KEY FACTS

ETIOLOGY/PATHOGENESIS

- Viral infection transmitted by exposure to infected animals or humans
- Individuals with symptoms and appropriate travel or exposure history should be tested

CLINICAL ISSUES

- Outbreak originating in Wuhan, China in December 2019
- Declared pandemic by WHO on 3/11/20
- Presentation: Fever, headache, myalgias, cough, dyspnea
- CT: Bilateral multiple lobar consolidation or ground-glass opacity with subsegmental areas of consolidation
- Labs: RT-PCR, serology, viral isolation (not recommended)
- Supportive therapy: Antipyretics, oxygen, ventilation, antivirals (under investigation), convalescent plasma
- Estimated fatality rates: 0.7-13% (higher in older individuals; hypertension, diabetes, obesity, and cardiovascular disease)

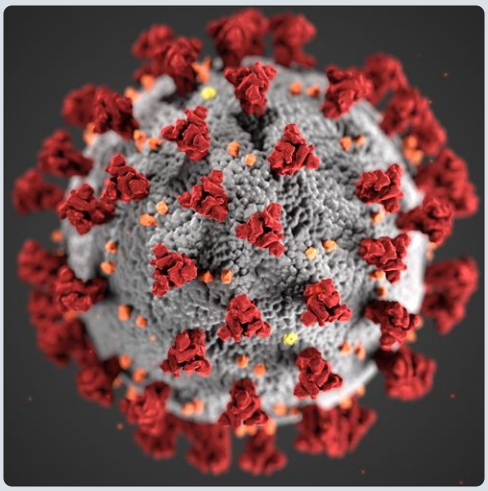
MICROSCOPIC

- Initial pathology reports: Diffuse alveolar damage, edema, cellular fibromyxoid exudates, pneumocyte desquamation, hyaline membrane formation, lymphocyte-predominant inflammatory infiltrates, multinucleated syncytial cells, and no obvious viral inclusions

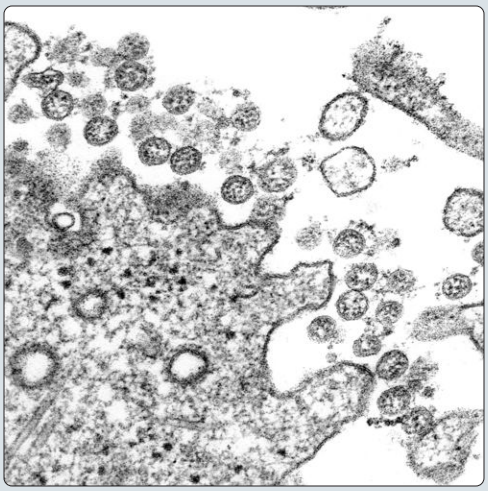
TOP DIFFERENTIAL DIAGNOSES

- Other respiratory viral infections, including other coronaviruses, influenza A or B, respiratory syncytial virus, cytomegalovirus, and herpes simplex virus
- Bacterial, mycobacterial, and fungal infections, including *Mycoplasma pneumoniae*, *Mycobacterium avium* complex, and *Cryptococcus*
- Noninfectious causes of diffuse alveolar damage, including complications of transplantation, connective tissue diseases, acute exacerbation of idiopathic pulmonary fibrosis, drugs, radiation therapy, and acute interstitial pneumonia

Severe Acute Respiratory Syndrome Coronavirus 2

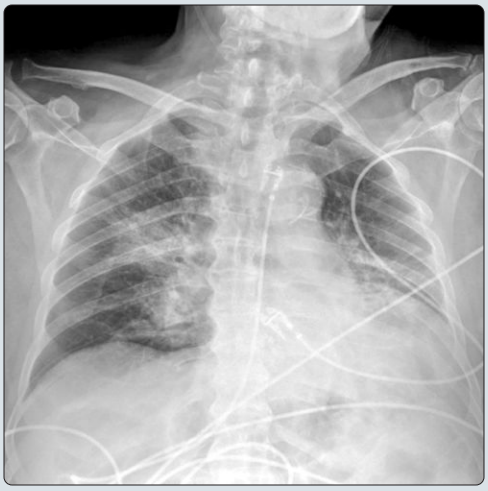


Ultrastructural Features

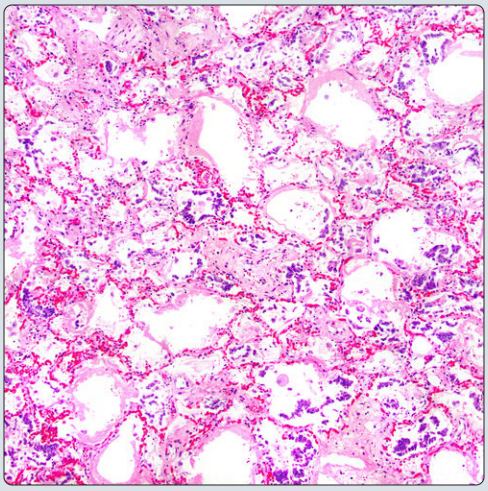


(Left) *This illustration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) shows surface spikes (red), giving a halo appearance incorporated into the name "corona." (Courtesy A. Eckert, MS and D. Higgins, MAMS.)* **(Right)** *This transmission electron micrograph shows spherical extracellular particles with surface spikes and cross sections through the viral genome (black dots), features characteristic of SARS-CoV-2. (Courtesy C. Goldsmith, CDC and A. Tamin, CDC.)*

Chest X-Ray



Histopathologic Features



(Left) *This portable chest X-ray shows parenchymal opacities with asymmetric distribution, consolidation in the right perihilar region, and opacity in left lung base, findings consistent with COVID-19 pneumonia.* **(Right)** *This autopsy lung section shows hyaline membranes, interstitial edema and inflammation, and squamous metaplasia, features consistent with diffuse alveolar damage. Confirmation of SARS-CoV-2 infection requires IHC, ISH, or PCR. (Courtesy R. Padera, Jr., MD, PhD.)*

TERMINOLOGY

Definitions

- Severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2)
- Previously referred to as 2019 novel coronavirus (2019-nCoV)
- Coronaviridae family: "Corona" (crown, halo) ultrastructural appearance

ETIOLOGY/PATHOGENESIS

Infectious Agents

- Viral illness with human-to-human transmission by respiratory droplets
- No evidence for intrauterine vertical transmission
- Unknown animal source (likely bats)
- *Betacoronavirus* belonging to *Sarbecovirus* subgenus; virus sequences similar to bat coronaviruses and SARS-CoV
- Angiotensin-converting enzyme 2 (*ACE2*) used for cellular entry and serine protease *TMPRSS2* used for spike protein (S) priming
- Organ damage likely due to combination of cytokine storm, microthrombosis, hypoxemia, and ischemia
- Incubation period: 2-14 days
- Contagious period unknown; may extend beyond symptom resolution

CLINICAL ISSUES

Epidemiology

- Initial source of virus is unknown
- 1st identified cases linked to seafood and animal market in Wuhan, China
- Declared pandemic by World Health Organization on 3/11/20
- > 3 million confirmed cases and > 210,000 deaths reported in 185 countries/regions worldwide (as of 4/27/20)
  - Highest number of confirmed cases in United States, Europe (Spain, Italy, France, Germany, United Kingdom), Turkey, Iran, China, Russia, and Brazil
  - > 1 million cases and > 56,000 deaths in United States (as of 4/27/20)
  - Overall mortality rate uncertain due to unknown number of asymptomatic cases (estimated 0.7-13%)
- Majority of cases in adults; severe cases relatively uncommon in pediatric population

Presentation

- Infections may be asymptomatic or associated with mild symptoms
- Severe respiratory illness in ~ 16% of cases
- Common symptoms include fever, cough, dyspnea, chills, myalgia, headache, sore throat, and new loss of taste or smell; variable skin manifestations also reported
- Laboratory abnormalities may include leukopenia, leukocytosis, lymphopenia, thrombocytopenia, elevated alanine aminotransferase and aspartate aminotransferase levels

Laboratory Tests

- RT-PCR and serology (performed by public health and some hospital and commercial laboratories)
- Nasopharyngeal (NP) swab preferred initial testing specimen
- Other upper respiratory (oropharyngeal, nasal midturbinate, anterior nares, and NP wash/aspirate) and lower respiratory (bronchoalveolar lavage, tracheal aspirate, and sputum) specimens can also be tested
- CDC recommendations for postmortem specimen collection in suspected cases
  - NP swab and swabs from each lung
  - Formalin-fixed tissue from lungs, upper airway, and other major organs

Treatment

- No vaccines or specific antiviral treatments currently available
  - Remdesivir (RNA polymerase inhibitor), lopinavir/ritonavir (protease inhibitors), interferon-β, chloroquine, tocilizumab (anti-interleukin-6 monoclonal antibody), and convalescent plasma from recovered individuals are under investigation
  - Messenger RNA vaccine technology and other advanced techniques currently employed
- Avoid potential for exposure by washing hands and avoiding close contact with sick individuals
- Spread of disease from asymptomatic individuals may be decreased through use of face masks
- Treatment is primarily supportive (antipyretics, oxygen, ventilation)

Prognosis

- Complications include acute respiratory distress syndrome, viremia, acute cardiac injury, and secondary infection
- Higher risk in older adults, people living in nursing homes or long-term care facilities, and individuals of any age with severe underlying conditions (e.g., cardiovascular disease, diabetes, pulmonary disease, liver disease, chronic kidney disease, and severe obesity)
- 80% of deaths reported in individuals over 65 years old; worst outcomes in individuals > 85 years old

IMAGING

Radiographic Findings

- CT: Bilateral multiple lobar consolidation (ICU cases) or ground-glass opacity (non-ICU cases) with subsegmental areas of consolidation

MICROBIOLOGY

Virus Features

- Enveloped, single-stranded RNA virus
- 60-140 nm in size, helical nucleocapsid, 9- to 12-nm surface projections (spikes)
- ~ 30,000-nucleotide genome (encoding nonstructural proteins, as well as spike, envelope, membrane, and nucleocapsid)

Culture

- Virus isolated in human airway epithelial cells and Vero-CCL81, Vero E6, and Huh-7 cell lines
- Cytopathic effects observed after 4-6 days
- Not recommended for diagnosis

MACROSCOPIC

General Features

- Primary finding is heavy edematous lungs
- Reported skin manifestations include erythematous rash, widespread urticaria, and varicella-like vesicles

MICROSCOPIC

Histologic Features

- Limited reports of biopsy or postmortem histopathology
  - Lungs: Reactive type II pneumocytes and acute to organizing diffuse alveolar damage in majority of cases; subset with acute bronchiolitis, bronchopneumonia, and multinucleated giant cells
    - Possible viral inclusions reported in minority of cases
  - Trachea: Mild to moderate edema; rare acute tracheitis
  - Heart: Rare lymphocytic myocarditis; changes of prior injury and hypertension
  - Spleen: Occasional white pulp depletion
  - Kidneys: Assessment of acute injury limited by autolysis; chronic changes from preexisting disease
  - Liver: Mild periportal lymphocytic inflammation and patchy necrosis; chronic changes from preexisting disease

Biosafety Considerations

- Autopsies should be performed in negative pressure rooms, using standard personal protective equipment and N95 respirator or higher, with avoidance of bone saws or other aerosol-generating procedures
- Routine cleaning and disinfection procedures are considered appropriate
- Frozen sections should be avoided to prevent cryostat-generated aerosols
- Routine formalin fixation and heating during paraffin infiltration should inactivate virus

ANCILLARY TESTS

Immunohistochemistry

- Anti-nucleocapsid and anti-spike antibodies stain cytoplasm of infected cells

In Situ Hybridization

- Viral RNA can be detected with targeted probes

Electron Microscopy

- Viral particles reported in lung (type I and type II pneumocytes), trachea (epithelial cells and extracellular mucus), kidney, (tubular epithelium and endothelial cells) and large intestines
- Spherical particles (60-140 nm in diameter) with some pleomorphism and distinctive spikes (9-12 nm)

DIFFERENTIAL DIAGNOSIS

Other Coronavirus Infections

- HCoV 229E, NL63, OC43, and HKU1; MERS-CoV, SARS-CoV
  - Confirmation by molecular testing or serology

Other Respiratory Viral Infections

- Influenza A or B, respiratory syncytial virus, cytomegalovirus, herpes simplex virus, etc.
  - Confirmation by histology, IHC, molecular testing, or serology

Bacterial, Mycobacterial, and Fungal Infections

- *Mycoplasma pneumoniae*, *Mycobacterium avium* complex, *Cryptococcus* infections, etc.
  - Positive Gram, MSS, or AFB stains, molecular testing, culture results, or serology

Noninfectious Causes of Diffuse Alveolar Damage

- Complications of transplantation, connective tissue diseases, acute exacerbation of idiopathic pulmonary fibrosis, drugs, radiation therapy, acute interstitial pneumonia
  - Negative viral serology, molecular testing, and cultures

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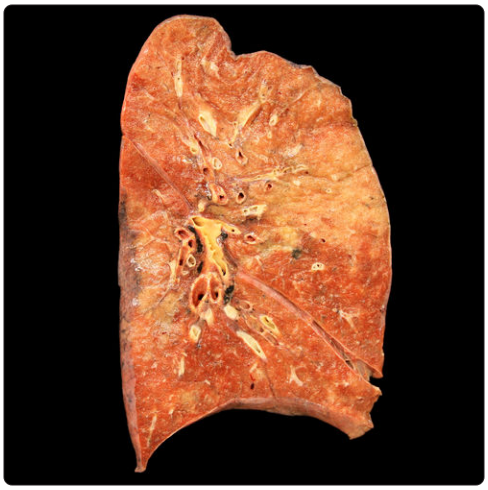
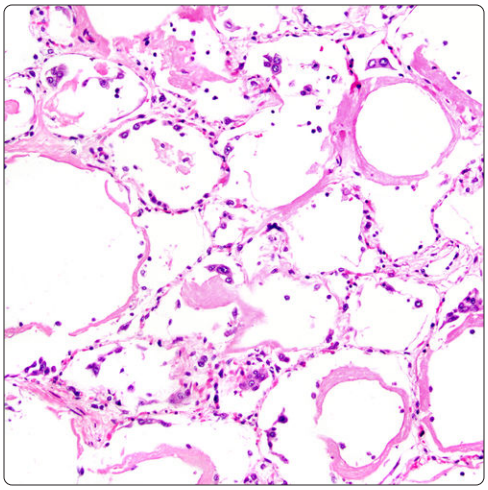
Gross Features

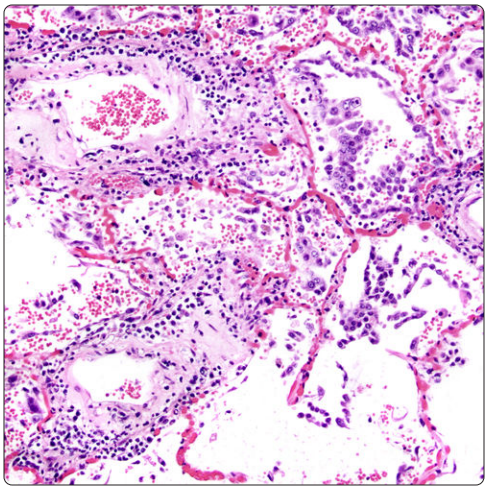


Hyaline Membranes

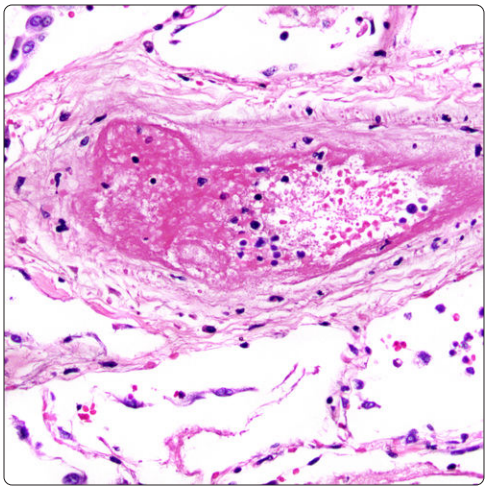


(Left) *This section of lung from a fatal case of COVID-19 shows areas of red congested and edematous parenchyma, consistent with diffuse alveolar damage. (Courtesy R. Padera, Jr., MD, PhD.)* **(Right)** *Early histologic findings in COVID-19 pneumonia include eosinophilic hyaline membranes consistent with exudative (acute) diffuse alveolar damage. (Courtesy R. Padera, Jr., MD, PhD.)*

Interstitial Inflammation and Edema

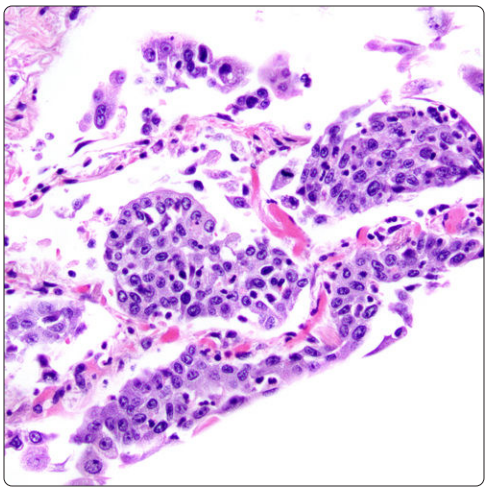


Fibrin Thrombi

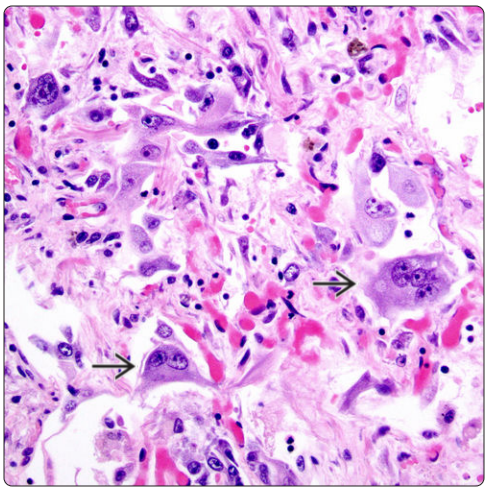


(Left) *COVID-19 pneumonia includes variable amounts of interstitial and perivascular chronic inflammation and edema. (Courtesy R. Padera, Jr., MD, PhD.)* **(Right)** *Fibrin thrombi involving small vessels are occasionally present in COVID-19 pneumonia. (Courtesy R. Padera, Jr., MD, PhD.)*

Squamous Metaplasia

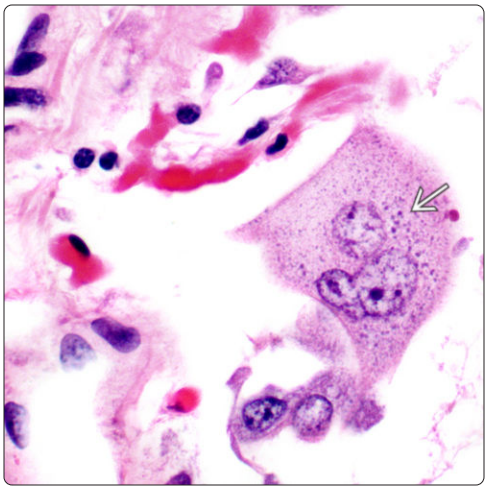


Multinucleated Giant Cells

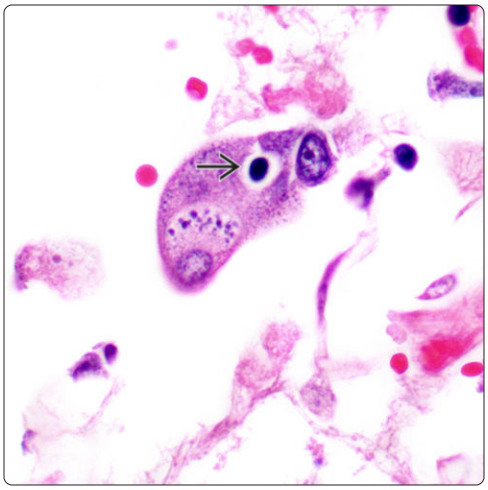


(Left) *Squamous metaplasia is frequently present in the lungs in COVID-19 pneumonia, and can exhibit significant cytologic atypia. (Courtesy R. Padera, Jr., MD, PhD.)* **(Right)** *Multinucleated giant cells with prominent reactive-appearing nucleoli are variably present in COVID-19 pneumonia. (Courtesy R. Padera, Jr., MD, PhD.)*

Cytoplasmic Inclusions

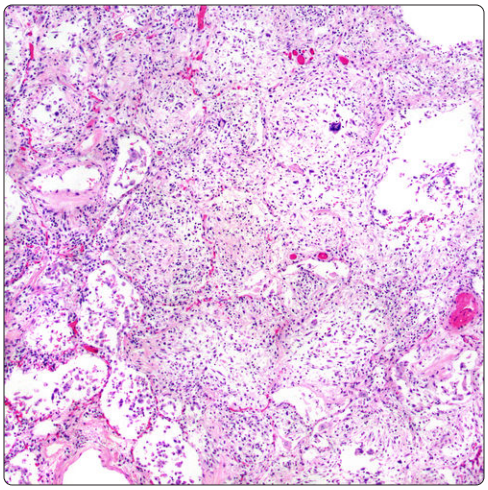


Lymphophagocytosis

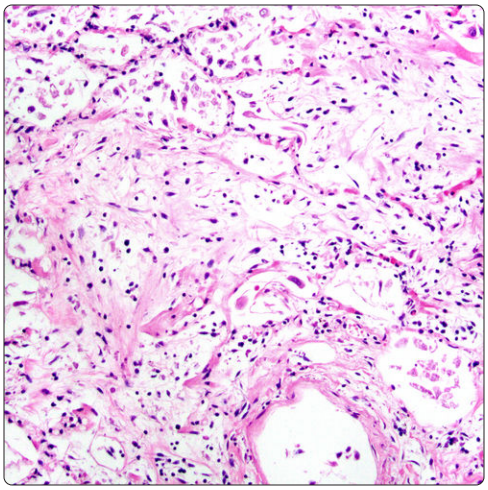


(Left) *Multinucleated giant cells may contain basophilic cytoplasmic inclusions of unclear etiology ⇨. (Courtesy R. Padera, Jr., MD, PhD.)* **(Right)** *A reactive histiocyte is present containing an engulfed lymphocyte ⇨ that should not be confused with a viral inclusion. (Courtesy R. Padera, Jr., MD, PhD.)*

Proliferative (Organizing) Phase

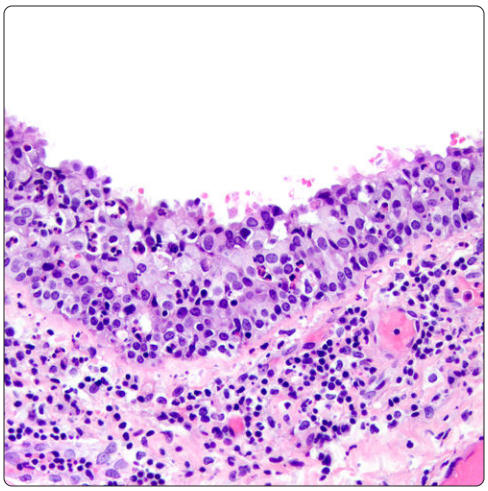


Fibroblast Proliferation

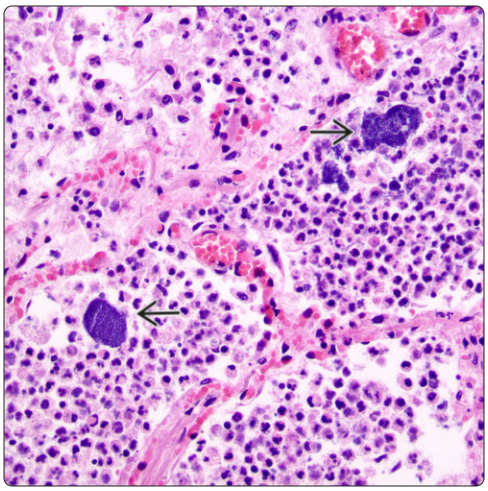


(Left) *Later changes in COVID-19 pneumonia include proliferation of pneumocytes and fibroblasts to form loose organizing connective tissue. (Courtesy R. Padera, Jr., MD, PhD.)* **(Right)** *Fibroblast proliferation and collagen production in alveolar spaces reflects organized alveolar damage. (Courtesy R. Padera, Jr., MD, PhD.)*

Large Airway Involvement



Bacterial Bronchopneumonia



(Left) *Large airways in COVID-19 occasionally show lymphocytic bronchitis/bronchiolitis with reactive epithelial changes and occasional intraepithelial neutrophils. (Courtesy R. Padera, Jr., MD, PhD.)* **(Right)** *Coinfections with bacteria, fungi, and other respiratory viruses are common with COVID-19. This section shows multiple collections of basophilic bacteria ⇨ embedded in intraalveolar neutrophils. (Courtesy R. Padera, Jr., MD, PhD.)*