

SARS CoV-2 Illness: Focus on Pulmonary Disease

By: Joseph A. Tonner, MD

Date of Release; December 15, 2020 **Expiration Date:** December 14, 2021 **Estimated Completion Time:** 30 minutes

How to Earn this CME Credit:

1. Read the Article and complete the post-test online at UF CME.

CME Credit Eligibility:

A minimum passing grade of 80% must be achieved. Certificates of credit/completion will be emailed automatically after completion of post-test with a passing grade, and a course evaluation.

Learning Objectives: Upon completion of this activity, participants should be able to:

1. Identify the common symptoms of COVID-19 disease
2. Know how COVID-19 is primarily transmitted
3. List current inpatient treatments for COVID-19

Target Audience: This educational activity is intended for physicians.

Accreditation: The University of Florida College of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit: The University of Florida College of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosures: Dr. Tonner disclosed that he has no relevant financial relationships. No one else in a position to control content has any financial relationship(s) to disclose.

CME Advisory Committee Disclosure: Conflict of interest information for the CME Advisory Committee members can be found on the following website: <https://cme.ufl.edu/disclosure/>.

Contact Information: For questions, please contact Jackie Owens at evp@acms.net.

SARS CoV-2 Illness: Focus on Pulmonary Disease



Joseph A. Tonner, MD, SIMEDHealth Pulmonology



Introduction:

Severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2"), or COVID-19 was first identified as a cluster of pneumonia cases in Wuhan, China at the end of 2019. SARS-CoV-2 was declared a pandemic by the World Health Organization (WHO) in February 2020. The virus is a beta coronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus. The COVID-19 RNA sequence is similar to bat coronavirus and experts feel bats are the likely primary source. Globally, as of early November over 50

million COVID-19 cases have been confirmed and the virus has claimed the lives of approximately 1.3 million individuals worldwide. There were over 240,000 deaths in the US, over 17,000 in Florida, and 78 in Alachua County. COVID-19 death rates per 100,000 reported COVID-19 cases in Florida were 79, compared to a US high of 184 in New Jersey, and a low of 9 in Vermont (286 in New York City).

Epidemiology:

Historically, annual death rates from pneumonia and influenza in the US vary between 5-8% of all reported deaths. In the 15th week of 2020 the deaths from COVID-19 accounted for approximately 26% of all US deaths. The percentage of deaths due to pneumonia/influenza/COVID-19 have steadily declined since late July, levelling off in mid-September, and by November are now increasing again statewide and nationally.

As of early November approximately 3.7% of Alachua County residents have tested positive for COVID-19 since the onset of testing, with a hospitalization rate of 5% and a death rate of 0.7%. (The Alachua County death rate is well below the state and national rates primarily due to the significantly lower average age of COVID-19 patients in the county, and in a biased opinion, due to the high quality of medical care provided in the Alachua community.) Unfortunately, age-adjusted hospitalization rates for Hispanic/Latino, Native American, and Black persons are 4.5, 4.4, and 4.3 times the Caucasian hospitalization rates respectively. It is believed this disparity is multifactorial and related to health care access and prevalence of comorbid conditions.

We now know transmission of COVID-19 is largely through respiratory droplets, which may extend beyond 6 feet from the person spreading the droplets. Long-range airborne transmission does not seem to be a primary mode of transmission. COVID-19 has been detected in stool, blood, ocular secretions and semen, but these are not likely sources of transmission. For example, transfusion-transmission has not been reported, and COVID-19 has not been reported to be transmitted through non-mucous membranes such as abrasions/cuts.

Infected individuals are thought to transmit the virus two days before the onset of symptoms. Transmission after 7 to 10 days of illness is unlikely, hence the 14-day quarantine recommended by many experts upon exposure to a known COVID-19 positive person, and the ten day period of isolation after diagnosis of COVID-19. It is possible to have prolonged COVID-19 viral RNA detected on testing, but importantly, the continued detection does not indicate prolonged infectiousness. Transmission of COVID-19 in asymptomatic patients has been documented, but it is unclear how much this contributes to the current pandemic. Transmission rates amongst household contacts have been reported variously between 15% and 37%. Transmission from pets is not a major source of human infection, although pets may become infected with COVID-19, cats more so than dogs.

Protective immunity after COVID-19 infection may be humoral or cell-mediated. Authorities feel the magnitude of antibody response may be associated with the severity of disease in the patient. A durable CD4 and CD8 T cell response has been detected in COVID-19 patients and also in individuals who have received investigational vaccines. Reinfection risks in the same individual previously infected with COVID-19 appears low but there have been case reports. We do not yet know whether having a positive COVID-19 antibody test after infection provides immunity.

Clinical features of COVID-19:

Asymptomatic infections may be as high as 30 to 40% based on population-based testing, however longitudinal follow-up was absent in most of these reports. Asymptomatic individuals may go on to develop symptoms which occur at a median of 4 days after the initial positive RT-PCR (reverse-transcription polymerase chain reaction) test, with a range of 3-7 days.

The CDC reports the prevalence of the following symptoms among 370,000 confirmed COVID-19 individuals:

- Cough – 50%.
- Fever (greater than 100.4°F) – 43%.
- Myalgias – 36%.

- Headache – 34%.
- Dyspnea – 29%.
- Sore throat – 20%.
- Diarrhea – 19%.
- Nausea/vomiting – 12%.
- Abdominal pain – < 10%.
- Loss of smell or taste – < 10%.
- Rhinorrhea – < 10%.
- Conjunctivitis – < 10%.
- Abdominal pain – < 10%
- Falls, general health decline, delirium: Mainly reported in individuals greater than 80 years old.

Laboratory findings: lymphopenia is frequent with 90% having lymphocyte counts less than 1,500. Both leukocytosis and leukopenia were reported in approximately 15%. The following are often elevated: CRP, D-dimer, ferritin, LDH, troponin, platelets, liver enzymes, pro time, and CPK. Prolactin is initially usually normal, but often is elevated in ICU patients. Acute kidney injury is also reported (please see Dr. George’s article in this issue of House Calls).

Imaging characteristics: a small retrospective study from Hong Kong suggested 20% of COVID-19-positive patients had a normal initial chest x-ray. Commonly though, chest x-rays show consolidation and “ground-glass opacities” bilaterally, and with a predominance in the peripheral lower lung zones. Transporting the patient to the CT scanner is problematic and frequently not performed for infection control reasons. When done, chest CT scans may show “ground-glass opacifications,” with or without mixed consolidations, peripherally thickened pleural thickening, intra-lobular septal thickening, and air bronchograms. Less common features include “crazy paving,” bronchiectasis, pleural effusion, pericardial effusion and lymphadenopathy.

Unfortunately, hypercoagulability is quite common with COVID-19 infections, and is poorly understood. One study reported a 30% incidence of venous thromboembolic disease in COVID-19 ICU patients. The risk of pulmonary venous thromboembolism in non-ICU patients was found to be 8.3% by chest CT angiogram in 1,240 hospitalized patients. Endothelial injury, stasis, and a general hypercoagulable state all play a role. Prothrombotic factors have been reported: elevated factor VIII, elevated fibrinogen, circulating prothrombotic microparticles, neutrophil extracellular traps, and hyperviscosity. Risk factors for hypercoagulability include older age, male sex, Hispanic ethnicity, CAD, prior MI and D-dimer greater than 500 at the time of presentation.

Treatment

Outpatient Management:

Guidelines for treatment of COVID-19 are still developing and the Food and Drug Administration (FDA) has only recently approved two agents for treatment in hospital settings, and one for those at risk for progressing to severe disease. As of this writing there are no FDA-approved medicines to be used for those with mild disease. Mild disease is defined as those who maintain oxygen saturation of 95% or higher, or those with only mild dyspnea. We do now know from double-blinded randomized trials published in the New England Journal of Medicine that hydroxychloroquine has no COVID-19 prophylactic or treatment advantage.

Outpatient management is recommended for patients who are less than 65 years of age with little or no comorbid conditions, with no or only mild dyspnea, and an oxygen saturation of 95% or greater. Initial telephone triage and subsequent telemedicine services are highly recommended for evaluation and ongoing care of these patients. Risk factors for progression to more severe disease include: age 65 years or older, resident of long-term care facility, chronic lung disease (COPD, moderate-severe asthma, cystic fibrosis, pulmonary fibrosis), cardiovascular disease, cancer, hypertension, BMI greater than 30, diabetes mellitus, chronic kidney disease, chronic liver disease, cerebrovascular disease, neurologic disorders including dementia, tobacco smoking, hematologic disorders (sickle cell disease, thalassemia), and pregnancy.

Consideration should occur for referring patients to designated outpatient clinics with capabilities to evaluate patients with COVID-19 or persons under investigation if they have mild dyspnea and oxygen saturation in the range of 91-94% or have risk factors as listed above for severe disease. Any patients with moderate dyspnea or any other concerning symptoms such as orthostasis should also be referred to designated outpatient clinic settings.

Referral to an emergency department should be considered only for patients with shortness of breath at rest - including inability to speak in complete sentences, - those with oxygen saturations less than 91%, or experiencing altered mentation.

Inpatient Management:

A detailed description of COVID-19 inpatient management is beyond the scope of this article, but a few comments are appropriate.

There has been speculation that ACE inhibitors and ARBs might adversely affect COVID-19 patients, but observational studies have not supported this theory.

Statin use has not been associated with increased risk of COVID-19-induced liver injury, and a retrospective study suggested ICU patients on statins may have a lower death rate.

Dexamethasone has some benefit and is recommended for severely ill patients (those requiring high flow oxygen, or mechanical ventilation). The recommended dose is 6 mg daily for 10 days or until discharge, whichever is shorter. Equivalent doses of other steroids can be substituted if dexamethasone is not available, but some studies suggest minimal statistical difference. The CDC and several highly respected authors did not recommend dexamethasone for prevention of COVID-19 illness, or mild to moderate illness where the patient is not requiring supplemental oxygen. Overall, when dexamethasone was used in severely ill patients the 28-day mortality was reduced by approximately 17%. There was a 36% relative reduction in mortality in mechanically ventilated patients or patients on ECMO, and the mortality reduction was approximately 18% in patients on high flow oxygen or BiPAP.

Remdesivir has received FDA approval for emergency use in hospitalized COVID-19 patients with severe illness. Remdesivir is a novel nucleotide analog inhibitor RNA-dependent RNA polymerases and has been seen to have antiviral activity against COVID-19 in vitro. The multinational, randomized, placebo-controlled ACTT-1 study showed remdesivir resulted in a faster recovery, defined as cessation of oxygen therapy or faster time to discharge. It is not yet clear whether remdesivir reduces mortality, as there was a 29-day trend towards reduced mortality but it was not clinically significant. The suggested dose of remdesivir is 200 mg intravenously on day one followed by 100 mg daily for 5 days, with extension to 10 days in mechanically ventilated patients who have no initial response. Remdesivir is not recommended for patients with a GFR less than 30, and remdesivir did not appear to reduce the time to recovery in 119 patients followed who did not experience hypoxia or tachypnea.

Clinical trials are ongoing for convalescent plasma/neutralizing antibodies (CP/NA). The FDA has granted emergency authorization for the use of CP/NA in hospitalized patients. High levels of neutralizing antibody could be beneficial, but randomized double blinded clinical trials are lacking.

Preliminary results suggest a combination of two human monoclonal antibodies, one derived from a convalescent patient, and one derived from recombinant antibody, reduced the rate of emergency department visits and hospitalizations and lowered viral levels. The monoclonal antibodies work by neutralizing a COVID-19 spike protein, preventing viral entry into the cell. Bamlanivimab is a monoclonal antibody product recently approved under the FDA's emergency use authorization for those who are positive for COVID-19 and are at high-risk for progressing to severe illness.

Other treatments under investigation include Favipiravir (RNA polymerase inhibitor), interferons (especially interferon-beta), interleukin-6 receptor blockers such as Tocilizumab which could potentially block the cytokine storm associated with COVID-19, IL-1 RB (anakinra), mesenchymal stem cells, other cytokine inhibitors, complement inhibitors, bradykinin pathway inhibitors, recombinant hematopoietic colony-stimulating factors, and anti-protozoal/anti-parasite therapy (nitazoxanide and ivermectin).

To date there is no clinical data to support the use of famotidine, colchicine, vitamin D, or zinc.

Essentially, it is recommended that patients with non-severe disease receive supportive care only.

Long-term COVID-19 symptoms and complications:

According to WHO, the time to recovery for patients who had mild COVID-19 symptoms is approximately 2 weeks, but up to 6 weeks for those who had severe disease. Fortunately, most patients recover completely and few with mild symptoms will develop long-term complications. The risk factors for developing long-term complications include older age and existence of comorbid conditions. The common persistent symptoms include: fatigue (53%), dyspnea (43%), joint pain (27%), chest pain (22%), and headache. Fever does not appear to be a persistent symptom.

More serious complications of COVID-19 appear to include cardiomyopathy, arrhythmias, post-inflammatory pulmonary fibrosis, stroke, seizure, Guillain-Barré syndrome, thrombosis of arteries or veins for up to 1-2 months after the illness, chronic fatigue syndrome, posttraumatic stress disorder (especially in recovered ICU patients), vertigo, and hair loss. And there may be an increased risk of Parkinson's disease and Alzheimer's.

Approximately 25% of hospitalized patients with COVID-19 develop myocardial injury and/or risk of arrhythmia. The risk factors identified for these cardiac complications include hypertension, obesity, hyperlipidemia, and diabetes mellitus. Pathogenesis includes viral infiltration, inflammation, micro-thrombi and down-regulation of the ACE-2 receptors. Presumably, endothelial cells in patients with cardiac risk factors respond adversely by releasing pro-inflammatory cytokines.

Pulmonary fibrosis is a devastating complication of COVID-19. The incidence is evolving as the period of recovery time expands, and more people are recovering. Patients with underlying fibrotic lung disease are at the highest risk of developing increased pulmonary fibrosis, including those patients with pre-existing idiopathic pulmonary fibrosis (IPF). Other risk factors include age, illness severity, ICU length of stay, mechanical ventilation, smoking, and chronic alcoholism. Extrapolation from SARS or Middle East Respiratory Syndrome (MERS) data suggest up to 30% of COVID-19 patients may have some persistent pulmonary abnormality or complaint. Follow-up of healthcare workers from Hong Kong and Beijing with MERS (2 years and 15 years respectively) showed most had only mild abnormalities such as a mild reduction in the diffusion capacity (70-80% of predicted). However, 38% of the 71 patients in the Beijing study had persisting ground-glass opacities and cord-like consolidations on CT scan, but after 12 months these generally occupy less than 10% of the lung.

Pathologically, the lungs show acute and organizing diffuse alveolar damage and fibrosis with honeycomb-like remodeling and bronchial metaplasia. In addition to the changes commonly found in diffuse alveolar damage (DAD), there are also changes commonly found in interstitial lung disease such as fibrotic areas with honeycomb-like remodeling and bronchial metaplasia.

Currently we have no proven, effective, targeted therapy against COVID-19-induced pulmonary fibrosis. Therefore risk reduction measures and protecting the lung from other incidental injuries are paramount. Limiting the factors perpetuating the cycle of lung injury, inflammatory response, and fibroproliferation will be key as we learn more about COVID-19 pulmonary disease. All COVID-19 patients should be counseled to achieve 100% abstinence from cigarette smoking. Also avoidance of indoor and outdoor particulate matter is highly recommended.

Vaccines:

Numerous vaccine trials are underway - sponsored by many large pharmaceutical companies and heavily funded by governments, including the United States with Operation Warp Speed, a \$10 billion initiative. There are reportedly around 200 potential vaccines under investigation, 45 of them in clinical trials. Some vaccines will require 2 doses, usually 14-21 days apart and some as long as 56 days apart.

Reportedly, phase 3 trials will have to demonstrate at least 50% effectiveness for the US Food and Drug Administration (FDA) to contract with these vaccine-producing companies. Experts suggest herd immunity needs to approach 60%, to make a dent in the COVID-19 pandemic (this includes individuals recovered from COVID-19 infection with neutralizing antibodies/cell-mediated immunity, and those who mount an effective immunologic response to a vaccine).

Types of vaccines under investigation include nucleic acid-based (mRNA and DNA), viral-vector vaccines, and inactivated or recombinant protein vaccines.

The vaccine issues are complex. Some express caution and advise to wait for a very effective vaccine. Their theory is that a less effective vaccine may mitigate future neutralizing antibody formation, thereby resulting in less antibody response when what could be a more effective vaccine is later administered.

Summary:

The COVID-19 pandemic has triggered an unprecedented explosion of research, high-quality journal articles and vaccine development. Unfortunately, there has also been a plethora of mindless chitchat on mainstream and social media promoting unsubstantiated remedies. We as clinicians should advise our patients to rely on evidence-based medicine, and we have a responsibility to be suppliers of evidence-based advice. The dissection of the data will continue on for years to help us learn more about early and accurate diagnosis, and acute and long-term treatments. Multiple COVID-19-related clinical trials are open for patient enrollment in our region through SIMEDHealth, the Gainesville VA, and the University of Florida.

Social distance! Wear a mask! Don't smoke! Wash your hands! And, when available, get an effective vaccine. Stay safe!

Bibliography:

UpToDate: Coronavirus Disease 2019 (COVID-19): Epidemiology, Virology, and Prevention. Kenneth McIntosh, M.D. (Author); Martin S. Hirsch, M.D. (Section Editor); Allyson Bloom, M.D. (Deputy Editor).

UpToDate: Coronavirus Disease 2019 (COVID-19): Hypercoagulability. Adam Cuker, M.D., M.S. and Florida Peyvandi, M.D., Ph.D. (Authors); Lawrence LK Leung, M.D. (Section Editor); Jennifer S. Tirnauer, M.D. (Deputy Editor).

UpToDate: Coronavirus Disease 2019 (COVID-19): Outpatient Evaluation and Management in Adults. Peter Cohen, M.D. and Jessamyn Blaue, M.D. (Authors); Joan G. Elmore, M.D., M.P.H. (Section Editor); Lisa Cunins, M.D. and Allyson Bloom, M.D. (Deputy Editors).

UpToDate: Coronavirus Disease 2019 (COVID-19): Management in Hospitalized Adults. Arthur Y. Kim, M.D., FIDSA and Rajesh T. Gandhi, M.D., FIDSA (Authors); Martin S. Hirsch, M.D. (Section Editor); Allyson Bloom, M.D. (Deputy Editor).

Long Term Respiratory Complications of COVID-19; Emily Fraser; The BJM; August 3, 2020; BJM2020 370:m3001

Pulmonary Embolism in Patients Hospitalized with COVID-19 (From a New York Health System); Hai Xu, M.D., et al; Journal of American Cardiology, October 15, 2020; www.ajconline.org .

Histopathologic Observations in COVID-19: A Systemic Review; Deshmukh, Vishwajit, et al; Journal of Clinical Pathology, August 18, 2020; doi: 10.1136/jclinipath-2020-206995

Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies; Ademola S. Ojo, Simon A. Balogun, Oyeronke T. Williams, Olusegun S. Ojo; Pulmonary Medicine, August 10, 2020; Article ID: 6175964, 2020; <https://doi.org/10.115/2020/6175964>

CME Post-Test

Center for Disease Control: <https://www.cdc.gov/coronavirus/2019-ncov>

SARS CoV-2 Illness: Focus on Pulmonary Disease

By: Joseph A. Tonner, MD

CME Questions (select one answer)

1. Age-adjusted hospitalization rates in which the following groups of Covid-19 patients are higher than in caucasians:

- A. Hispanics / Latinos
- B. Native Americans
- C. African Americans
- D. All of the above

2. Transmission of Covid-19 occurs largely through which one of the following:

- A. Abrasions / Cuts
- B. Transfusions
- C. Respiratory droplets
- D. Contact with surfaces

3. Which of the following are the most prevalent symptoms among Covid-19 patients:

- A. Loss of smell and taste
- B. Abdominal pain and diarrhea
- C. Rhinorrhea and sore throat
- D. Cough and fever

4. The following drugs have shown some benefit in Covid-19 inpatients:

- A. Hydroxychloroquine alone
- B. Hydroxychloroquine and Dexamethasone
- C. Hydroxychloroquine and Remdesivir
- D. Dexamethasone and Remdesivir

5. Serious complications of Covid-19 include which of the following:

- A. Cardiomyopathy
- B. Cardiac arrhythmias
- C. Pulmonary fibrosis

D. All of the above

6. Herd immunity needs to approach what percent to make a dent in the Covid-19 pandemic:

- A. 10%
- B. 30%
- C. 60%
- D. 90%

7. Hypercoagulability is quite common with Covid-19 infections:

- A. True
- B. False

8. Risk factors for progression to more severe Covid-19 disease include:

- A. Age 65-years or older
- B. Resident of long-term care facility
- C. Chronic lung disease
- D. Cardiovascular disease
- E. All of the above.

9. To date there is clinical data in Covid-19 patients to support the use of:

- A. Famotidine
- B. Colchicine
- C. Vitamin D
- D. Zinc
- E. None of the above

CME Post-Test

10. Pulmonary fibrosis is a devastating complication of Covid-19-risk factors include:

- A. Underlying fibrotic lung disease
- B. Older age
- C. Illness severity
- D. Smoking and alcoholism
- E. All of the above

SARS CoV-2 Illness:

Focus on Pulmonary Disease

By: Joseph A. Tonner, MD

CME Credit Information -

Post Test Link:

<https://www.proprofs.com/quiz-school/ugc/story.php?title=1438-2178-sars-cov2-illness-focus-on-pulmonary-disease-alachua-county-medical-societyjj>

To take the Post-test, click on the link above to access the UF CME ProProfs program. Please complete the evaluation form after receiving a passing grade. Your test will be graded upon submittal with a Certificate emailed automatically upon completion.