ABSTRACT:
What we have learned about COVID-19 is ongoing as research continues to evolve. This article will serve to provide a succinct, comprehensive overview of SARS-CoV-2 with respect to epidemiology, risk factors, prevention, presentation, management and vaccinations.

KEYWORDS:
COVID
COVID-19
SARS-CoV-2

EPIDEMIOLOGY, RISK FACTORS, PREVENTION

Currently, nearly 120 million cases of SARS-CoV-2 have been reported worldwide. Cross-sectional and population-based studies have estimated actual infection rates may be at least 10-fold higher than reported based on seroprevalence of anti-SARS-CoV-2 antibodies in certain areas that were studied, although more research is needed to support these findings. The initial outbreak of SARS-CoV-2 occurred on December 8, 2019, in Wuhan, China, and its surrounding province of Hubei. Twenty-two days later, SARS-CoV-2 was first isolated in the bronchoalveolar lavage fluid of three COVID-19 patients from Wuhan Jinyintan Hospital. Epidemiologists found an association with a local seafood market that sold live animals, where most patients had worked or visited. SARS-CoV-2 quickly spread to all 31 provinces of China and outside countries soon thereafter, with Antarctica as the only continent without any reported cases of SARS-CoV-2.

SARS-CoV-2 is primarily transmitted through direct person-to-person transmission via respiratory droplets, which may travel up to 6 feet. Additionally, if a person’s hands become contaminated by droplets or if the person touches a contaminated surface and then touches their eyes, nose or mouth, they may become infected. The virus has also been detected outside of respiratory droplets, including in stool, although according to a World Health Organization (WHO)-China Joint Mission report, transmission through fecal-oral route does not seem to be a significant method of transmission.

The risk of transmitting SARS-CoV-2 is highest in the first week of illness, even if asymptomatic, when viral RNA levels from upper respiratory specimens are greatest. The risk of transmission after contact with an infected individual increases with closeness and duration of exposure, especially with household contacts, at healthcare or long-term-care facilities with insufficient personal protective equipment, or at congregate areas where individuals reside or work near each other, as well as at work or social gatherings. Serious illness, hospitalization and death can result with COVID-19 infection at any age but most commonly is found in older adults and those with chronic kidney disease, diabetes mellitus (30%), hypertension, cardiovascular disease (32%), obesity, chronic lung diseases (18%), smoking or certain cancers.

Personal protective measures are recommended for preventing the spread of COVID-19, including social distancing of 6 feet, face masks, hand hygiene, disinfecting surfaces, and avoiding crowds or those who are symptomatic. The U.S. Centers for Disease Control and Prevention (CDC) recommends that people older than the age of 2 properly wear a mask over the mouth and nose when social distancing cannot be maintained and when with those who are not of the same household. Masks with valves or vents for exhalation are not recommended by the CDC because they may not prevent people from spreading COVID-19 to others, as the valve allows respiratory droplets to pass through and possibly infect others. Masks are shown to be a barrier preventing respiratory droplets from spreading, which can happen when someone talks, coughs or sneezes. Covering a cough or sneeze to practice proper respiratory hygiene is advised. Masks, however, do not filter out all the viral particles. This had led some to study the concept of “variolation,” whereby smaller viral loads that are not filtered by the mask may cause asymptomatic or mild infections (assuming viral load exposure impacts the severity of disease). This would theoretically be beneficial—pending a vaccine—by building a natural immunity to
a less severe disease, further favoring the use of widespread face masks. Many studies demonstrate overwhelming reduction in viral particles filtered on exhalation and inhalation by cloth masks, upwards of 80% and 50%, respectively. Furthermore, there are several epidemiologic and observational studies from around the world and in the healthcare setting that demonstrate a strong association with community mask use and overwhelming reduction of COVID-19 transmission. Another form of protection advised by the CDC is to avoid all nonessential travel, thereby decreasing risk of exposure or asymptomatic transfer of infection.

**OBJECTIVE FINDINGS & DIAGNOSIS**

Diagnosis of COVID-19 is based on clinical manifestations, polymerase chain reaction (PCR) tests, blood tests and imaging. Several symptoms have been associated with severe infection, including cough (50%), fever (43%), dyspnea (29%) and bilateral infiltrates on imaging. Other symptoms are widely variable and include myalgias, headaches, diarrhea, abdominal pain, nausea/vomiting and loss of taste/smell. Dermatologic findings, including urticarial rash, livedo reticularis and disclored nodules on distal digits, have been reported. Acute respiratory distress syndrome (ARDS) is one of the most serious complications of COVID-19. Studies have revealed hematologic sequelae of COVID-19, including cardiovascular and thromboembolic manifestations. Reported complications include acute cardiac injury, arrhythmias, cardiogenic shock and cardiomyopathy. The inflammatory response in COVID-19 patients is impressive, with fevers along with elevated inflammatory markers, transaminases, lactate dehydrogenase and cardiac markers. Patients commonly have lymphopenia and coagulation abnormalities. Evidence supports an increased risk of pulmonary embolism and stroke in severely affected patients. Symptoms can take 2–14 days after exposure to appear, with studies suggesting the median incubation period to be about 4 days.

Chest x-rays and computed tomography (CT) scans have been used in the workup and diagnosis of COVID-19. In most cases of mild to moderate disease, chest radiographs were normal. In more severe disease, bilateral ground-glass opacities with or without consolidation were most prevalent on imaging, peaking between 10 and 12 days. CT scans most commonly found ground-glass opacities +/- consolidation, followed by pleural thickening and air bronchograms. Findings may also be unilateral, though more often are bilateral, peripheral and in the lower lobes.

All symptomatic patients should be tested. Patients may complain of cough, fever, dyspnea, anosmia, sore throat, myalgia, headache, nausea, vomiting, diarrhea or fatigue. Testing is also indicated if patients have traveled within 14 days to a location where COVID-19 has community transmission, if patients have had close contact with a confirmed or suspected case, or if dyspnea becomes prominent between the 4th and 10th day after initial symptoms. Furthermore, asymptomatic patients should be tested in certain circumstances, including those at long-term care facilities and hospitalized patients in highly prevalent areas of transmission—prior to aerosolizing procedures and arguably 5–7 days after exposure to an individual known to have COVID-19.

If testing resources are limited, highest priority should be given to critically ill patients, health care and critical workers, individuals with close contact to a confirmed COVID-19 case in the last 2 weeks, and immunosuppressed patients.

Nucleic acid amplification testing with PCR is the preferred test, with several variations targeting different genes of the virus that have been approved and are in use. The CDC recommends nasopharyngeal swabs, oropharyngeal swabs or nasal swabs from both nares, although it is uncertain which route is optimal, and the Infectious Diseases Society of America (IDSA) further recommends to reserve lower respiratory tract specimen testing for patients who may be suspicious for false negative pharyngeal swabs.

Positive nucleic acid amplification tests confirm the diagnosis of COVID-19, and negatives typically exclude the diagnosis, although repeat testing is recommended if suspicion remains high (repeat should be done after 24 hours of initial testing). The nucleic acid amplification tests are highly specific, although false negative rates have varied upwards of 40% (limited comparison standards and the accuracy of testing may be variable depending on type of specimen collected). If the patient is tested immediately after exposure, the probability of false negatives is up to 100%, but false negatives drop significantly between days 5 and 8. Point-of-care antigen testing is typically less sensitive than PCR, and negative testing does not exclude COVID-19 infection and should be repeated with PCR based on clinical suspicion.

To detect past infection, immunoglobulin G (IgG) antibody testing is highly specific and can be useful if done 3–4 weeks after the onset of symptoms in patients with high pretest probabilities. Although the IDSA recommends IgG antibody testing in this context, immunoglobulin M and immunoglobulin A are not encouraged as they perform poorly with respect to their specificity/sensitivity profiles.

Patients may remain positive on COVID-19 testing weeks later, which can complicate the picture when patients who have recovered present weeks or perhaps months later with unexplained respiratory symptoms. The CDC has recommended against repeating testing within 3 months of a positive test, as it is unclear whether a repeat positive result represents an active infection. The natural immunity that may develop is a poorly understood process. The CDC recommends considering isolation and quarantining if patients present fewer than 3 months after their first COVID-19 infection with a positive test. Retesting within 3 months of the first infection may be a consideration if there is concern for initial false positives, in immunocompromised patients (short-lived immunity) or suspected exposure to variant forms of COVID-19. Nevertheless, patients presenting with symptoms consistent with COVID-19 within 3 months of a prior positive test who have other etiologies ruled out should still quarantine, especially as variants become more prominent.

**INPATIENT AND OUTPATIENT MANAGEMENT**

Outpatient management of patients with suspected COVID-19 begins with home self-assessment and—if providers and patients are capable—a virtual encounter with a medical professional to help decrease the possible spread of the virus. Patients should...
be encouraged to monitor for temperature spikes above 100.3°F (37.9°C), shortness of breath, chest pain, extremity swelling, loss of taste or smell, and signs of gastrointestinal distress, including nausea, vomiting, abdominal pain and non-bloody diarrhea.27,28,31,36,29,54 Moderate or severe dyspnea, initial oxygen saturation lower than 90%, chest pain, low blood pressure or mental status change should prompt referral to the emergency department.

If the patient's oxygen saturation is between 90% and 94% or if there is moderate dyspnea (especially in high-risk patients), this warrants an in-person evaluation. Low-risk patients with minimal dyspnea can be managed at home. Self-isolation and preventive measures as described previously are encouraged. Symptomatic treatment involves over-the-counter medications for the associated myalgias, fevers and general symptoms. Antipyretics and analgesics, cough medications (benzonatate, dextromethorphan), rest, activity as tolerated, and prone positioning can be encouraged.55,56 Prone positioning is thought to reduce the gravitational pressure of the heart and abdominal viscera on the pulmonary system, improving ventilation perfusion (V/Q) mismatch and recruiting collapsed alveoli.57,58

Precautions can be discontinued in mild nonhypoxic or asymptomatic patients if at least 10 days have passed or if 2 tests 24 hours apart are negative and at least 1 day has passed since the last fever and there is improvement in symptoms.59,60

The recommendations for hospitalization depend on the severity of illness, a term defined by the National Institutes of Health (NIH) based on the patient's clinical picture and broken down into mild, moderate, severe and critically severe.61 Per NIH guidelines, mild illness refers to those who have nonspecific symptoms of the disease without respiratory distress or evidence of disease on chest imaging (x-rays, CT scans, etc.). Moderate illness refers to those who develop respiratory disease but are still able to maintain their oxygen saturation above 94%. Severe illness refers to those who have tachypnea with a respiratory rate greater than 30 breaths per minute, have an oxygen saturation as measured by pulse oximetry under 94% on room air or an alveolar-arterial difference (or gradient) in partial pressure of oxygen with a fraction of inspired oxygen less than 300 mm Hg. Lastly, critical illness refers to those who have developed respiratory failure, septic shock or multisystem organ failure.61 Patients with mild disease are usually not admitted to the hospital. Patients with moderate illness can be admitted to the general medical floor with precautions in place. It is recommended that these patients perform awake self-proning to improve V/Q mismatch and to recruit collapsed alveoli.56,60 High-flow nasal cannula (HFNC) is preferred to continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), because these devices can aerosolize the virus and potentially increase the transmission of COVID-19.62,63 Critically ill patients have ventilator-dependent respiratory failure and require admission to the intensive care unit (ICU). NIH recommends that these patients be intubated by video laryngoscopy when able.61

Pharmacotherapy is variable and evolving. Rosenberg et al performed a 1,438-patient study showing that the use of hydroxychloroquine—with or without azithromycin—did not reduce mortality, consistent with other studies showing potential harm.64,65 The NIH COVID-19 panel currently recommends against the use of hydroxychloroquine with or without azithromycin.66 The Adaptive COVID-19 Treatment Trial (ACTT-1) trial studied remdesivir, an adenosine nucleoside that binds RNA-polymerase to prevent viral replication. This study enrolled 1,063 patients and demonstrated that COVID-19 hospitalized patients who required supplemental oxygen, but not noninvasive or invasive positive pressure ventilation, recovered at 11 days, compared to 15 days with placebo. This study showed no benefit compared to placebo in patients receiving noninvasive positive pressure ventilation, intubation or extracorporeal membrane oxygenation (ECMO).66 Goldman et al performed a randomized, open-label trial comparing 5- and 10-day intravenous remdesivir treatment regimens. The results showed no mortality benefit between the two groups and more adverse reactions in the patients assigned to the 10-day regimen.67 Nevertheless, although the WHO does not recommend the use of remdesivir, the IDSA and the NIH suggest remdesivir can be used in hospitalized patients requiring oxygen.61,68 The IDSA also suggests adding tocilizumab—an IL-6 receptor antagonist (blocking inflammatory pathways)—in patients with critical disease and elevated inflammatory markers, based on data suggesting improved outcomes in critical patients.68,69 Convalescent plasma taken from previously recovered COVID-19 patients can give passive immunity; however, there is no clear role for the use of convalescent plasma, as available evidence is not convincing.70,71 Monoclonal antibodies are currently being studied, with limited evidence so far on efficacy. They are recommended for patients as part of a clinical trial.72

Per the RECOVERY trial, any patient requiring supplemental oxygen should be given up to a 10-day course of dexamethasone at 6 mg per day, with the substitution of other corticosteroids if dexamethasone is not available. This trial showed that the mortality rate was lower among patients who received corticosteroids than placebo.73 The International Society on Thrombosis and Haemostasis currently recommends prophylactic anticoagulation for hospitalized patients, preferably with low–molecular-weight heparins, which have shown mortality and anti-inflammatory benefit in COVID-19 infection.74 Paranjpe et al suggest that therapeutic anticoagulation could be beneficial to hospitalized patients with COVID-19, but the risks should be weighed against the benefits of increasing anticoagulation.75

VACCINATIONS

On November 9, 2020, Pfizer and BioNTech announced that their vaccine candidate BNT162b2 against COVID-19 was successful in the first interim analysis—with over 90% efficacy in preventing symptomatic disease—which was followed shortly thereafter with similar results from Moderna’s mRNA 1273 vaccine candidate.76,77 Both products are mRNA vaccines that are delivered in lipid nanoparticles to express a full-length spike protein.78,79 Subsequent trial results revealed roughly 95% efficacy in preventing symptomatic infection 7 days and 14 days after the second dose for BNT162b2 (given 3 weeks apart) and mRNA 1273 (given 4 weeks apart), respectively.78,79 Both vaccines exceeded the U.S. Food and Drug Administration (FDA) threshold guidance of at least 50% efficacy.80 After extensive review of the data, the FDA
found strong evidence of safety and effectiveness of the vaccines, and both BNT162b2 and mRNA 1273 were approved for the public under Emergency Use Authorization (EUA) for patients at least 16 and 18 years of age, respectively.81,82 Expert organizations have given guidance on distribution of the vaccine in the setting of limited resources. The National Academies of Sciences, Engineering and Medicine, as well as the Advisory Committee on Immunization Practices (ACIP), have both recommended prioritizing vaccination initially to healthcare workers, first responders, high-risk populations (eg, long-term-care residents, elderly, those with comorbidities) and essential workers, although each state can have its own plan for distribution.83,84 As of mid-January 2021, there have been more than 16 million vaccine doses administered in the United States, with more than 35 million doses distributed.85

Local and systemic effects of both mRNA vaccines were relatively common and transient after the second dose and did not usually prevent regular daily activities.86,87 Fever (16%–17%), severe fatigue (4%–10%) and severe headache (3%–5%) were the most common adverse effects of BNT162b2 and mRNA 1273.86,87 Per the CDC, individuals with a history of SARS-CoV-2 do not have to be retested and should still be vaccinated, although it is reasonable to delay the vaccine for 3 months in individuals who have recently recovered from symptomatic infection due to low immediate reinfection risk in the setting of limited resources.88 As immunocompromised patients may have potentially severe COVID-19 infections, the benefits of the vaccine likely outweigh the risks.88 Safety has not been established for children or pregnant individuals, although pregnancy is not necessarily a contraindication to the vaccine, and vaccination can be considered on a case-by-case basis.88 Individuals with any history of immediate or severe reaction to a previous mRNA vaccine should not receive BNT162b2 or mRNA 1273 without further expert consultation.88 All vaccine recipients should be monitored for at least 15 minutes in settings where acute adverse reactions can be managed.88

The Janssen COVID-19 vaccine, which has also been authorized for use in the United States, is based on an adenovirus recombinant vector that produces a spike protein, given intramuscularly as one dose.89 Janssen’s Ad26.COV2.S vaccine had a 66.9% efficacy in preventing moderate to severe COVID-19 starting 2 weeks after vaccination, while efficacy regarding critical disease approached 80% in the same time interval.90 Injection site pain, headache, fatigue and myalgia were reported between 30% and 50% of the time, with fever 9% of the time.90

While pregnant patients have not been included in trials of COVID-19 vaccines, early evaluations of CDC databases of self-reported pregnancies and adverse events did not show any additional side effects in this population compared with the national baseline.91 The CDC and the American College of Obstetricians and Gynecologists do not recommend necessarily withholding these vaccines based on pregnancy status alone. As a result, many experts suggest a personalized approach evaluating the risks of exposure, underlying health conditions and individual patient preferences in the setting of ongoing research.92,93

Although vaccination has been a welcome development during the COVID-19 pandemic, several questions remain unanswered. It is unknown how long a vaccinated individual will have protection from the virus or whether booster doses will be necessary. Furthermore, the impact on community transmission is not well understood. As research on this novel virus evolves, there will be further insight into these questions as well as the discussed epidemiology, risk factors, prevention, and management strategies. Furthermore, challenges regarding vaccine distribution, mutations, hesitancy to get vaccinated and access are important considerations that have not been addressed in this review. Nevertheless, the research and progress made so far during the pandemic is a testament to the commitment and cooperation of scientists, experts, medical professionals and the general population around the world. Their dedication will continue to be a vital aspect of successfully responding to the challenges of this pandemic.

REFERENCES:


Midwestern University Job Advertisement
Clinical Assistant Professors Arizona College of Osteopathic Medicine Family Medicine or OMM

Arizona College of Osteopathic Medicine (AZCOM) is seeking academic/clinical faculty members. These individuals will spend 0.4 FTE for the Department of Osteopathic Family and Community Medicine teaching clinical skills and/or OMM labs, lecturing, assisting with standardized patient testing of students, grading, and participating in clinical clerkship rotation recruitment and rotation site visits. The remaining 0.6 FTE will involve a clinical practice in the Family Medicine and/or Osteopathic Manipulative Medicine Clinic of the Midwestern University (MWU) Multispecialty Clinic, depending in which specialty or specialties the faculty member has board certification.

- Duties include participation in hands-on bedside training of medical students, residents, and ONMM residents at the Midwestern University Multispecialty Clinics.
- Clinic Family Medicine and/or Osteopathic Manipulative Medicine Clinics.
- This position, at the rank of Clinical Assistant Professor, requires a DO degree, board eligibility/certification in Family Medicine and/or board eligibility/certification in Neuromuscular Medicine, a valid Arizona medical license, and DEA licensure. This position also must be able to be credentialed by third party insurance and must be able to be insured for medical liability.
- Position reports to the Chair of the Department of Osteopathic Family and Community Medicine academically and to the Medical Director of the MWU Multispecialty Clinic clinically.

About Midwestern University
Midwestern University is an independent institution of higher education committed to the education of health care professionals. The Glendale campus is located on 156 acres in Glendale, Arizona, 20 miles northwest of Phoenix. The Glendale campus is located on 156 acres in Glendale, Arizona, 20 miles northwest of Phoenix, and is home to the Arizona College of Osteopathic Medicine, the College of Pharmacy Glendale, the College of Dental Medicine Arizona, Arizona College of Optometry, College of Graduate Studies, the College of Veterinary Medicine, the College of Health Sciences, and the College of Podiatric Medicine. The University is accredited by The Higher Learning Commission, a Commission of the North Central Association of Colleges and Schools.

Contacts:

Shannon Scott, D.O.
Medical Director
sscott1@midwestern.edu
623-572-3753

Tracy Middleton, D.O., FACOFP
Chair, Family Medicine
tmiddl@midwestern.edu
623-572-3274

Application Instructions:
- Please submit your application packet through MWU’s online job board at www.midwestern.edu.
- Select “Employment at MWU” from the Quick Links.
- Click “View Current Job Openings” to view the job board.

Shannon Scott, D.O.
Medical Director
sscott1@midwestern.edu
623-572-3753

Tracy Middleton, D.O., FACOFP
Chair, Family Medicine
tmiddl@midwestern.edu
623-572-3274