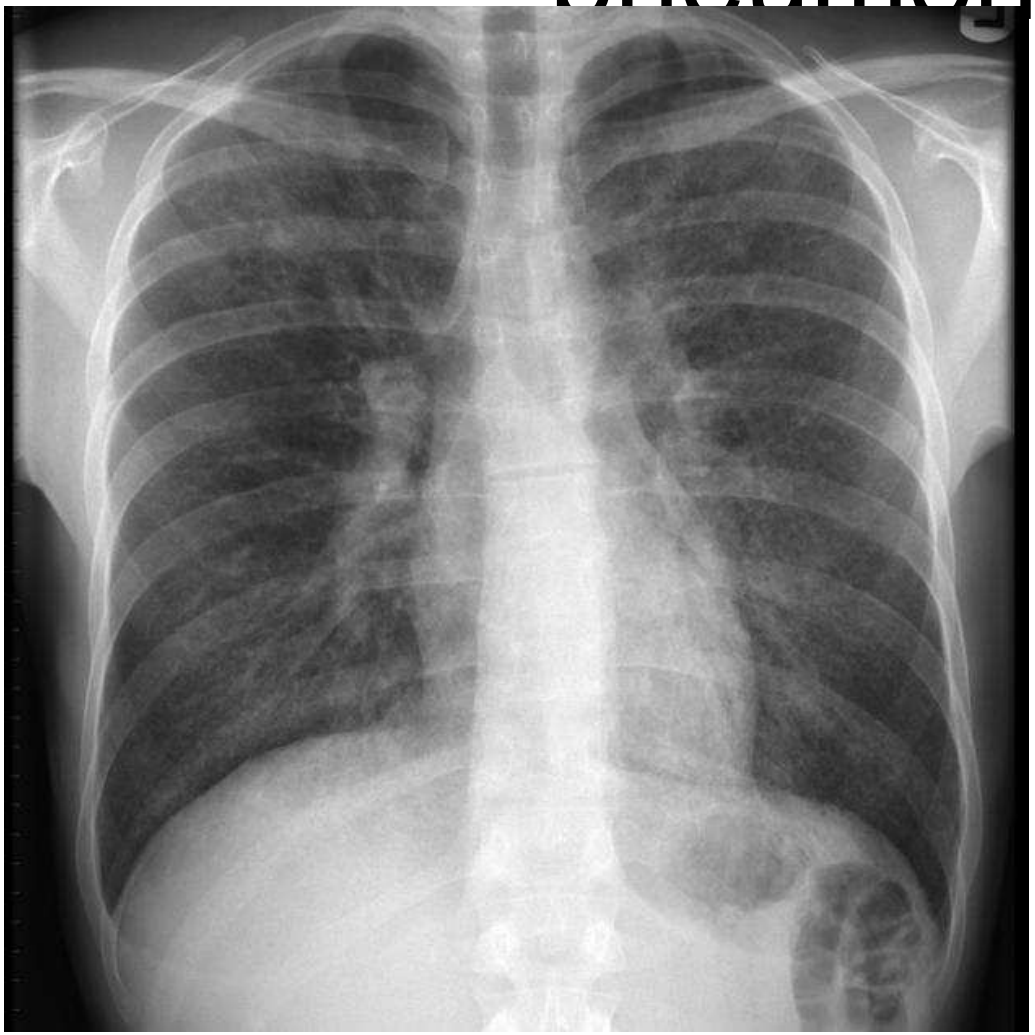
Cryptococcus pneumonia



Mucicarmine stain. Widened alveolar septae containing a few inflammatory cells and numerous yeasts of C. neoformans. The inner layer of the yeast capsule stains red.

Centers for Disease Control and Prevention's Public Health Image Library **#3138** **Accessed 01/24/2020**

Pneumocystis jiroveci pneumonia



Bilateral, diffuse, often perihilar, fine, reticular interstitial opacification, which may appear somewhat granular (ground glass).

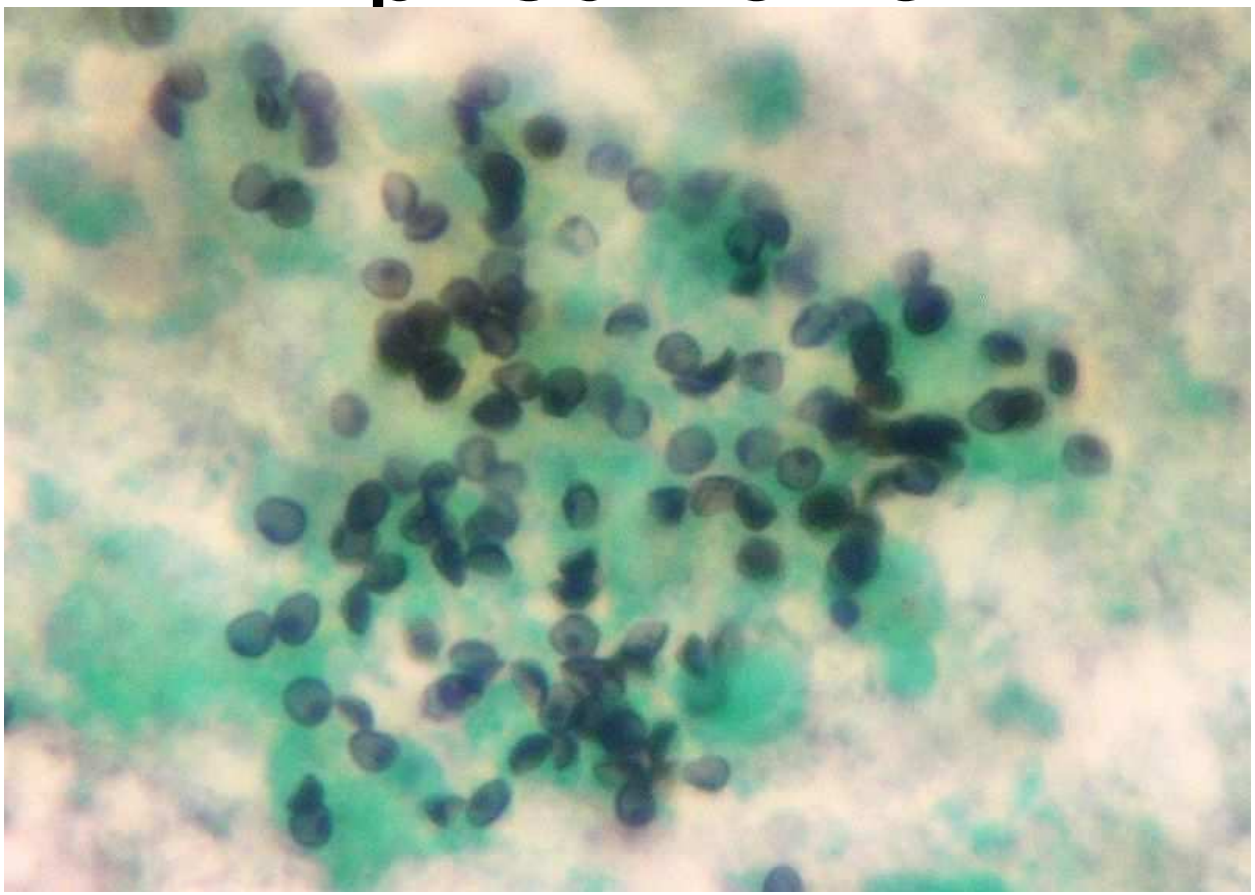
May see pneumatoceles in 30%.

Insidious presentation. Dyspnea out of proportion to clinical findings.

Isolated elevated LDH in serum.

https://radiopaedia.org/articles/pulmonary-pneumocystis-jiroveci-infection?lang=us
Accessed 12/10/2019

Pneumocystis jiroveci pneumonia



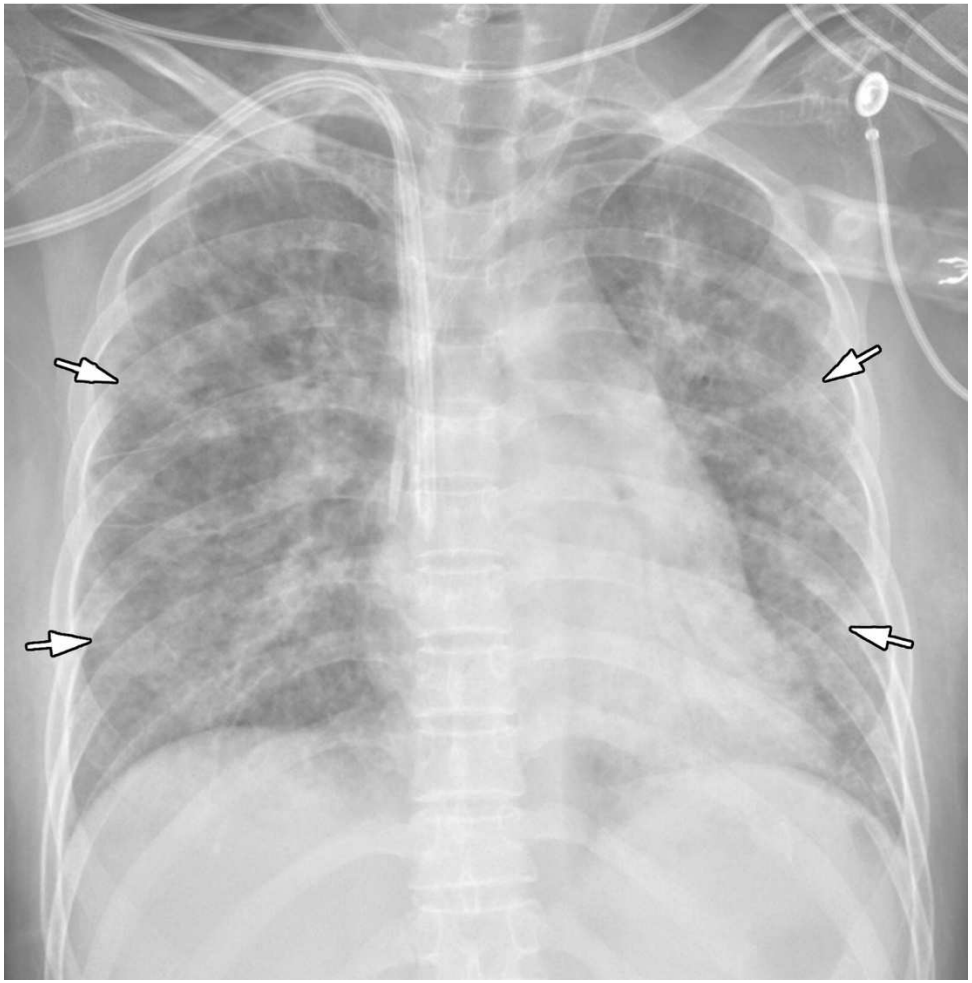
Gomori Methenamine Silver stain demonstrating the sporozoites in sputum. This is a yeast.

https://en.wikipedia.org/wiki/File:Pneumocystisjiroveci.jpg
Accessed 12/10/2019

Viral pneumonia

- Signs and symptoms
- Acute onset
- High fever
- Non-productive cough.
- Chest x-ray may demonstrate unilateral or patchy bilateral areas of consolidation but no lobar change
- Nodular opacities
- Flattened diaphragms
- Hyperlucency at apices.
- Pleural effusion common.
- May require CT for further characterization

Chest x-ray in viral pneumonia



Extensive patchy consolidation (arrows) with air bronchogram (arrowheads) in both lungs, especially in the middle to lower lung zones.

This is influenza.

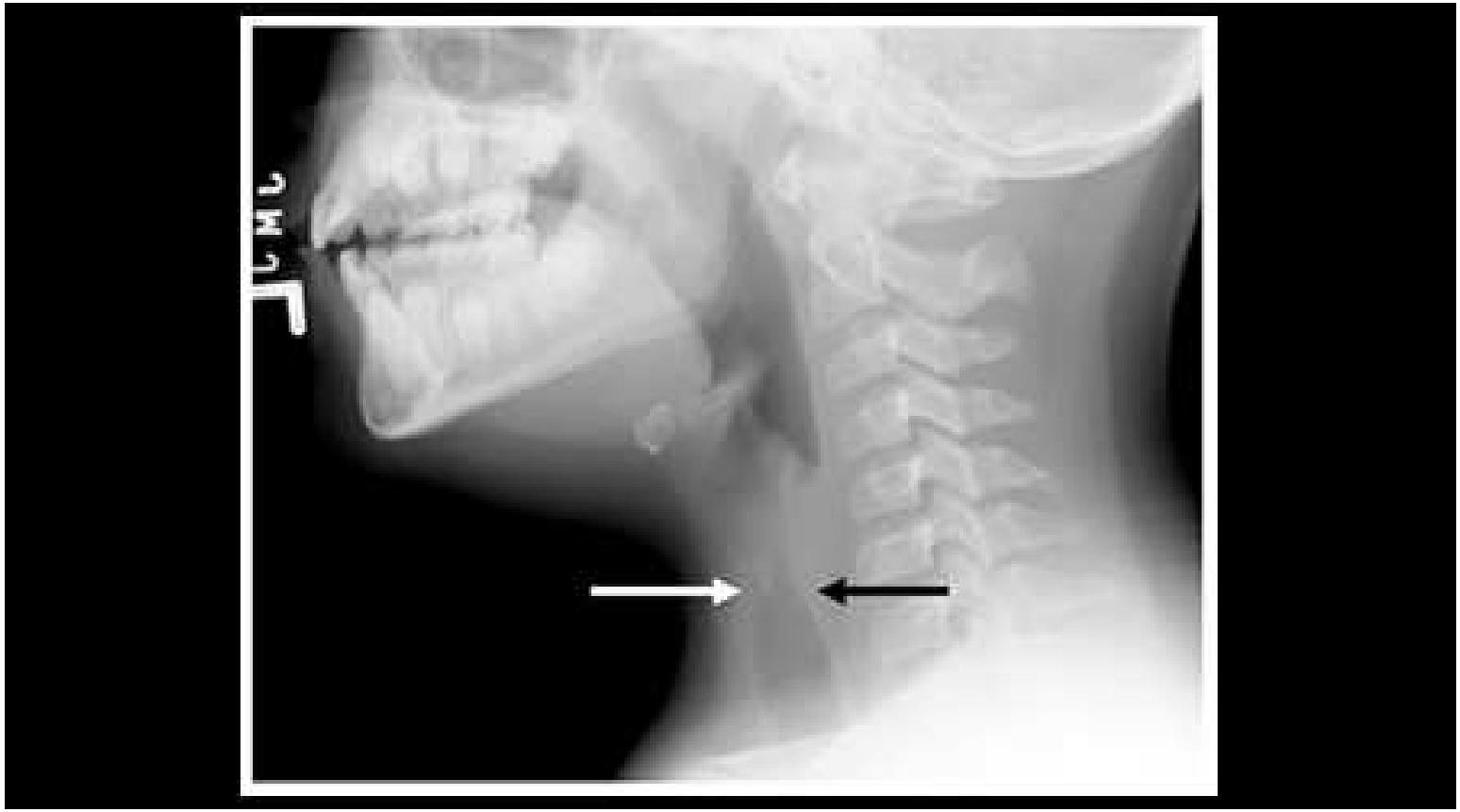
https://pubs.rsna.org/doi/full/10.1148/rg.2018170048 Accessed 12/10/2019

Viral pneumonia

- Clinically indistinguishable from Influenza
- Parainfluenza
- Respiratory syncytial virus (eosinophilia)
- Otitis media
- Human metapneumovirus (paramyxovirus)
- Children and elderly
- Collections of sloughed epithelium lead to obstruction of small bronchioles and subsequent air trapping. Reabsorption of trapped air leads to atelectasis (collapse of parts of the lung).
- Diffuse alveolar damage with hyaline membrane formation in severe disease.

Bronchiolitis (croup)

- In infants and children
- Usually caused by Parainfluenza (type 1) (laryngeotracheobronchitis or croup)
- Tend to occur in Fall
- Respiratory syncytial virus, adenovirus infection, influenza A and B.
- Tend to occur in Winter and Spring
- Brassy cough (stridor)
- Anterior x-ray of neck shows “steeple sign”
- Mucosal edema at site of tracheal obstruction



https://www.msdmanuals.com/en-nz/professional/pediatrics/respiratory-disorders-in-young-children/croup

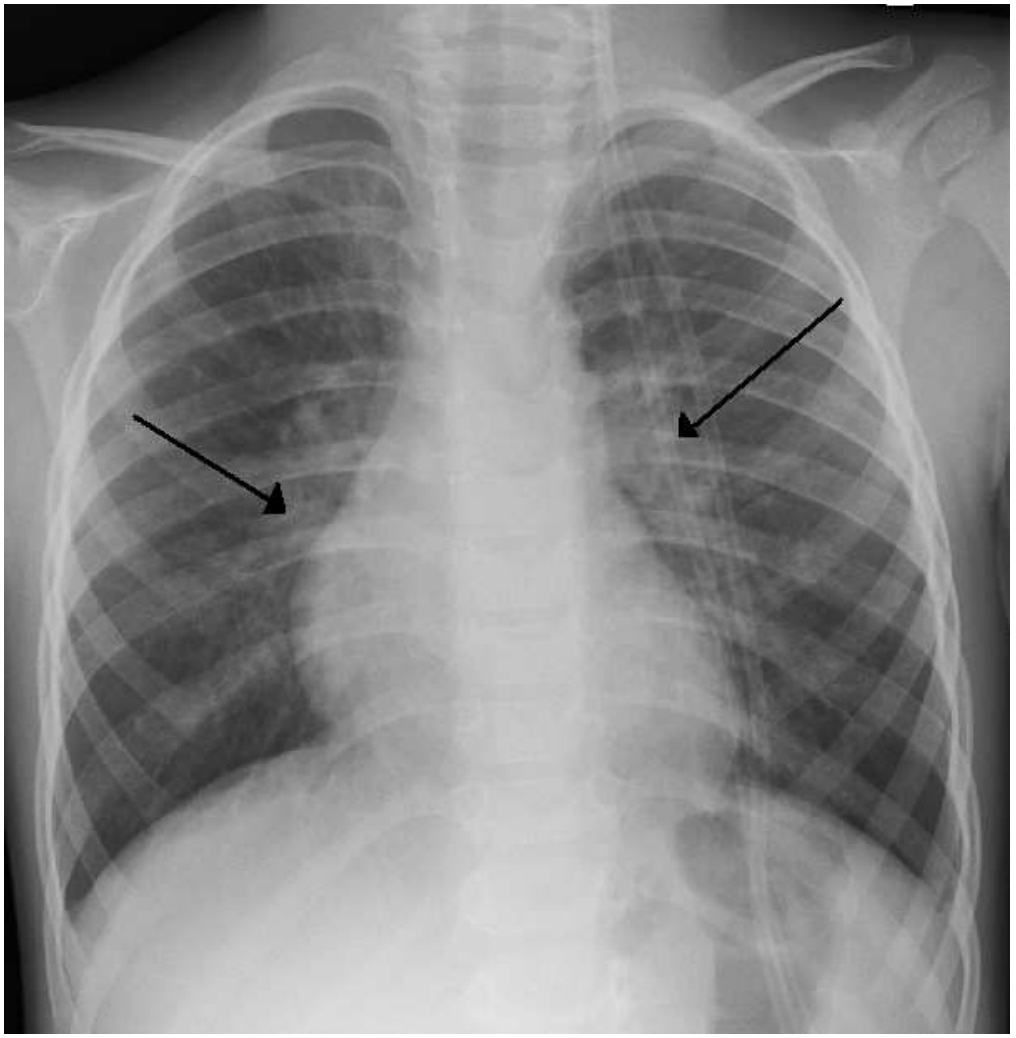
Cytopathic viruses

- Respiratory syncytial virus
- RNA virus
- Range from the common cold to pneumonia.
- Usually involve the upper respiratory tract with prominent rhinorrhea.
- ICAM-1 is receptor.
- Some cases can progress to the lower respiratory tract and cause bronchiolitis.
- 70% of cases of bronchiolitis in infants
- Because of inflammation at the level of the bronchiole, there is air trapping and decreased ventilation.

Respiratory syncytial virus

- Low grade fever, tachypnea, tachycardia and expiratory wheezes.
- Giant cells found in lungs.
- Fusion protein as virulence factor.
- Usually self-limited however, can be fatal in infants.
- Vaccine attempts abandoned as vaccinated infants later challenged with RSV became quite ill; many died (Antibody Dependent Enhancement)
- Ribavarin therapy

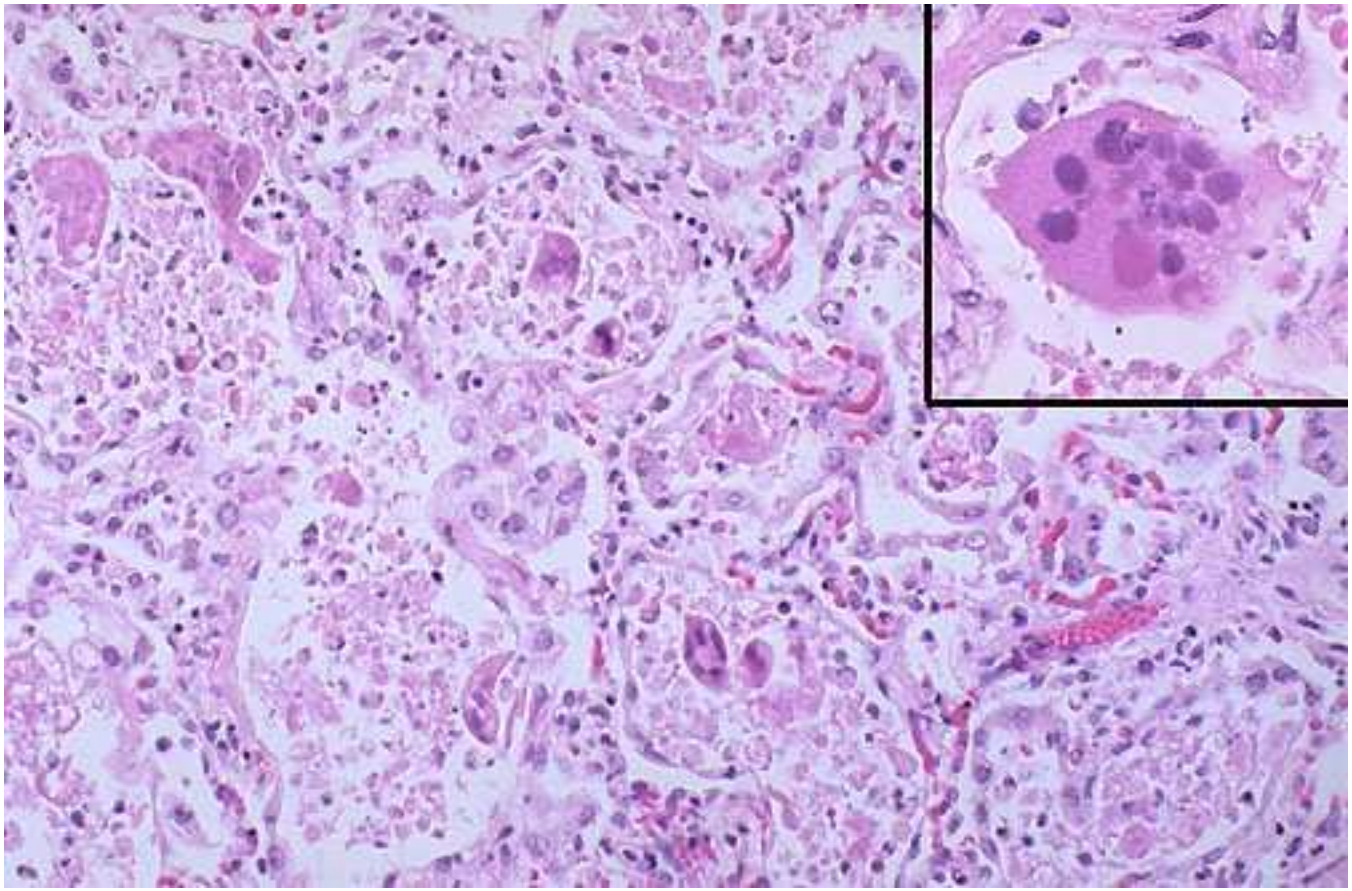
Respiratory syncytial virus bronchiolitis



Perihilar fullness

https://en.wikipedia.org/wiki/Respiratory_syncytial_virus#/media/File:RSV.PNG

Respiratory syncytial virus pneumonia



https://webpath.med.utah.edu/LUNGHTML/LUNG158.html
Accessed 12/10/2019

Cytopathic viruses

- Influenza virus
- RNA virus
- Affects the epithelium diffusely
- May result necrotizing bronchitis and/or bronchiolitis and diffuse alveolar damage.
- Histologic features are epithelial necrosis of the airways with submucosal chronic inflammation.

Influenza

- Influenza A
- The Hemagglutinin (HA) and Neuraminidase (NA) proteins of influenza viruses are the major sites for antibody recognition on the virus.
- To help the virus evade antibody detection, the RNA segments that encode HA and NA are able to mutate so that their functions are kept intact but they are less well recognized by antibodies. (Antigenic drift)

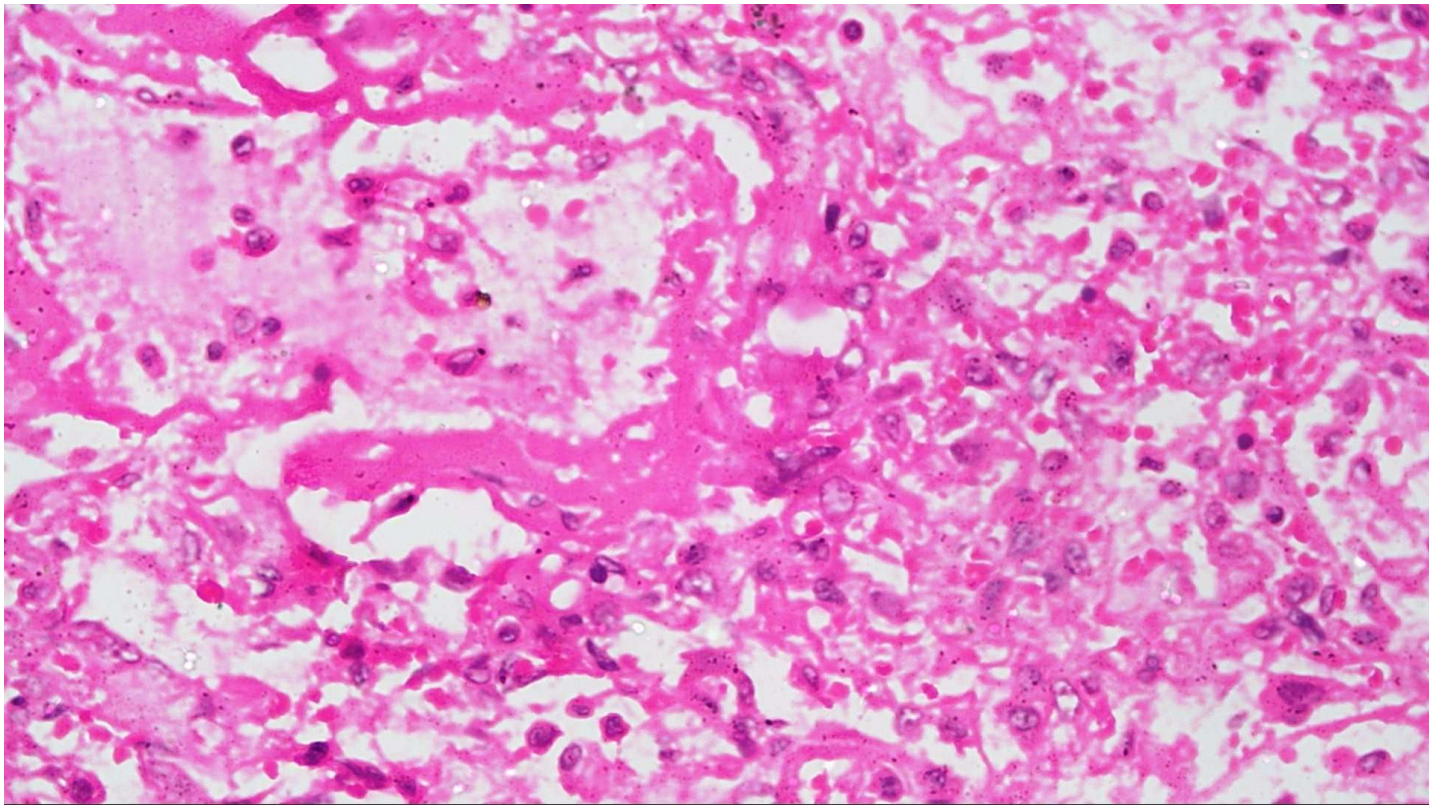
Influenza

- Because the RNA genomes of influenza viruses are segmented they can undergo reassortment if two different influenza viruses infect the same cell. (Antigenic shift)
- One strain predominates in epidemics
- H5N1 associated with pandemic of 2009
- Occurs from December to May in the Northern Hemisphere
- B and C strains cause mild disease
- Children

Influenza

- Rapid influenza tests in patients with fever and cough combined with a history of acute onset have a high likelihood of being positive (LR+, 4.7; LR- 0.06).
- Virus propagated in birds, but may pass to pigs and horses

Influenza pneumonia



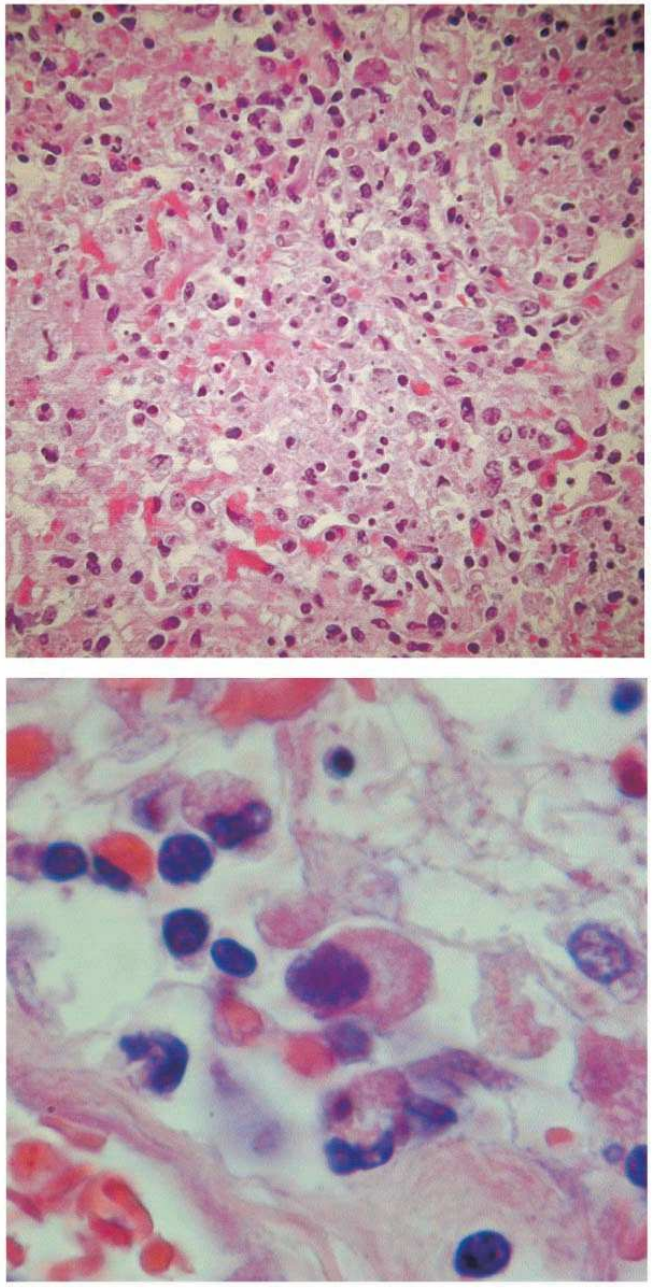
Diffuse alveolar damage with hyaline membrane formation.

http://www.pathologyoutlines.com/topic/lungnontumorinfluenza.html Accessed 12/10/2019

Cytopathic viruses

- Adenovirus
- DNA virus
- Causes pharyngoconjuctival fever or pool fever
- Common in military recruits
- Pharyngitis, conjuctivtis, cervical lymphadenopathy
- Greatest effect in the terminal bronchioles
- May produce necrotizing bronchiolitis and result in a necrotizing bronchopneumonia with diffuse alveolar damage

Adenovirus pneumonia



Interstial pneumonia with necrotizing exudate. Nuclear inclusion shown at higher power.

https://www.semanticscholar.org/paper/Fatal-type-3-adenoviral-pneumonia-in-adult-twins.-Barker-Luby/9a9abc007cb161280b25561d970df0bef1ab72ff/figure/5
Accessed 12/20/2019

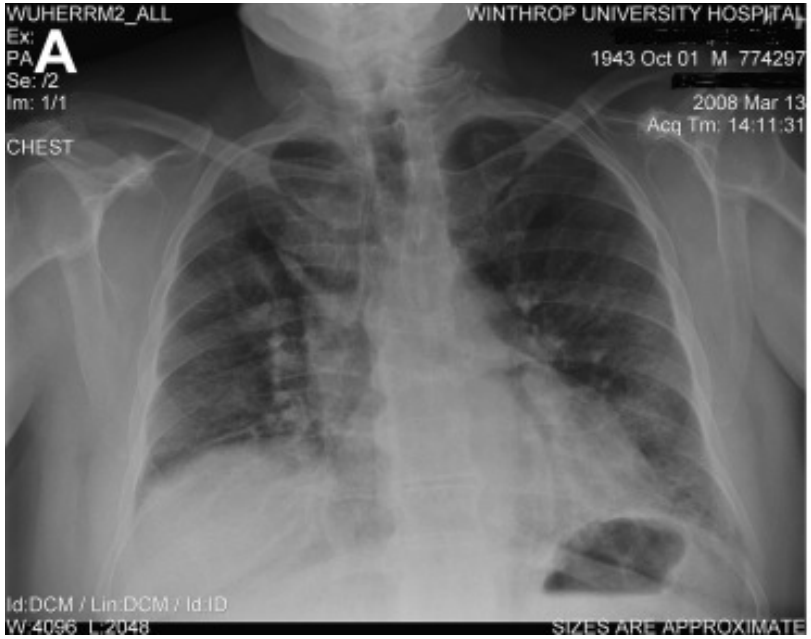
Cytopathic viruses

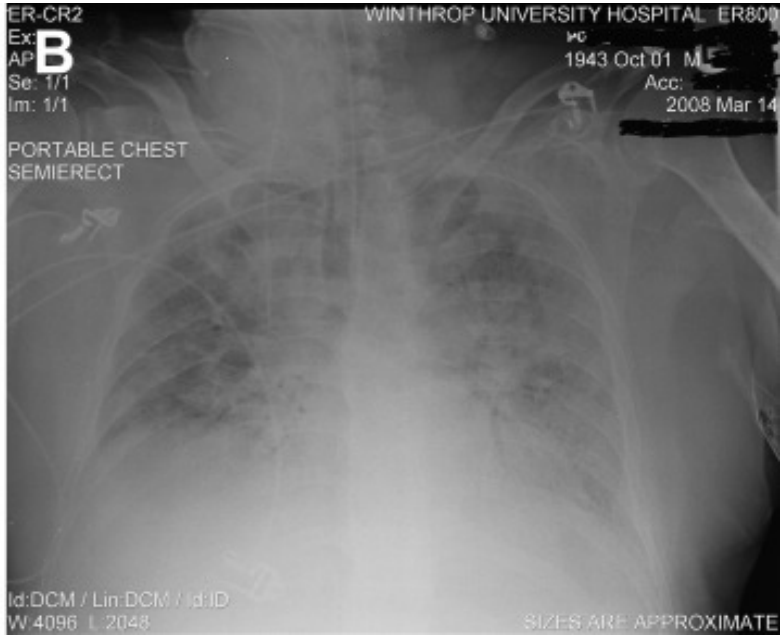
- Herpes virus
- DNA virus
- May cause focal cytopathic effects in the airway or the alveoli.
- There is necrosis of the airway epithelium
- Necrotizing pneumonia as the reaction spreads to the adjacent parenchyma
- An acute lung injury pattern may be present, with interstitial edema, congestion, and inflammation.
- Diffuse alveolar damage may result

Cytopathic viruses

- Nodules
- Multicentric areas of hemorrhage may appear centered on airways.
- An acute lung injury pattern may be present, with interstitial edema, congestion, and inflammation.
- Both Herpes simplex virus (HSV) and Cytomegalovirus (CMV) produce intranuclear inclusions
- Only CMV produces cytoplasmic inclusions (dense bodies)
- Only CMV produces perinuclear cytoplasmic inclusions

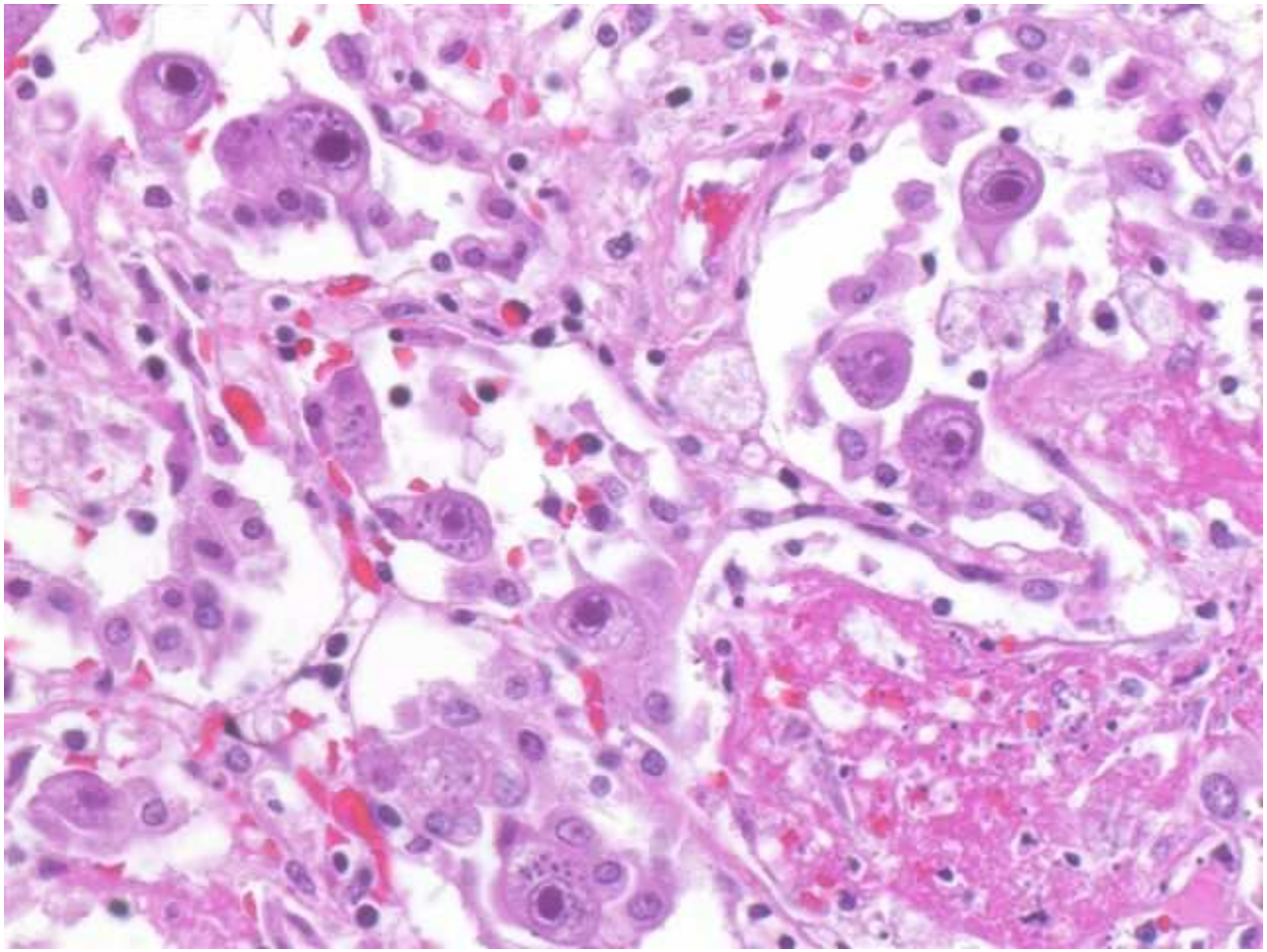
Cytomegalovirus pneumona





https://pubmed.ncbi.nlm.nih.gov/20171550

Cytomegalovirus pneumonia



Pp65 (matrix protein) positive

http://www.pathologyoutlines.com/images/lungcmv2.jpg Accessed

Cornavirus

- Coronaviruses are the most common viruses associated with cold symptoms
- SARS and MERS (coronavirus)
- β-coronaviruses
- Presents 2-10 days after infection
- Fever and chills with dry cough
- Malaise
- Myalgias

Coronavirus

- Virus confined to pneumocytes
- Spike protein attacks ACE2 receptor (SARS)
- Spike protein attacks CD26 (MERS)
- Viral origin from bats to wild masked palm civets (China); from bats to camels (Middle East).
- Epidemiology differs, however
- Covid-19 is lab generated, gain of function research
- Hydrochloroquine and invermectin as effective antimicrobial agents if used less than 5 days after onset of symptoms
- Pneumonia is secondary to ARDS (acute respiratory distress syndrome)

Cornavirus

- Cytokine storm (SIRS) may lead to respiratory insufficiency, multi-organ failure, and encephalitis.
- Vaccine attempts abandoned as laboratory test animals later challenged with virus became quite ill; many died (Antibody Dependent Enhancement)
- The spike protein is toxic

SARS-Covid-19

- Covid 19
- Product of gain-of-function research
- SARS backbone with spike protein modified with introduction of furan ring that permits its cleavage in human cells, facilitating attack on ACE2 receptor
- ACE2 receptor is found in blood vessels as well as in pneumocytes
- The spike protein alone is sufficient to cause such damage; the virus is only a “vector”
- Vascular damage and cytokine storm (SIRS) explains disease manifestations and progression to ARDS

Mechanism

- Spike protein binds to ACE2
- ACE2 is found in every part of the body that
- interfaces with the circulatory system
- Vascular endothelial cells and pericytes, brain astrocytes, renal tubules and podocytes, pancreatic islet cells, bile duct and intestinal epithelial cells, and the seminiferous ducts of the testis, as well as the lungs

Mechanism

- The spike protein undergoes a conformational change
- S1 trimers flip up and extend, locking onto ACE2 bound to the surface of a cell. ACE2 is suppressed, leading to diminished degradation of bradykinin.
- TMPRSS2, or transmembrane protease serine 2, cuts off the heads of the Spike, exposing the S2 stalk-shaped subunit inside.

Mechanism

- The remainder of the Spike protein undergoes a conformational change that causes it to unfold, embedding itself in the cell membrane. Then, it folds back upon itself, pulling the viral membrane and the cell membrane together. The two membranes fuse, with the virus's proteins migrating out onto the surface of the cell.
- The nucleocapsid enters the cell, disgorging its genetic material and beginning the viral replication process, hijacking the cell's own structures to produce more virus.
- May lead to formation of syncytia

Mechanism

- The envelope protein, a viroporin, act as a calcium ion channel, introducing calcium into infected cells.
- Hypocalcemia marked in persons deficient in Vitamin D
- The natural interferon response is suppressed, resulting in delayed inflammation.
- The N protein can also directly activate the NLRP3 inflammasome. Also, it suppresses the Nrf2 antioxidant pathway.

Mechanism

- Bradykinin upregulates cAMP, cGMP, COX, and Phospholipase C activity.
- Results in prostaglandin release and vastly increased intracellular calcium signaling
- Promotes highly aggressive reactive oxygen species (ROS) release and ATP depletion.
- NADPH oxidase releases superoxide into the extracellular space. Superoxide radicals react with nitric oxide to form peroxynitrite.

Mechanism

- Peroxynitrite reacts with the tetrahydrobiopterin cofactor needed by endothelial nitric oxide synthase (NOS), causing nitric oxide synthase to synthesize more superoxide instead.
- Continues in a positive feedback loop until nitric oxide bioavailability in the circulatory system is depleted.
- Endothelial nitrogen oxide species (NOS) is antiviral against SARS-like coronaviruses as it blocks palmitoylation of the spike protein
- Viral replication is not impeded as endothelial NOS is depleted

Mechanism

- Cells of the innate immune system engulf invaders and attack them with superperoxide dismutase and myeloperoxidase
- Neutrophils also eject these enzymes into the extracellular space (neutrophil extracellular trap formation)
- Iron is removed from heme
- Red cells lose oxygen carrying capacity
- Unliganded iron, hydrogen peroxide, and superoxide in the bloodstream undergo the Haber-Weiss and Fenton reactions, producing extremely reactive hydroxyl radicals that oxidize fats and DNA

Mechanism

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Mechanism

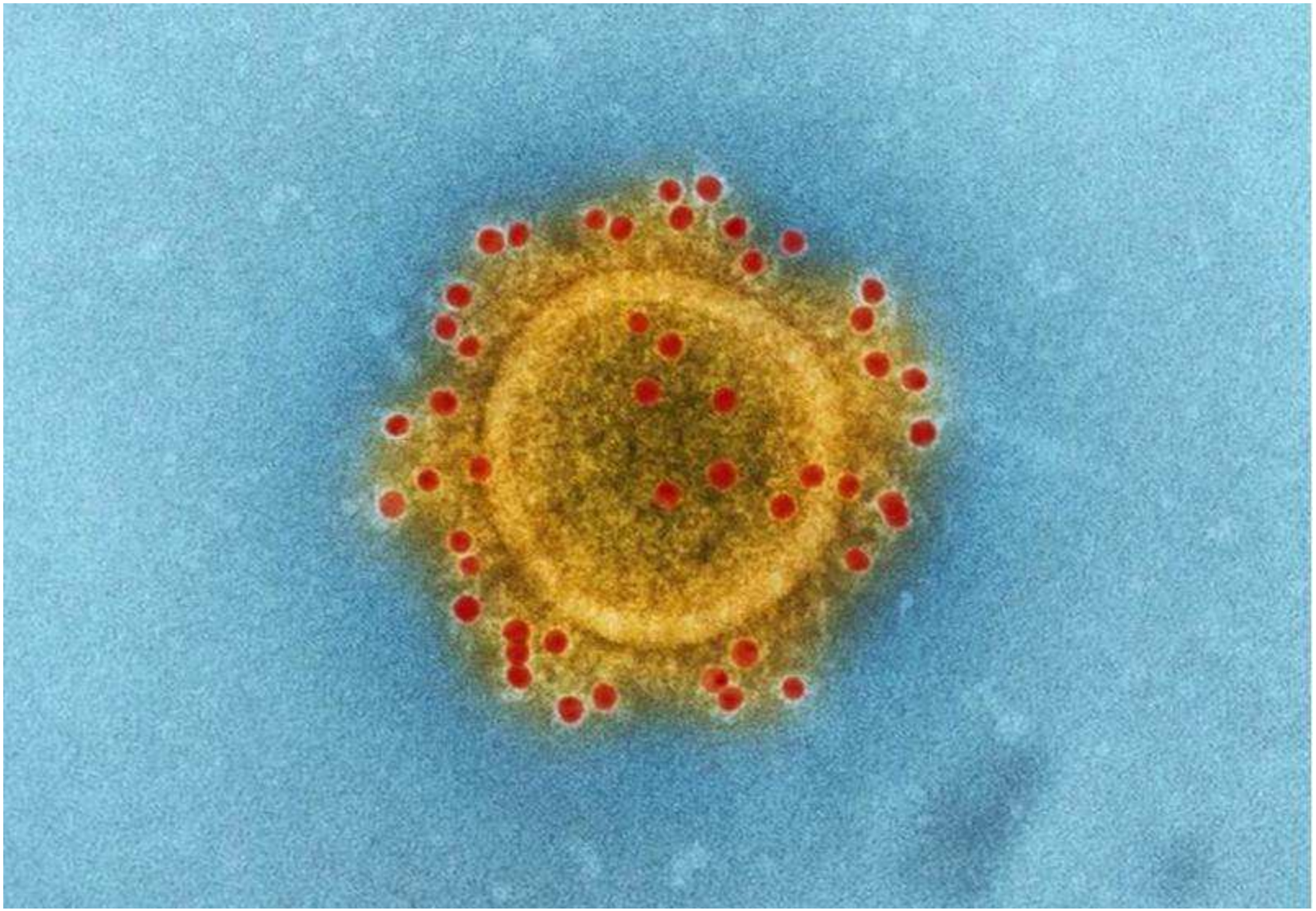
- COVID-19's pathology is dominated by extreme oxidative stress and neutrophil respiratory burst
- The end-stage of COVID-19 is severe lipid peroxidation
- Oxidized lipid epitopes drive autoimmune response
- The spike protein does not only bind to ACE2. It is suspected to have regions that bind to basigin, integrins, neuropilin-1, and bacterial lipopolysaccharides as well.
- The Spike S1 receptor binding domain may bind to heparin-binding proteins and promote amyloid aggregation (prion like).

Mechanism

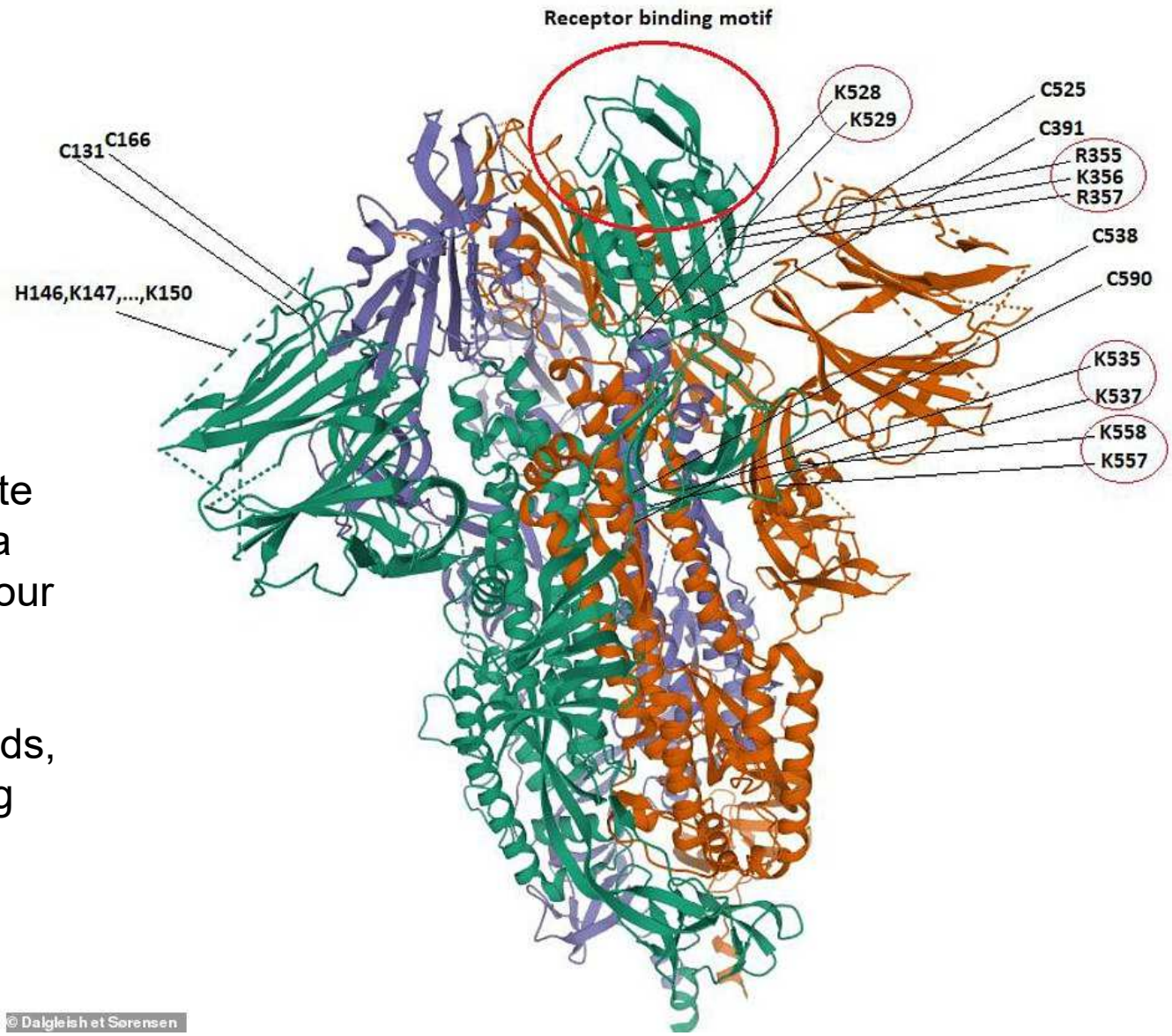
- Locally generated antibodies against the spike protein on the SARS-CoV-2 virus expressed upon human alveolar epithelium ignites the terminal complement cascade, specifically the C5-convertase.
- This in turn promotes the assembly of proteins derivative of the C5, C6, C7, and C8 pathways to construct the membrane attack complex (MAC).

Mechanism

- The MAC architecture includes a centrally localized channel which facilitates the passage of the terminal complement protein C9 from the opening orientation directly toward the alveolar space.
- Upon reaching the terminus of the MAC adhered to the epithelial surface, C9 then penetrates the alveolar cell membrane, inflicting an irreversible breach in the integrity of the cell's barrier.
- Complement dependent cytotoxicity
- Additionally, spike protein leads to impairment of immunoglobulin rearrangement as well as to T cell destruction.



Receptor binding site contains a string of four positively charged amino acids, enhancing infectivity.



Six inserts identified

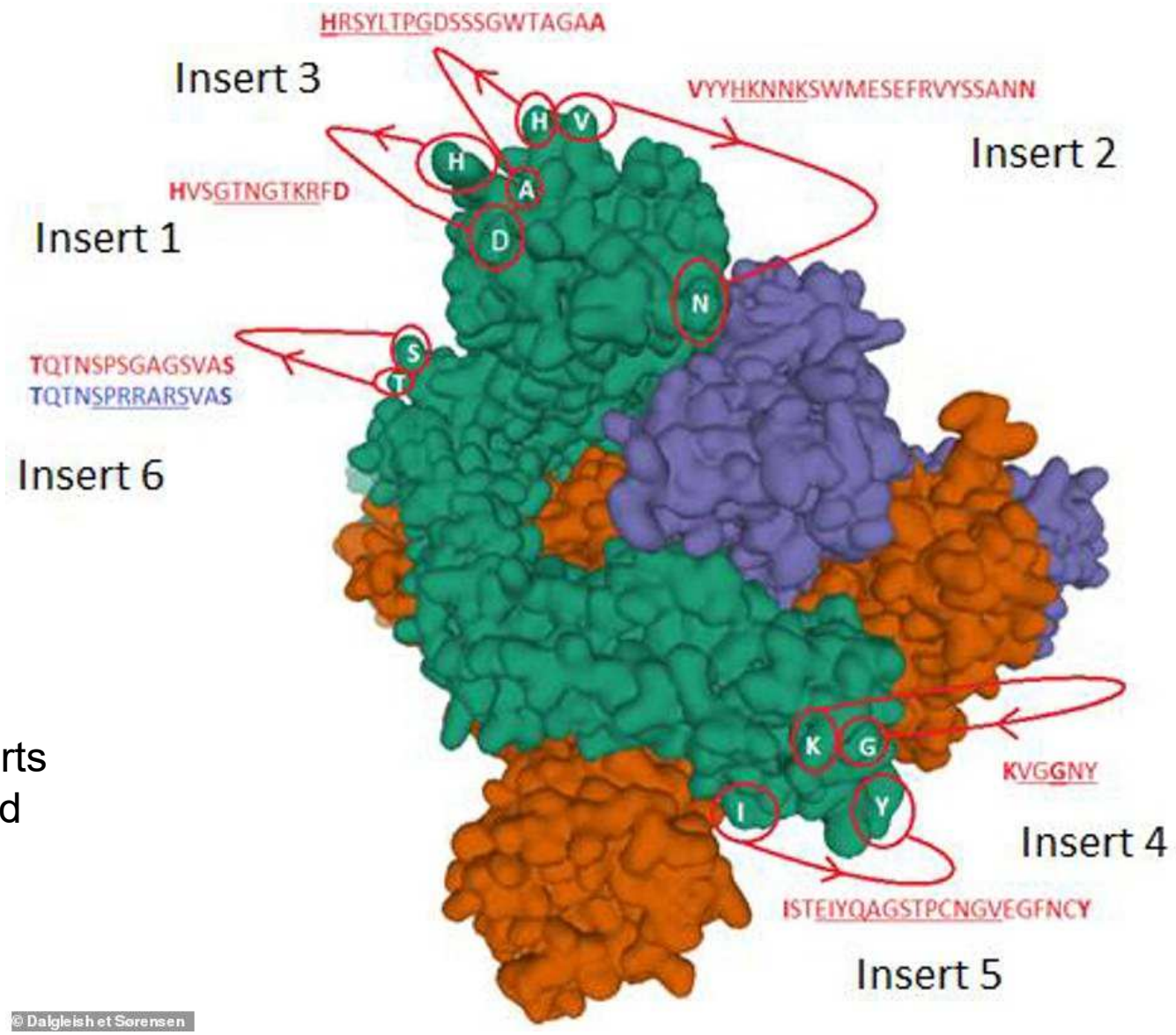
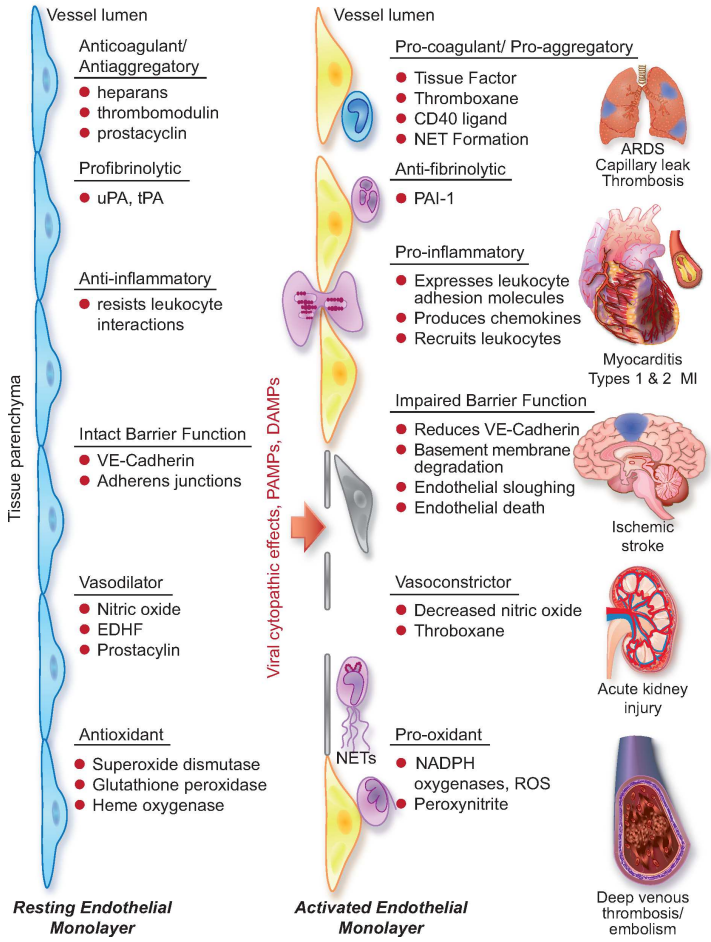
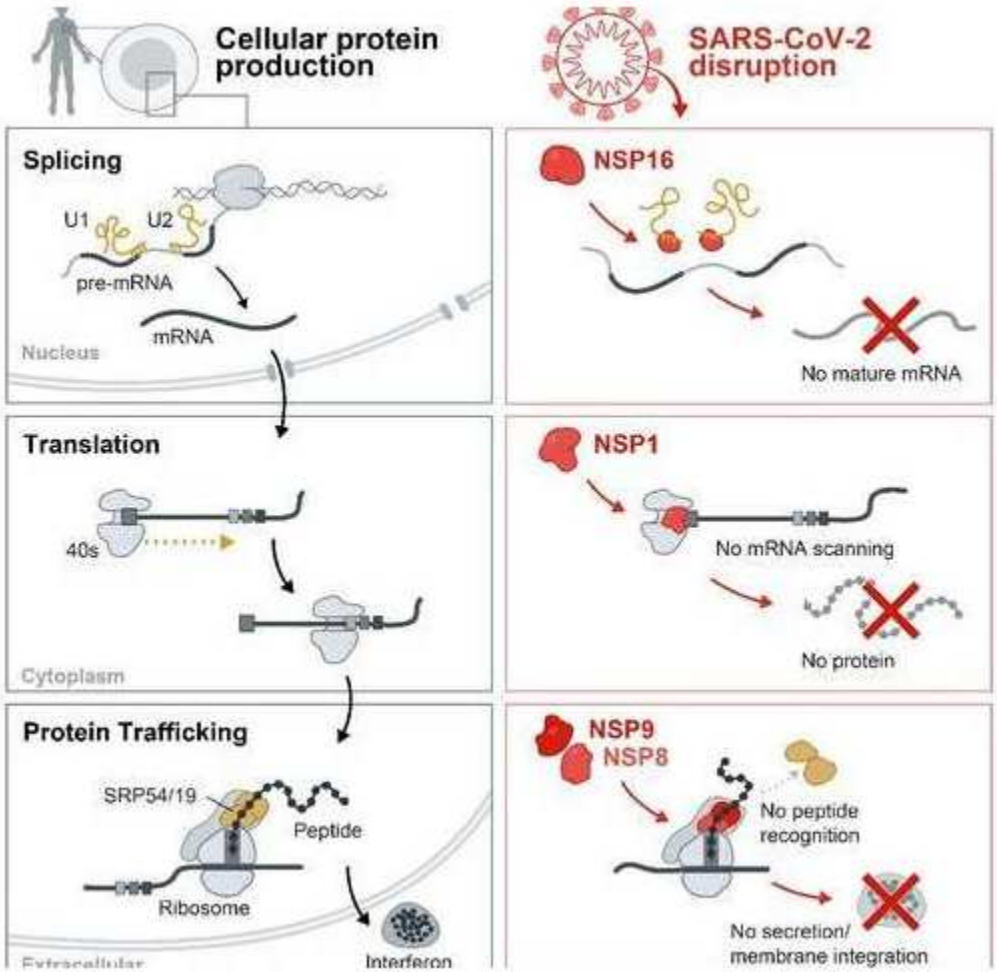


Figure 1 The left side of the diagram depicts a resting endothelial monolayer with the endothelial cells of squamous ...

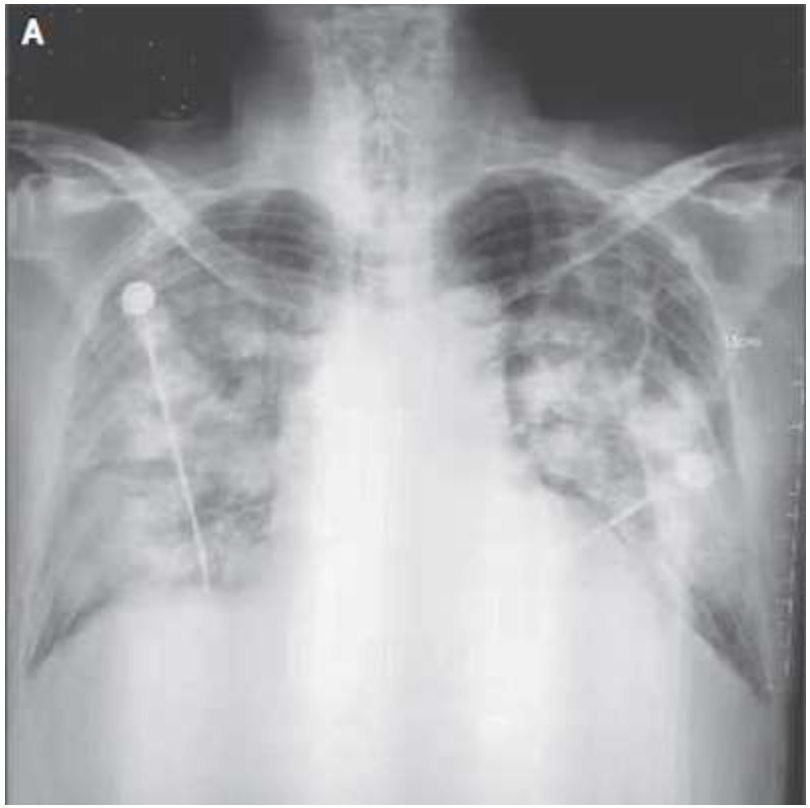


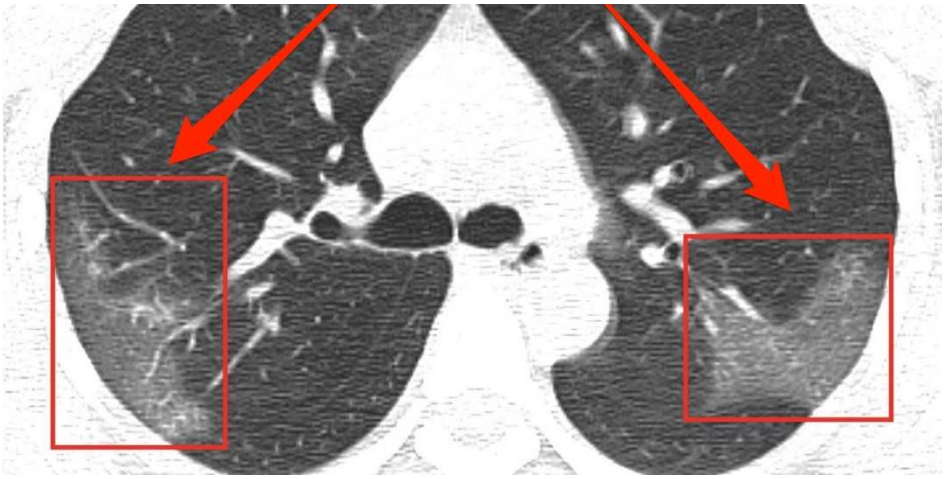
Eur Heart J, Volume 41, Issue 32, 21 August 2020, Pages 3038–3044, https://doi.org/10.1093/eurheartj/ehaa623



Abhik K. Banerjee et al. SARS-CoV-2 disrupts splicing, translation, and protein trafficking to suppress host defenses, Cell (2020). DOI: 10.1016/j.cell.2020.10.004

Coronavirus

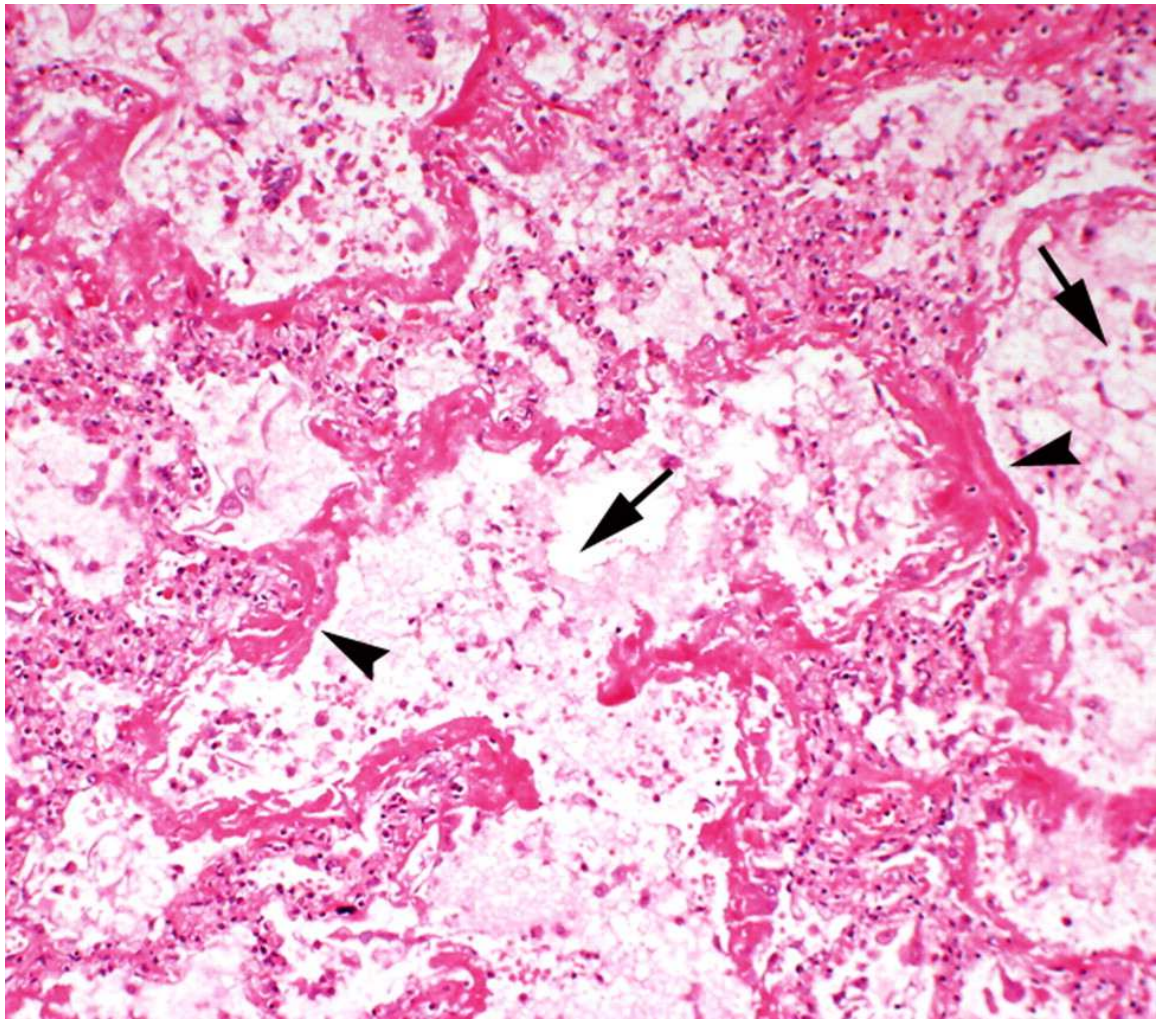




SARS-2019-nCoV has larger S spike than any other coronavirus, reflecting genome inserts that include a furan ring.

Left:
https://www.auntminnie.com/user/images/content_images/sup_xra/2020_01_24_23_14_8209_coronavirus_x-ray_A_400.jpg
Right:
https://duckduckgo.com/?t=ffab&q=coronvirus+chest+x-ray&ia=images&iax=images&iai=https%3A%2F%2Fi.insider.com%2F5e34b29d5bc79c0ebe5e0da4%3Fwidth%3D1200%26amp%3Bformat%3Djpeg%26amp%3Bimgtype%3D.jpg
Accessed 02/20/2020

SARS and MERS

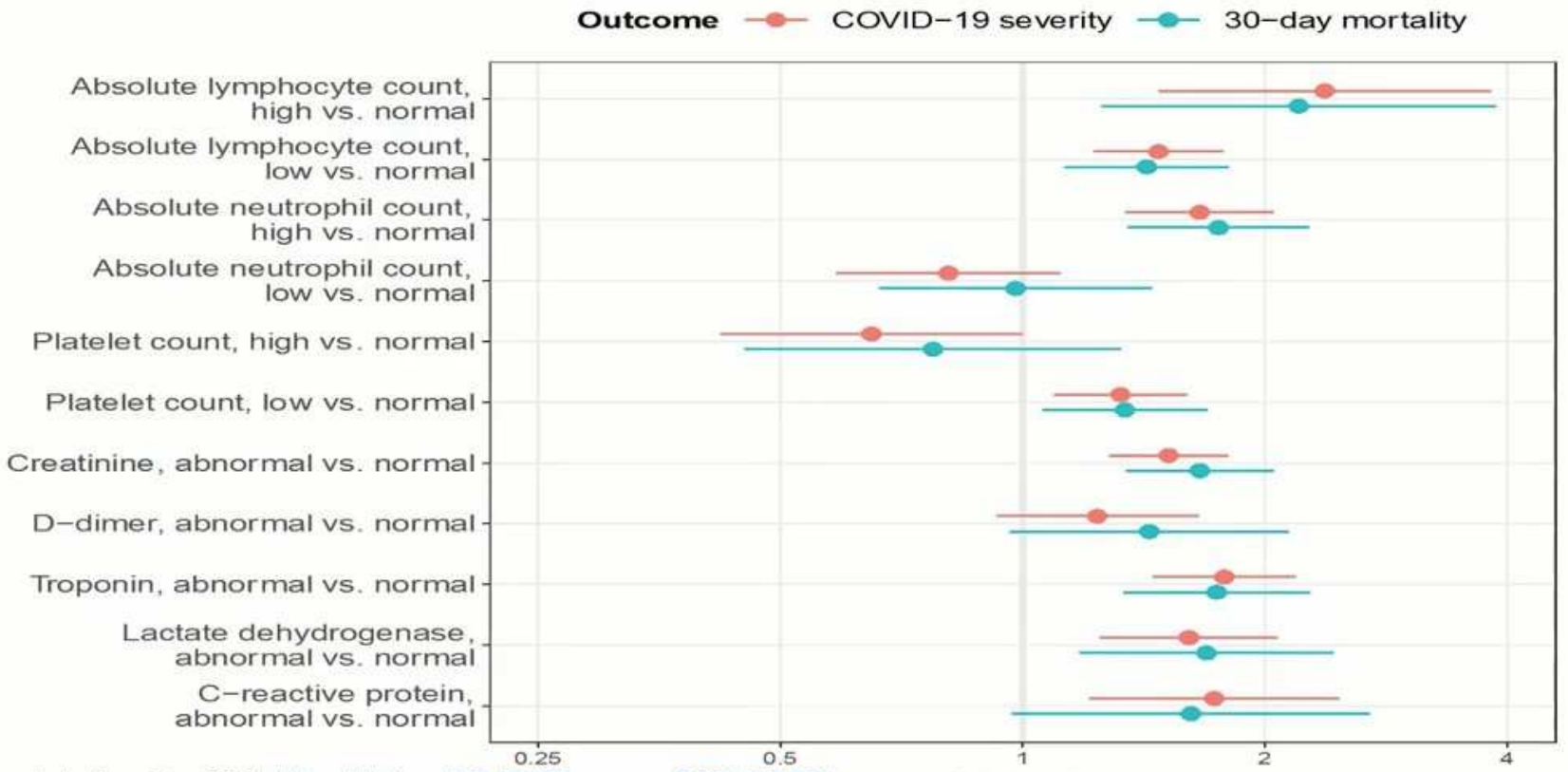


Diffuse alveolar damage with hyaline membrane formation (arrowhead).

Intra-alveolar edematous period is present (arrows).

https://pubs.rsna.org/doi/full/10.1148/radiol.11092149
Accessed 12/10/2019

Association of laboratory parameters with outcome in n=2872 **hospitalized patients**



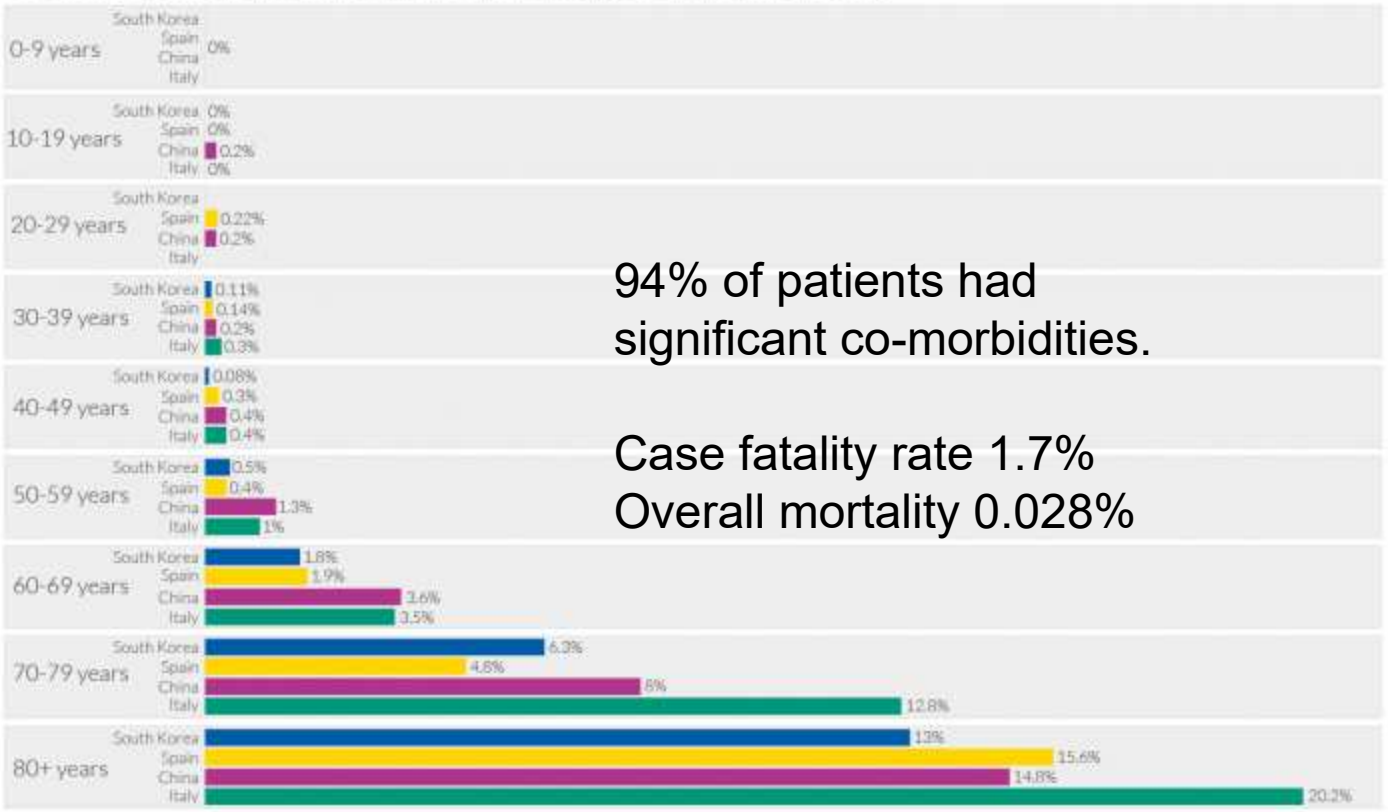
Grivas et al. *Ann Onc* 2021 https://doi.org/10.1016/j.annonc.2021.02.024

Coronavirus: case fatality rates by age

Our World in Data

Case fatality rate (CFR) is calculated by dividing the total number of confirmed deaths due to COVID-19 by the number of confirmed cases.

Two of the main limitations to keep in mind when interpreting the CFR:
(1) many cases within the population are unconfirmed due to a lack of testing.
(2) some individuals who are infected will eventually die from the disease, but are still alive at time of recording.



94% of patients had significant co-morbidities.

Case fatality rate 1.7%
Overall mortality 0.028%

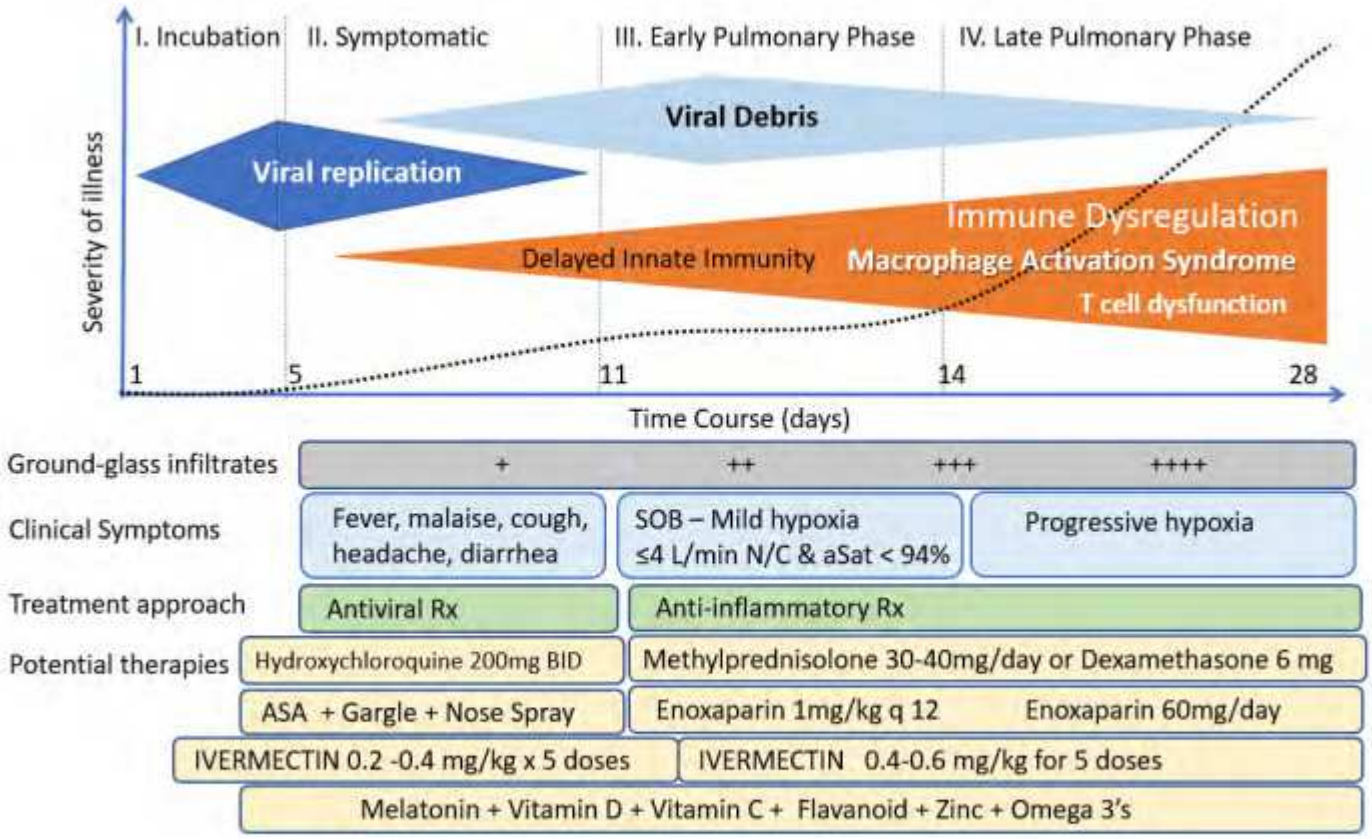
Note: Case fatality rates are based on confirmed cases and deaths from COVID-19 as of: 17th February (China); 24th March (Spain); 24th March (South Korea); 17th March (Italy).

Data sources: Chinese Center for Disease Control and Prevention (CDC); Spanish Ministry of Health; Korea Centers for Disease Control and Prevention (KCDC); Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA.

OurWorldinData.org – Research and data to make progress against the world's largest problems.

COVID 19 PROTOCOLS

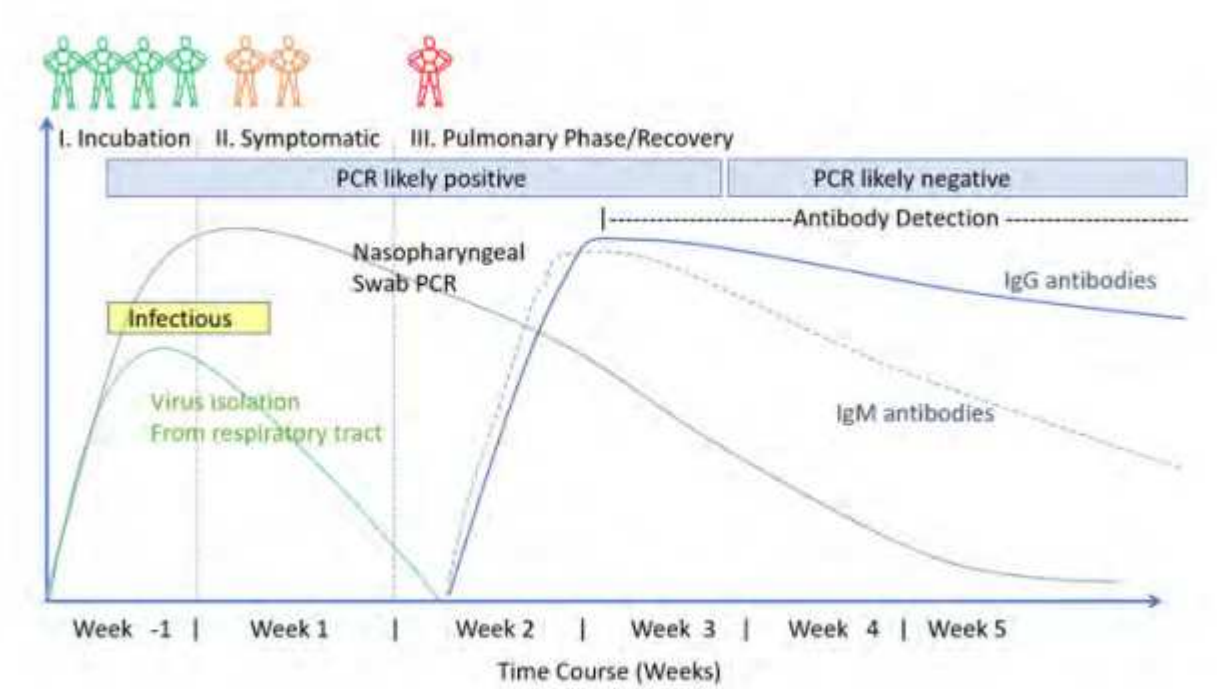
Figure 2. The Course of COVID-19 and General Approach to Treatment



Note. This time course was developed for the ancestral strain (Wuhan) as well as the Alpha, Gamma, and Delta strains. With the Omicron and newer strains, the time course has been compressed. Source: FLCCC

Accessed 01/18/2024

Figure 3. Time Course of Laboratory Tests for COVID-19



Note. This time course was developed for the ancestral strain (Wuhan) as well as the Alpha, Gamma, and Delta strains. With the Omicron and newer strains, the time course has been compressed. Source: FLCCC

Accessed 01/18/2024

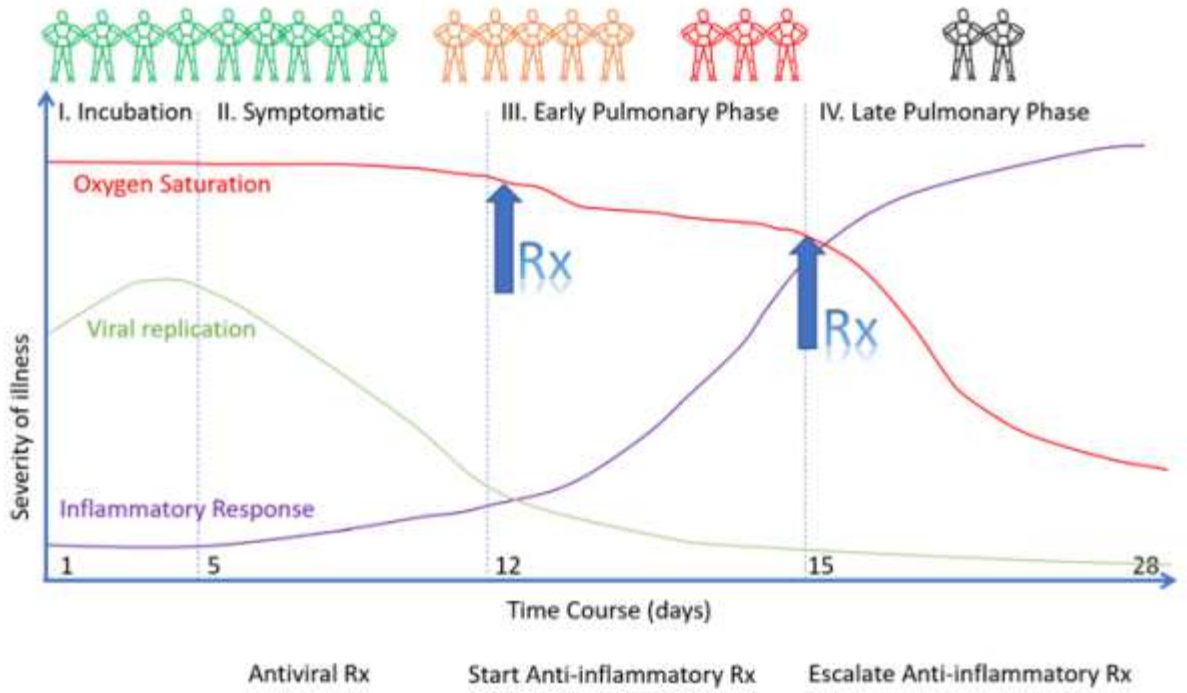
Table 1. Pharmacological Therapy for COVID-19 by Stage of Illness: What has worked and what has failed

	Pre-exposure/ Post-Exposure/Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Ivermectin	BENEFIT	BENEFIT	BENEFIT
Hydroxychloroquine	Benefit**	Benefit**	?Trend to harm
Corticosteroids	n/a	Trend to harm	BENEFIT
Anti-androgen Rx	? Benefit	Benefit	BENEFIT
LMWH	n/a	n/a	BENEFIT
Paxlovid/Molnupiravir	n/a	No Benefit	n/a
Monoclonal Abs	No Benefit	No benefit	HARM
Lopivinar-Ritonavir	n/a	No benefit	No benefit
Tocilizumab	n/a	n/a	Unclear Benefit
Convalescent Serum	n/a	No benefit	Trend to harm
Colchicine	n/a	Unclear benefit	No Benefit

Source: FLCCC

Accessed 01/18/2024

Figure 3. Timing of the Initiation of Anti-Inflammatory Therapy



Source: FLCCC

Ivermectin, low molecular weight heparin (LMWH) and corticosteroids form the foundation of care for the hospitalized patient.

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Severe Covid Pulmonary Disease

- I. Methylprednisolone 250 mg daily for at least 3 days, then titrate guided by clinical status and CRP
- II. Ivermectin 1 mg/kg for 5 days
- III. Melatonin 10 mg by mouth at night
- IV. Enoxaparin 60 mg daily; critically ill patients usually have some degree of renal impairment and will require a renally adjusted lower dose. Patients with very high D- dimer and or thrombotic complications may require full anticoagulant doses of Lovenox. It may be prudent to monitor Xa levels aiming for 0.4-0.8 IU/ml (a somewhat lower anti-Xa).
- V. Vitamin C 3 g every 6 hours to 25 g every 12 hours

Severe Covid Pulmonary Disease

- Consider:
- VI. Cyproheptadine 4–8 mg by mouth every 6 hours
- VII. Fluvoxamine 50-100 mg twice daily
- VIII. Spironolactone 100 mg twice daily
- IX. Thiamine 200 mg every 12 hours
- X. NAC 1200 mg by mouth twice daily [154]
- XI. Finasteride 10 mg daily or dutasteride 2 mg day 1 then 1 mg daily or bicalutamide 150 mg daily
- XII. Omega-3 fatty acids 4 g/day
- XIII. Famotidine 40 mg twice daily
- XIV. Calcifediol (0.014 mg/kg) use as a single dose