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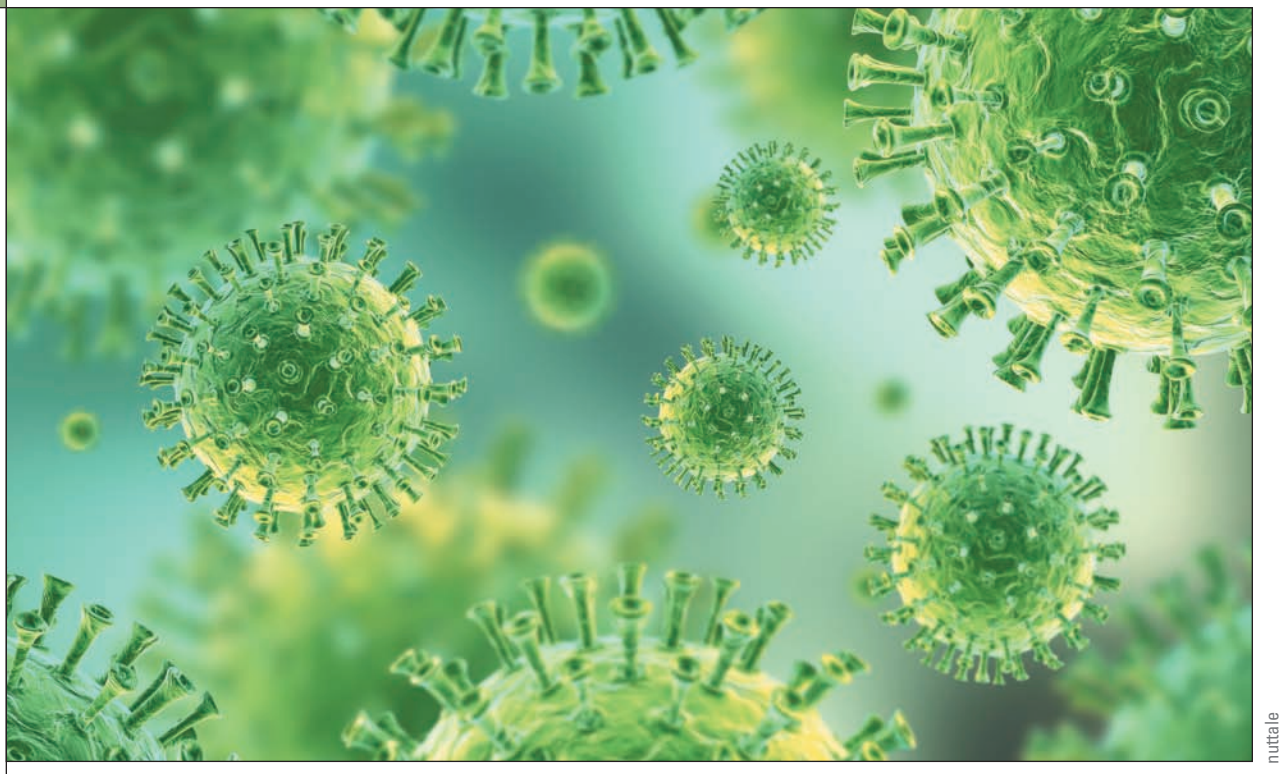

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COVID-19: Epidemiology and clinical practice implications

Abstract: In 2019, a novel coronavirus infection was detected in humans. As coronavirus disease 2019 (COVID-19) spread around the world, often confusing and contradictory information about the disease proliferated rapidly. This article reviews what is currently known about COVID-19, including transmission, epidemiology, immunologic responses, clinical manifestations, and disease management.

By Mary Madeline Rogge, PhD, RN, FNP-BC and Bibha Gautam, PhD

In December 2019, health officials reported a cluster of acute respiratory illness cases in the city of Wuhan, China.[1] A week later, officials reported that a novel coronavirus, then termed 2019-nCoV, was associated with this initial cluster. In late January, the World Health Organization (WHO) declared the virus outbreak an international public health emergency.[2] On February 4, 2020, the National Health Commission of China confirmed a total of 20,471 cases, including 2,788 (13.6%) with severe illness, and 425 deaths (2.1%).[3] By then, cases had been reported in 26 locations outside of mainland China, and person-to-person transmission had been documented; 11 cases had been reported in the US.[4] An international virology committee officially named the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to facilitate communication about the virus due to its genetic similarities to the coronavirus that caused the severe acute respiratory syndrome (SARS) outbreak in 2002-2003.[5] Subsequently the WHO named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19) and declared the outbreak a pandemic.[6,7]

Keywords: coronavirus disease 2019, COVID-19, epidemiology, pandemic, SARS-CoV-2

The initial disease surveillance criteria defined COVID-19 as a severe acute respiratory infection, with "history of fever and cough requiring admission to hospital, with no other etiology that fully explains the clinical presentation," and advised clinicians to be "alert to the possibility of atypical presentations in patients who are immunocompromised."[8] Because there was no diagnostic test specific to the novel virus, clinicians were advised to rule out other causes of severe respiratory infections, such as *Streptococcus pneumoniae, Haemophilus influenzae* type b, *Legionella pneumophila*, and other recognized primary bacterial pneumonias, influenza, and respiratory syncytial virus. By early November 2020, more than 47,600,000 people worldwide and more than 9,390,000 people in the US were confirmed to have contracted COVID-19. More than 1.2 million deaths from COVID-19 have been reported globally, with over 230,000 of these in the US.[9] Based on CDC case report data between February and May 2020, in the US, 79.3% of deaths were among individuals age 65 years or older, and the median age of decedents was 78 years. The mortality for patients with COVID-19 has been disproportionate within the US population: Hispanic 15.9%, Black 20%, White 54.4%, and Asian 4.6%, as of early November 2020.[10,11] Although only 6% of pandemic cases in the US have occurred among patients and staff in long-term care facilities, these cases account for 38% of the country's COVID-19 fatalities, as of late October 2020.[12] Within a few months of its identification and definition, the new severe respiratory infection known as COVID-19 took on a much more complicated clinical picture. Evidence emerging from disparate sources has often seemed confusing and contradictory. The purpose of this review is to describe the cause of COVID-19, its signs and symptoms, and evolving clinical management.

SARS-CoV-2 infectivity

SARS-CoV-2 is a round single-strand RNA virus. The viral envelope contains spike-like structures that give the virus a characteristic crownlike appearance and facilitate attachment to host cells.[13] As with other coronavirus infections (SARS, Middle East Respiratory Syndrome [MERS]) and some other respiratory pathogens, including influenza and rhinovirus, SARS-CoV-2 transmission occurs primarily through respiratory droplets from coughing and sneezing. Aerosol transmission, or dispersal of smaller respiratory droplets and particles that can remain suspended in the air over long distances, is possible in cases of prolonged exposure to elevated concentrations in closed spaces.[12,14] There is also concern that SARS-CoV-2 may be transmitted via the orofecal route.[15] Health officials at the University of Arizona successfully tested wastewater from several dormitories for the presence of the virus. Based on their data, the university was able to identify two asymptomatically infected students, quarantine the students early, and stop the spread of infection among returning students.[16] Analysis of data related to the spread of SARS-CoV-2 in China seemed to show that close contact between individuals is necessary for transmission, with the spread primarily limited to family members, healthcare professionals, and other close contacts.

Early data from China and subsequent studies showed that the viral incubation period generally ranged from 3 to 14 days, and the longest time from infection to symptoms was 12.5 days.[13,17] Cases doubled about every 7 days, and on average, each patient transmitted the infection to an additional 2.2 individuals, slightly below the rate of infection of the 2002-2003 SARS epidemic. Among patients hospitalized for COVID-19, average duration of viral shedding in survivors was 20 days, with the longest duration being 37 days. SARS-CoV-2 was detectable until death in nonsurvivors.[18] Some investigators have found the vast majority of those infected who develop symptoms do so within 11.5 days, but symptoms may still develop more than 15 days after infection.[17] The virus invades the body via the mouth, nose, and eyes. After entering the body, SARS-CoV-2 attaches to angiotensin-converting enzyme 2 (ACE2), widely embedded in epithelial membrane cells throughout the body.[19] The virus membrane fuses with the cell membrane and the transmembrane protease serine 2 (TMPRSS2) enzyme clears away the ACE2 and activates the spike protein, allowing virus entry into the cell.[19] SARS-CoV-2 RNA is released into the cytosol (the intracellular fluid), and

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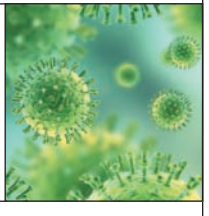

begins viral replication, following which new viruses are released and infect other cells.[20] The widespread distribution of ACE2 and TMPRSS2 in the cells of the respiratory tract and lungs, intestine, kidneys, adipose tissue, heart, blood vessels, and testes make these tissues hospitable hosts for viral replication, and account for the high variability in clinical presentations.

During times of stress, the renin-angiotensin-aldosterone system (RAAS) increases circulation by vasoconstriction and sodium and water retention. Angiotensin-converting enzyme (ACE), a major component of RAAS, initiates inflammation and cardiovascular remodeling through fibrosis and oxidative stress.[21] The counterregulatory enzyme ACE2 counterbalances the normal effects of RAAS on circulation and inflammation. The counterregulatory forces mediated by ACE2 constrain excessive cardiovascular load and inflammation through vasodilation; lowering of sodium and water concentrations; and reduction of inflammation, fibrosis, and oxidative stress.[21]

Several factors increase ACE2 expression in epithelial membrane cells. Obesity and smoking are associated with increased ACE2.[22,23] ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) increase ACE2 in patients with hypertension and cardiovascular disease, and type 1 and type 2 diabetes mellitus.[24-26] In late-stage (stages 4 to 5) chronic kidney disease, ACE2 levels increased, while ACE2 was diminished in the early stages of chronic kidney disease.[27]

ACE inhibitors and ARBs increase ACE2 to counterbalance the unfavorable vasoconstrictive and proliferative effects of ACE and keep ACE-related proinflammatory effects under control.[24,28] Early in the pandemic, researchers proposed that ACE inhibitors and ARBs could theoretically increase the risk of developing severe COVID-19.[29] Professional cardiac societies in the US have recommended against discontinuation of these medications unless indicated by standard clinical practice.[30] In the first randomized clinical trial on the subject, researchers confirmed that patients hospitalized with COVID-19 can safely continue taking ACE inhibitors and ARBs.[31]

It is not clear if Americans who identify as Black or Hispanic have higher ACE2 activity than other races independent of comorbidities. However, both populations may have higher rates of hypertension, diabetes, and chronic kidney disease, which upregulate ACE2 and increase available targets for SARS-CoV-2 binding and penetration.[32,33] The expression of ACE2 by adipocytes and preadipocytes is similar between those who are obese and nonobese,[34] but people who are obese have more adipocytes and preadipocytes, increasing the number of ACE2-expressing cells in adipose tissue.[35] Several types of cancer also have greater ACE2 expression in tumor tissues than adjacent tissue, partially explaining why cancer may be a comorbid condition that increases the risk of COVID-19.[36] Men have higher ACE2, which may make them more susceptible to severe disease and death than women.[24]

ACE2 as a binding site on epithelial cell membranes for SARS-CoV-2 helps to explain the variability in its constellation of signs and symptoms, as well as its severity in older adults and those with preexisting conditions. Increased ACE2 expression due to higher rates of comorbidities may also partially explain why COVID-19 is more devastating in Black and Hispanic communities.

COVID-19 activation of immune functions

Inside host cells, SARS-CoV-2 replicates and provokes the innate immune response, including activation of lymphocytes and macrophages to attack the virus and the cells they occupy.[37] These immune cells release an array of cytokines to destroy the virus, but these chemicals also damage the host cells. Additionally, they attract neutrophils to combat the virus by promoting inflammation. The inflammatory response leads to increased cell membrane permeability, increased vascular permeability, and edema.[38] The inflammation is especially detrimental in the lungs where alveoli fill with exudate and gas exchange is reduced, leading to hypoxia. The T-lymphocytes also initiate the development of specific memory cells and induce plasma cells to produce specific anti-SARS-CoV-2 antibodies.[39]

It has been suggested that some people mount a more robust immune response (cytokine storm), which results in severe disease. Patients with COVID-19 were shown to have a marked increase of 14 cytokines compared with healthy controls, and certain cytokine expression profiles were associated with increased disease severity and fatal outcomes.[40] Research has also shown that by degrading ACE2 during virus internalization, SARS-CoV-2 may exhaust pulmonary ACE2 and depress the counterregulatory system, clearing the way for more intense inflammatory effects.[41] The progressive exhaustion of pulmonary ACE2 corresponds to the two-phase disease pattern commonly observed in

patients with COVID-19, that is, a sudden deterioration in the patient's condition after a few days of mild-to-moderate lung symptoms.[41,42]

Moreover, an increased immune response can be expected within a few days as the host begins to develop specific anti-SARS-CoV-2 antibodies. Immunoglobulin M antibodies begin to develop against the virus within a few days of the onset of symptoms and peak at about day 14 of the infection. Anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies begin to appear in the serum about 7 to 14 days after the virus is contracted and peak between days 21 and 28.[43,44] The duration of detectable IgG antibodies and their ability to confer long-lasting immunity has not yet been determined.[44] At least four cases of reinfection with COVID-19 have been confirmed, indicating that antibodies are not 100% effective in conferring immunity or that they are ineffective in preventing infection with a genetic variant of the virus.[45] Other studies found that a higher total antibody titer for SARS-CoV-2 was correlated with a worse disease classification,[44,46] reinforcing the hypothesis that patients with greater symptomatology are likely to have more significant immune responses.

Signs and symptoms of COVID-19

COVID-19 is often asymptomatic, and among children and adolescents, 16%-45% of infections are asymptomatic.[47] The early symptoms of COVID-19 are nonspecific and may include changes in taste and smell; fever, which is often unresponsive to conventional antipyretic therapy; and fatigue and malaise. These maybe followed by mild respiratory symptoms such as rhinorrhea or nasal congestion, sore throat, and headache. The reason for seeking healthcare is usually a persistent nonproductive cough. Some patients experience gastrointestinal symptoms, such as diarrhea. By infecting the epithelial linings of the eye, the virus causes mild conjunctivitis in some patients. Myalgia and anorexia have also been reported.[13,46,48] Dermatologic manifestations may be seen in otherwise asymptomatic patients. Red or purple papules and blisters may develop, along with swelling of the toes and fingers resembling frostbite. The patient may complain of the lesions burning or itching. The cause of the dermal lesions is unknown, but may be related to inflammation, vasculitis, or small blood clots in the toe's microvasculature.[49]

Most symptomatic patients with COVID-19 have a mild respiratory infection for 1 to 2 weeks that resolves without complication.[50] However, other patients, especially older adults and those with preexisting conditions, may deteriorate rapidly as they develop signs and symptoms of more severe complications caused by the virus and the host's immune responses. Predictors of severe infection are preexisting hypertension, cardiovascular disease, diabetes, obesity, chronic lung disease, chronic kidney disease, and cancer. However, in a cohort of hospitalized adults in Georgia, one in four patients with COVID-19 had no recognized risk factors for severe disease.[51]

One of the most serious effects of COVID-19 is the development of pneumonia requiring respiratory support.[48,52,53] After 5-7 days, patients may develop rapidly progressive dyspnea and reduced oxygen saturation (less than 93%) requiring hospitalization and administration of supplemental oxygen. Oddly, patients with COVID-19 can have hypoxia with minimal or no symptoms, and this silent or "apathetic" hypoxia can be a harbinger of rapid deterioration.[54] It is unclear why these patients develop hypoxia that does not trigger respiratory distress.

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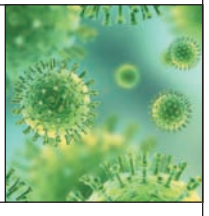

Infiltration of inflammatory neutrophils and macrophages provides innate immunity, but can also induce lung injury. Furthermore, activation of T lymphocytes can help contain the virus and initiate adaptive immunity, but they release cytokines that can also be toxic to host cells.[55-57] T cells can become depleted from stimulation by the virus, resulting in loss of cytokine production and decreased function.[58] Profound lymphopenia can occur in patients with COVID-19 when SARS-CoV-2 infects and kills T lymphocyte cells.[59] On admission, most patients exhibit lymphopenia along with characteristic ground-glass opacities or diffuse infiltrates bilaterally on imaging.[48,51-53,60] Inflammation and deterioration of respiratory status may lead to severe pneumonia and acute respiratory distress syndrome and the need for mechanical ventilation.[13] Some patients require extracorporeal membrane oxygenation (ECMO) therapy.[13,61]

Many patients seriously ill with COVID-19 develop coagulopathy, thrombosis, pulmonary embolism, and disseminated intravascular coagulation.[62-64] Endothelial injury in the pulmonary vasculature can exacerbate lung dysfunction and platelet aggregation. Early evidence of hypercoagulability in patients with COVID-19 are elevated d-dimer and fibrinogen levels.[51] Anticoagulation may be required to manage the coagulopathy, and ECMO or renal replacement therapy may be indicated to manage the resulting respiratory and renal dysfunction seen in these patients.[13,61]

Among 5,449 adult patients with COVID-19 hospitalized at 13 metropolitan hospitals in New York in March and early April 2020, 1,993 (36.6%) developed acute kidney injury (AKI), and 14.3% of these patients required renal replacement therapy.[65] Furthermore, AKI often coincided with respiratory failure requiring intubation and ventilation; 89.7% of patients requiring mechanical ventilation developed AKI, while only 21.7% of patients who did not need mechanical ventilation developed AKI. AKI in COVID-19 is thought to be the result of complex interactions involving "virus-mediated injury, cytokine storm, AngII pathway activation, dysregulation of complement, hypercoagulation, and microangiopathy."[66] Patients using drugs blocking the RAAS at hospital admission were not found to have a higher risk of AKI.

Other vascular effects have been observed in cases of COVID-19. In the US and globally, clinicians noted a rise in the incidence of a syndrome with Kawasaki disease-like manifestations during the COVID-19 pandemic.[67-69] Kawasaki disease is a rare condition that causes vasculitis and may cause inflammation of the heart and Kawasaki disease shock syndrome.[68] It is sometimes associated with a viral infection and is usually seen in children under the age of 5 years. A similar syndrome has been observed in children, adolescents, and young adults during the COVID-19 pandemic, and was referred to as a Kawasaki disease-like syndrome.[67,68,70] Many of these patients were previously asymptomatic, but sought healthcare for fever, abdominal pain, and skin rashes. Some cases were confirmed reverse transcription-polymerase chain reaction (RT-PCR) positive for SARS-CoV-2, while others were RT-PCR negative, and some individuals showed antibody evidence of possible preceding COVID-19 infection. The nomenclature for the syndrome was refined on May 14, 2020, when the CDC published a health advisory summarizing the manifestations of multisystem inflammatory syndrome in children, issued a case definition, which included "positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms," and asked clinicians to report suspected US cases to local or state health departments.[71,72]

An increased incidence of large-vessel ischemic stroke in patients younger than 50 years of age has been reported.[73] Oxley and colleagues describe five patients over a 2-week period under the age of 50 with confirmed COVID-19 who presented to their health system with new-onset symptoms of large-vessel ischemic stroke.[73] This incidence was in contrast with the previous 12 months where they treated an average of 0.73 patients younger than 50 years of age with large-vessel stroke every 2 weeks.[73] However, whether the strokes are actually related to SARS-CoV-2 infection remains uncertain, since reports of large-vessel strokes as a feature of COVID-19 in patients younger than 50 are not consistent across the nation.[74] Vigilance is needed to recognize stroke and initiate emergency care among patients with COVID-19 regardless of age.

Finally, the pandemic, the closures of schools and businesses, job layoffs, and home schooling have increased personal stress for many Americans. According to data collected by a company providing legal documents, the number of people seeking divorces was 34% higher from March through June 2020 compared with 2019.[75] Weiner has reported worrisome trends in substance use during the pandemic, with alcohol sales increasing by more than 25%, and suspected drug overdoses rising 18% from mid-March through May 2020.[76-78] In addition, a national lab service found in their analysis of 500,000 urine drug tests an increase of 32% for nonprescribed fentanyl, 20% for methamphetamine, 12% for heroin, and 10% for cocaine during the same period.[76,79] Suicide rates are expected to rise both during the COVID-19 pandemic and after the crisis has abated due to distress, anxiety, fear of contagion, chronic stress, economic hardship, depression, and insomnia.[80]

Clinical management

No medication has been recommended by national or state health officials for infection prophylaxis. Remdesivir, an antiviral medication, was seen to be superior to placebo in shortening recovery time for adults hospitalized for COVID-19 and lower respiratory tract infection; on October 22, 2020, it was approved by the FDA for use

in patients age 12 and older and weighing at least 40 kg for the treatment of COVID-19 requiring hospitalization.[81,82] The Infectious Diseases Society of America (IDSA) recommends remdesivir over no antiviral treatment for patients hospitalized for COVID-19 with SpO_2 94% or less on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.[83]

Administering antibodies derived from the blood of patients who have recovered from COVID-19 is under investigation in clinical trials. Convalescent plasma therapy received emergency authorization on August 23, 2020, from the FDA for use in hospitalized patients; it may also be used under an investigational new drug application.[84] The emergency use authorization was based on available evidence from published and unpublished data on convalescent plasma for the treatment of COVID-19; however, no randomized controlled studies have been completed. The level of evidence for the FDA recommendation has made it controversial, but the emergency use authorization has not been rescinded.[85] Without results from randomized trials, the US National Institutes of Health states: "There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19" and "convalescent plasma should not be considered standard of care for the treatment of patients with COVID-19."[86] NPs should explain to eligible patients and their families that convalescent plasma contains antibodies to SARS-CoV-2 that may augment elimination of the virus.[87]

Pharmaceutical companies worldwide are competing to develop vaccines against COVID-19, and extensive human clinical trials are underway. Because vaccine development is costly, has a high failure rate, and requires a lengthy manufacturing process, a safe and effective vaccine is not expected to be available before the end of 2020.[88] NPs need to track vaccine development and engage in discussions about prioritizing immunization delivery within their healthcare settings in anticipation of limited supplies.

Glucocorticoids are a cornerstone of COVID-19 therapy. Researchers in the United Kingdom studied the effect of daily dexamethasone administered orally or I.V. for 10 days compared with usual care alone.[89] Preliminary results showed that 28-day mortality among patients who received standard care was highest in those who required ventilation (41%), intermediate in patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%). Treatment with dexamethasone reduced deaths by a third in patients requiring ventilation and by a fifth in other patients receiving oxygen only. However, no benefit was found among patients who did not require respiratory support.[90] The IDSA now recommends the use of glucocorticoids rather than no glucocorticoids in hospitalized patients with severe or critical COVID-19.[83]

The Endocrine Society issued an advisory early in the pandemic emphasizing that patients who have been maintained on corticosteroids for any reason be identified as high risk for severe disease, and that patients with COVID-19 who have a history of taking chronic corticosteroids be considered for early treatment with parenteral glucocorticoid therapy.[91]

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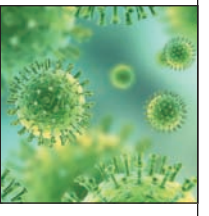

Implications for NPs

NPs are central to the prevention and management of COVID-19. Containment of the disease remains largely preventive through careful and specific patient education, case identification, and contact tracing. Many NPs are also participating in research studies to test a range of treatment modalities.

As stated previously, different segments of the population are disproportionately affected by severe COVID-19. Those who are Hispanic or Black, older adults, males, and those who have comorbidities need special attention. These disparities may be due in part to differences in susceptibility to the virus from ACE2.[19,21,24,28] However, other factors include disadvantaged socioeconomic conditions, such as housing conditions, work circumstances, education, physical mobility, language barriers, and healthcare access. Patients need meticulous instructions in their language and at their level of comprehension about how the virus is spread and how infection can be prevented. Signs and symptoms of infection need to be detailed along with instructions to obtain healthcare and intervention early. Social service referrals, as well as appropriate referrals for prescription assistance must be made for those at high risk.[92,93]

Until a vaccine becomes available, social distancing, proper use of face masks, frequent handwashing and disinfection of surfaces, and remaining home when ill are essential preventive interventions.[94] Additional interventions need to focus on stress management and sleep hygiene to promote good mental health during the uncertainty surrounding the pandemic. NPs need to regularly screen patients for anxiety, depression, insomnia, and suicidal thoughts.[80] Strategies to assist individuals in coping with the pandemic include avoiding excessive consumption of coronavirus-related information and only obtaining information from reputable sources. Staying active, maintaining healthy nutrition, implementing good sleep hygiene, and avoiding excessive amounts of caffeine, alcohol, and other substances are also helpful practices. Staying connected with friends and loved ones and talking about subjects unrelated to the pandemic can also increase emotional support in the COVID-19 era.

COVID-19 arrived on the clinical scene suddenly. With the rapid rise of cases and deaths, researchers and healthcare providers alike scrambled to gather and share information about the disease, its signs and symptoms, and potential therapies.[95] In the rush to gain knowledge and improve treatment, sources of information have often been of low quality, incomplete or premature, and even contradictory. It is imperative that NPs remain cautious in evaluating and adapting reliable sources to guide their practice. NP

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