

## REVIEW ARTICLE

# SARS-CoV-2 and COVID-19: A Brief Review for Family Physicians

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**ABSTRACT:** SARS-CoV-2, the newest coronavirus, causes COVID-19, a disease that runs the gamut of symptoms from none too mild to severe to death. The severe cases are most often due to acute respiratory distress. In addition to pulmonary symptoms, the virus causes a wide variety of pathological manifestations involving multiple other systems, including eliciting an exaggerated immune response that contributes to fatalities. The elderly are at the highest risk of severe disease. Higher mortality is seen among males, along with individuals with pre-existing comorbidities such as cardiovascular disease and diabetes, among others. Although pregnancy has not been identified as a risk factor yet, more research is needed to assess vertical transmission and strict perinatal precautions are recommended to minimize infecting newborns. Although COVID-19 in children is less likely to be severe, recent cases, albeit rare, have emerged of a multiorgan inflammatory syndrome, similar to Kawasaki disease. Early diagnosis can be done using molecular tests that detect viral genome, while cases manifesting late symptoms can be detected using serological tests looking for antibodies. Although there are no FDA-approved vaccines or therapeutics for prophylaxis, there are many viable vaccine candidates either in clinical trials or awaiting study in humans. Of the several drugs being considered for treatment, some target the virus, while others address the host factors that facilitate virus infection, from proteases that enable virus entry, to cytokines that elicit a harmful and out-of-control immune response. While we await a standardized prophylactic regimen, it is our collective responsibility to continue engaging in prevention measures.

## INTRODUCTION

Viral infections begin when the virus binds to the host cell receptor. Before host cell entry, the newest coronavirus, SARS-CoV-2, the etiologic agent of COVID-19, uses an envelope protein called the spike (S) glycoprotein to attach to the human angiotensin-converting enzyme 2 (hACE2).<sup>1,2,3</sup> Subsequently, upon cleavage by host proteases, such as Type II transmembrane serine protease (TMPRSS2), the S1 and S2 subunits of the S protein, enable host cell receptor recognition and membrane fusion, respectively.<sup>1,4</sup> It is the S1 C-terminal domain (CTD) that acts as the receptor-binding domain (RBD) in the case of two other coronaviruses, SARS-CoV and MERS-CoV, the etiologic agents of Severe Acute Respiratory Syndrome (SARS) and Middle-East Respiratory Syndrome (MERS).<sup>5,6</sup>

The SARS-CoV-2-CTD is structurally homologous to its SARS-CoV counterpart, not surprising, considering the approximately 73.9% shared identity between the two coronaviruses.<sup>7</sup> However, SARS-CoV-2-RBD shows a higher binding affinity to hACE2 when compared with SARS-CoV-RBD.<sup>7</sup> The SARS-CoV-2 RBD is less exposed (i.e., more hidden) than SARS-CoV RBD. The S protein gets preactivated by proprotein convertase furin, reducing its dependence on cell proteases for entry.<sup>8</sup> This could explain why SARS-CoV-2 can efficiently enter host cells while avoiding immune surveillance, which in turn may enable the dissemination of the virus.<sup>8</sup> A study of ACE2 expression levels across 31 normal human tissues revealed highest ACE2 expression levels in the small intestine, testis, kidneys, heart, thyroid and adipose tissue.<sup>9</sup> Medium expression of ACE2 was observed in the lungs, colon, liver, bladder and adrenal gland, while lowest expression was noted in blood, spleen, bone marrow, brain, blood vessels and muscle.<sup>9</sup> The wide range of tissues expressing ACE2 contributes to the wide variety of pathological manifestations of COVID-19.<sup>10</sup>

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## CLINICAL COURSE IN ADULTS

Early reports from China consistently found fever, fatigue, cough, myalgia and dyspnea to be the most common symptoms in patients who were hospitalized for COVID-19.<sup>11,12</sup> These symptoms have been reported globally, with additional, less common symptoms such as chills, sputum production, sore throat, headache, dizziness and diarrhea.<sup>13</sup>

Newer symptoms being considered include cutaneous manifestations, along with olfactory and gustatory dysfunction. In a study of patients with mild COVID-19 in South Korea, 39.5% reported hyposmia and 33.7% reported hypogeusia.<sup>14</sup> In a European study of 417 mild to severe laboratory-confirmed COVID-19 patients surveyed for olfactory and gustatory dysfunctions, 88% reported ageusia. Of the 85.6% of patients who reported anosmia, 11.8% of the patients reported presentation of anosmia before any other symptom, while 22.4% and 65.8% presented presentation of anosmia at the same time or after other symptoms, respectively.<sup>15</sup> Dermatologic reviews report the following descriptors for cutaneous presentations of COVID-19: chilblain-like edematous and erythematous eruption, vesicular rash, urticaria, maculopapular rash, acral-ischemia and livedo.<sup>16,17</sup> While awaiting further data to confirm their association, these symptoms may be relevant in identifying possible SARS-CoV-2 infections before the development of classic symptoms.

The majority of patients infected with SARS-CoV-2 will be asymptomatic or present with mild or moderate disease, defined as symptoms without and with radiographic changes, respectively.<sup>14,18,19</sup> Progression to more severe disease, which most commonly manifests as acute respiratory distress, most often occurs in the second week of illness.<sup>11,12,20</sup> The accepted criteria for the classification of the severity of COVID-19 was first described by the National Health Commission of China based on the Infectious Diseases Society of America and the American Thoracic Society criteria for defining severe community-acquired pneumonia.<sup>21,22</sup> The criteria for severe infection are dyspnea with respiratory rate  $\geq 30$  breaths/min, resting oxygen saturation  $\leq 93\%$ , PaO<sub>2</sub>/FiO<sub>2</sub> (partial pressure of arterial oxygen to fraction of inspired oxygen ratio) ratio  $< 300$  mm Hg or a greater than 50% growth of the lesion on pulmonary imaging. Critical COVID-19 is defined as a deterioration of clinical status to respiratory failure requiring mechanical ventilation, shock or multiorgan failure requiring intensive care unit management. In a report of 44,672 laboratory-confirmed COVID-19 patients in China, 14% progressed to severe disease and 5% progressed to critical disease over the course of their illness.<sup>21</sup> In Italy, over four weeks between February and March 2020, 9% of the 17,713 laboratory-confirmed COVID-19 cases were admitted to the intensive care unit.<sup>23</sup>

Patients with pre-existing chronic conditions are prone to increasing severity, complications and increased case fatality rate (CFR) due to COVID-19.<sup>12,19,20</sup> Table 1 summarizes some of the complications reported in patients with COVID-19.

TABLE 1:

Complications reported in hospitalized COVID-19 patients

TYPE OF COMPLICATION	EXAMPLES OF COMPLICATIONS
Pulmonary <sup>20</sup>	Respiratory failure, acute respiratory distress syndrome, ventilator-associated pneumonia
Cardiovascular <sup>24</sup>	Myocardial injury and myocarditis, acute myocardial infarction, heart failure, cardiomyopathy, arrhythmia, shock, cardiac arrest
Hematologic <sup>25</sup>	Deep venous thrombosis, pulmonary embolism, acute limb ischemia clotting catheters, mesenteric ischemia, disseminated intravascular coagulation
Neurologic <sup>10</sup>	Encephalitis, seizures, large vessel stroke
Renal <sup>10</sup>	Acute kidney injury, renal failure
Immunologic <sup>20</sup>	Sepsis, secondary infections, hypoproteinemia, cytokine storm

The following pre-existing conditions have been reported most commonly in patients with severe or critical COVID-19: hypertension, cardiovascular disease, hypercholesterolemia, diabetes and chronic lung disease.<sup>12,19,23,26</sup> Patient age is also a strong risk factor for the degree of disease severity and increasing CFR.<sup>21,27</sup> A study of 44,672 laboratory-confirmed COVID-19 cases reported a 2.3% overall CFR, with the highest CFR in patients aged  $\geq 80$  (14.8%), followed by patients aged 70-79 years (8%).<sup>21</sup> Underlying cardiovascular disease was the comorbidity with the highest CFR (10.5%), followed by diabetes at 7.3%. Despite the higher association of age or comorbidities with severe COVID-19, critical cases, complications and case fatalities have also been reported in young and/or otherwise healthy individuals.<sup>27,28</sup>

Another factor in severity and CFR is the immunologic cytokine storm, which is the leading cause of death in COVID-19 patients who progress to acute respiratory distress.<sup>29,30</sup> The presentation is similar to cytokine release syndrome (CRS) and secondary hemophagocytic lymphohistiocytosis (sHLH) observed in SARS and MERS.<sup>29</sup> The cytokine storm, with its overwhelming release and impact of pro-inflammatory cytokines leads to an aberrant systemic immune response.<sup>29</sup> This, in turn, directs the immune system to attack its own body, ultimately leading to multiple organ failure and death in the most critical cases of COVID-19.<sup>31,32</sup>

## DOES COVID-19 AFFECT MORE MALES?

In an Italian study of 1,591 COVID-19 patients admitted to the ICU, 82% were male.<sup>23</sup> A New York City study of 5,700 hospitalized COVID-19 patients also reveals higher mortality in males across all age groups.<sup>33</sup> The clue might lie in the fact that the androgen receptor (AR) regulates TMPRSS2 even in the lung.<sup>34</sup> This opens up the possibility of using androgen-deprivation therapy and AR antagonists in males infected with SARS-CoV-2.<sup>35</sup>

## COVID-19 IN PREGNANCY AND PEDIATRICS

To date, there are no studies that suggest pregnancy is a risk factor for severe COVID-19. Limited reports show a similar clinical course of COVID-19 in women, regardless of pregnancy, with respect to severity, length of hospital stay and presenting symptoms.<sup>36,37</sup> However, there have been reports of a small number of cases of severe maternal morbidity and perinatal death attributed to COVID-19.<sup>38</sup> It has been suggested that pregnant women with severe or critical COVID-19 may have an increased risk of preterm birth when infected in the third trimester.<sup>38</sup> In a study of 33 newborns born to women with COVID-19 pneumonia, in Wuhan, China, three of the newborns were symptomatic for COVID-19, one of whom was born prematurely at 31-weeks gestation and needed resuscitation. The authors suggest that the seriously ill newborn suffered from complications due to his premature birth, rather than from SARS-CoV-2 infection. All three infants were negative for SARS-CoV-2 by day seven.<sup>39</sup> There are other cases of newborns who have tested positive for SARS-CoV-2.<sup>38,40</sup> Recently, there was a report from Wuhan, China, of a newborn with elevated IgM and IgG antibodies to SARS-CoV-2 just two hours after being born to a woman with COVID-19. Since IgM does not cross the placenta and two hours is too soon for IgM to be made in response to infection after birth, vertical transmission is thought to have possibly occurred in the 23 days between the time of mother's diagnosis and delivery.<sup>41</sup> More research is needed to assess the risk of vertical transmission. Although there has been no evidence that SARS-CoV-2 can be transmitted through breast milk, strict precautions while breastfeeding, are recommended to prevent horizontal transmission.<sup>37</sup>

While the number of pediatric patients with confirmed COVID-19 has grown, there is a paucity of data regarding the clinical course in this age group. Smaller cohorts have reported that while the symptoms of fever, cough, sore throat/pharyngeal erythema, headache and myalgia are similar to that of adults, symptoms appear less frequently in children.<sup>42,43</sup> Overall, COVID-19 in children is less likely to be severe and has a lower CFR.<sup>43,44</sup> Similar to adults, pre-existing comorbidities are associated with increasing severity of pediatric COVID-19. A study from North American pediatric intensive care units (PICU) reported that 83% of admissions to the PICU had at least one pre-existing comorbidity, with immunosuppression/malignancy or a medically complex history with long term dependence on technological support being the most common.<sup>44</sup>

Most recently, cases of a multiorgan inflammatory syndrome in children (MIS-C), similar to Kawasaki disease, have been temporally associated with the SARS-CoV-2 pandemic. While this rare presentation is estimated to occur in about one in 1,000 children exposed to SARS-CoV-2, the incidence is much higher than reports of Kawasaki disease in recent years.<sup>45,46</sup> Table 2 describes the World Health Organization's (WHO) preliminary case definition of MIS-C based on clinical and laboratory features of case reports from Europe and North America as of May 15, 2020.<sup>47</sup> More conclusive evidence is needed to better define this syndrome and its association with SARS-CoV-2.

TABLE 2:

WHO preliminary case definition of MIS-C<sup>47</sup>

<b>MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN AND ADOLESCENTS</b>
Children and adolescents 0–19 years of age with fever for $\geq$ three days
<b>AND TWO OF THE FOLLOWING</b>
Rash or bilateral non-purulent conjunctivitis or signs of mucocutaneous inflammation (oral, hands or feet)
Hypotension or shock
Feature of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiogram findings or elevated cardiac enzymes)
Evidence of coagulopathy: changes in prothrombin time or partial thromboplastin time or elevated d-Dimer
Acute gastrointestinal problems (diarrhea, vomiting or abdominal pain)
<b>AND</b>
Elevated markers of inflammation: eosinophil sedimentation rate, C-reactive protein or procalcitonin
<b>AND</b>
No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal toxic shock syndromes
<b>AND</b>
Laboratory evidence of COVID-19 (RT-PCR antigen test or positive serology) or likely contact with an individual with COVID-19

## DIAGNOSTIC TESTS AND RADIOGRAPHY

While radiographic changes have been used to identify possible infection, determine disease severity and diagnose COVID-19, there are two main types of laboratory tests currently used in diagnosis: tests that detect viral nucleic acid using the reverse transcriptase-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) detecting IgM and IgG antibodies against SARS-CoV-2 virus.<sup>48,49</sup> The viral RNA test is used to diagnose a current infection, while an antibody test can indicate a previous infection. The CDC has established guidelines on who should get tested and how to interpret the test results.<sup>50</sup>

The most reported radiographic findings in symptomatic patients are bilateral ground-glass opacities on chest CT scans.<sup>12,51</sup> One study reported that the most common finding in asymptomatic individuals was unilateral ground glass opacities at the lung periphery.<sup>18</sup> Conversely, another study reported that 56% of patients who presented within two days of diagnosis had no abnormalities on CT scan.<sup>52</sup> Changes over the course of illness have also been demonstrated on repeat CT scan, suggesting ground glass changes are replaced by consolidation and possible bronchiectasis.<sup>53</sup> Thus, while CT findings may be suggestive, radiographic imaging alone is not a reliable indicator of infection.

The most commonly used, reliable and accurate test for diagnosis of COVID-19 has been the RT-PCR test, with the sample of choice being nasopharyngeal swabs, other upper respiratory tract specimens collected from the posterior pharynx, or saliva.<sup>48</sup> In most symptomatic COVID-19 cases, the SARS-CoV-2 genome can

TABLE 3:

A few of the drugs currently being considered for the treatment of COVID-19

THERAPEUTIC	CURRENT STATUS
<b>ANTIVIRAL AGENT</b>	
Remdesivir	<ul style="list-style-type: none"> <li>It was recently issued an Emergency Use Authorization for treatment of adults and children with suspected or laboratory-confirmed COVID-19 and hospitalized with severe disease, i.e., with oxygen saturation (SpO<sub>2</sub>) ≤ 94% on room air or requiring supplemental oxygen/mechanical ventilation/ extracorporeal membrane oxygenation.<sup>63</sup></li> <li>Currently, it is not recommended for the treatment of mild or moderate COVID-19 outside a clinical trial setting.</li> <li>Remdesivir inhibits RNA-dependent RNA polymerase of SARS-CoV-2, resulting in premature termination of viral RNA transcription.</li> <li>Preliminary results from the first stage of the Adaptive COVID-19 Treatment Trial show this drug to be superior to placebo in shortening time to recovery in hospitalized adult COVID-19 patients and evidence of lower respiratory tract infection.<sup>64</sup></li> </ul>
<b>DRUGS TARGETING THE HOST</b>	
Camostat mesylate (CM)	<ul style="list-style-type: none"> <li>CM has been used for decades in Japan for acute symptoms of chronic pancreatitis.<sup>65</sup></li> <li>It has activity against TMPRSS2,<sup>66</sup> the main host protease that facilitates SARS-CoV-2 entry into host cells and has been shown to block SARS-CoV-2 infection of lung cells <i>in vitro</i>.<sup>1</sup></li> <li>It is currently in clinical trials (NCT04353284) to show its efficacy to inhibit SARS-COV-2 replication in early-stage, laboratory-confirmed, COVID-19 ambulatory patients.</li> </ul>
<b>CYTOKINES &amp; CYTOKINE DYSREGULATION:</b> Increasing studies highlight the utility of cytokine-targeted biological therapies to improve outcomes in CRS or Macrophage Activation Syndrome and are therefore beneficial in reducing ARDS.	
Gimsilumab	<ul style="list-style-type: none"> <li>It is a monoclonal antibody against granulocyte macrophage-colony stimulating factor, which is a myeloid cell growth factor and pro-inflammatory cytokine.</li> <li>It is currently in Phase 2 clinical trials for its ability to benefit patients with lung injury or ARDS secondary to COVID-19 (NCT04351243).</li> </ul>
Tocilizumab (TCZ)	<ul style="list-style-type: none"> <li>This is an anti-IL-6R biological therapeutic. TCZ binds to both membrane-bound and soluble forms of IL-6R.</li> <li>It has already been FDA-approved for Cytokine Release Syndrome (CRS), in addition to other immune dysfunction diseases such as rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis.<sup>67</sup></li> <li>It is hypothesized that TCZ can reduce severity and mortality in COVID-19 patients who are prone to CRS and ARDS. It is being used in an “off-label” indication in COVID-19 patients with severe life-threatening CRS.</li> <li>Currently, it is being evaluated in several multicenter, randomized controlled clinical trials. Preliminary data show that TCZ appears to improve clinical outcome immediately in severe/critical COVID-19 patients.<sup>68</sup></li> </ul>
ACE II Inhibitors & AT1R blockers	<ul style="list-style-type: none"> <li>Two clinical trials NCT04312009 and NCT04311177, are underway to determine if ACE inhibitors or angiotensin receptor blockers are beneficial in patients with COVID-19.</li> </ul>
<b>OTHER THERAPEUTICS</b>	
Convalescent Plasma (CP)	<ul style="list-style-type: none"> <li>The rationale for the use of this therapeutic comes from a pilot study on ten patients with severe COVID-19, who showed an increase in neutralizing antibody titers, improvement in clinical symptoms and radiological findings, with a tendency to improve lymphocytopenia and disappearance of SARS-CoV-2 genome.<sup>69</sup></li> <li>Several clinical studies are currently evaluating the safety and efficacy of CP transfusion (originating from COVID-19 survivors) in SARS-CoV-2-infected patients (NCT04343261; NCT04338360).</li> </ul>
Anticoagulation therapeutics as additional therapy	<ul style="list-style-type: none"> <li>The abnormal coagulation is seen in patients with COVID-19 results in a marked elevation of D-dimer and fibrinogen degradation products, both associated with poor prognosis of COVID-19 and patients receiving anticoagulants show decreased mortality.<sup>70</sup></li> <li>Heparin-binding causes a conformational change of the SARS-CoV-2 RBD, which could interfere with binding of the virus to the host cell receptor.<sup>71</sup></li> <li>A retrospective clinical study has shown the potential of low molecular weight heparin (LMWH) to mitigate the cytokine storm in severe COVID-19 patients.<sup>72</sup> The group reported that LMWH not only improved the coagulation dysfunction of COVID-19 patients but also served an anti-inflammatory role by reducing IL-6 and increasing the percentage of lymphocytes.</li> <li>Overall, anticoagulants seem to have a therapeutic benefit as an adjunct therapy for COVID-19 treatment.</li> </ul>

be detected in nasopharyngeal swabs by day 1 of symptoms, with a peak occurring within the first week of symptom onset. Genome detection usually declines by the third week and subsequently disappears. In a recent prospective study of COVID-19, with 43 mild cases and six severe cases, researchers found positive PCR results persisting past 45 days in both nasopharyngeal and fecal samples, regardless of disease severity.<sup>54</sup> A positive PCR result only reflects genome detection and not necessarily the presence of infectious virus.<sup>55</sup>

Serological diagnosis of a COVID-19 infection is especially important for patients with mild to moderate illness presenting with symptoms beyond the first two weeks of illness onset.<sup>49,50</sup> The most sensitive and earliest serological test detects total antibodies, levels of which begin to rise from the second week of symptom onset.<sup>56</sup> Although IgM and IgG ELISA may test positive even as early as the fourth day after symptom onset, higher levels occur in the second to fourth weeks of illness.<sup>57,58</sup> Although ELISA-based antibody tests have greater than 95% specificity for the diagnosis of COVID-19, antibodies may show cross-reactivity with common coronaviruses. Because of this potential for cross-reactivity, the United States Food and Drug Administration (FDA) requires testing laboratories to addend positive serology reports with a note that there may be false positives due to cross-reactivity with common coronaviruses. Testing of paired serum samples, one with the initial PCR test, followed by a serological test two weeks later can increase diagnostic accuracy. For more information on optimizing serological test outcomes and testing strategies, please refer to the CDC interim guidance.<sup>59</sup>

The rapid point-of-care tests that detect antibodies are of variable quality. These tests are qualitative in nature, only indicating the presence or absence of antibodies to SARS-CoV-2.<sup>49,50</sup> Neither these point-of-care tests, nor ELISA-based IgM/IgG tests can determine the presence of neutralizing antibodies that nullify the biologic effects of the virus, resolve the infection and hopefully prevent reinfection. The only confirmatory test for neutralizing antibodies is the plaque reduction neutralization test. However, it has been shown that high IgG antibody titers positively correlate with neutralizing antibodies.<sup>57</sup> How the presence of antibodies translates to clinical outcomes remains unknown at this time.

## TRANSMISSION

We refer you to Gandhi *et al.* for a great article on the transmission of SARS-CoV-2.<sup>60</sup>

## THERAPEUTICS

Currently, there are no FDA-approved or licensed therapeutics for treating COVID-19 infections. Potential therapeutics can be broadly divided into two categories based on the target: virus or host. The pathophysiology for SARS-CoV-2 likely resembles that of SARS-CoV in that the acute lung injury caused by SARS-CoV infection mainly results from aggressive inflammation initiated by viral replication.<sup>61</sup> Similarly, SARS-CoV-2 infection also causes increased secretion of cytokines and chemokines, such as IL-1  $\beta$ , IFN- $\gamma$ , IP-10, MCP-1, IL-4 and IL-10, all indicators

of aggressive inflammation.<sup>62</sup> As a result, possible therapeutic interventions may be applied to attenuate the inflammatory response to the virus. Table 3 summarizes a few of the therapeutics in development. While none of the therapeutics mentioned in Table 3 have been approved by the FDA for treatment of COVID-19, there are many clinical trials underway and many more potential treatment modalities not discussed in this brief therapeutic review.

## VACCINES

There are over a hundred vaccine candidates, a few of which are already in clinical trials, with a few of the furthest along being mRNA-1273 (NCT04405076), a DNA vaccine, INO-4800 (NCT04336410) and a recombinant vaccine, Ad5-nCoV (NCT04398147). In addition, there will be many other vaccine developers initiating clinical trials sometime this year, considering the fact that 115 vaccine candidates were developed globally as of April 8, 2020.<sup>73</sup>

## CURRENT PREVENTION MEASURES

The only approaches currently available to stop the disease spread are those of classical epidemic control. This includes processes such as case isolation, contact tracing and quarantine, physical distancing and hygiene measures.<sup>74</sup> Efforts to control the COVID-19 pandemic likely require a multifactorial approach. First, the human-to-human transmission must be limited. This also includes reducing secondary infections among close contacts and health care workers, prevention of transmission amplification events and containing further international spread. Second, infected patients must be rapidly identified, isolated and provided with optimized care. Third, we need to identify and reduce transmission from animal sources. Fourth, we need to address unknowns in our understanding of the disease and accelerate the development of diagnostics, therapeutics and vaccines.

## OSTEOPATHIC MANIPULATION

Osteopathic physicians use osteopathic manipulative treatment (OMT) to bring increased mobility to a patient's joints and soft tissues, which encourages the body's natural healing tendency.<sup>75</sup> When directed towards a target organ/system and condition, OMT may include techniques such as counter-strain, craniosacral and lymphatic drainage, high-velocity low amplitude, muscle energy and myofascial release.<sup>76</sup> The goal is to manipulate the body's structure, keeping in mind the underlying pathophysiology of a disease, so that normal physiologic function can be regained.<sup>76</sup> For instance, the efficacy of OMT as a treatment for chronic low back pain has been documented in a randomized, double-blind, sham-controlled study of 455 patients.<sup>77</sup> Patients received statistically significant moderate to substantial benefit from OMT compared to the control group who received sham treatment. In the same study, patients receiving OMT were significantly more likely to be very satisfied with their care and used fewer medications. Back in 2007, Hruby and Hoffman had proposed the use of OMT to treat avian influenza.<sup>78</sup> They cited retrospective data gathered on the delivery of OMT techniques during the Influenza pandemic of 1918–1919, which observed significantly lower morbidity and



mortality in their patients as compared to individuals treated by allopathic physicians. The authors also point to the limitations of the data, which include the fact that the study was not controlled and it lacked information on whether the populations treated by both arms of medicine were comparable. Sanderlin and Licciardone, in their very prescient article in 2007, point out the possibility that training others in OMT techniques could be critical to the success of OMT in mitigating the impact of a pandemic.<sup>79</sup> Most osteopathic family physicians will refer potential COVID-19 patients to the health department or the emergency department of the local hospital. These patients will be subjected to testing and/or follow-up for monitoring or treatment, depending on the severity of the symptoms, as well as the existence of risk factors such as advanced age, underlying comorbidities, etcetera. Given the limited exposure of osteopathic family physicians to COVID-19 patients due to the risk of transmission, some physicians are using telehealth to teach caregivers certain OMT techniques, such as suboccipital release, thoracic inlet release, pectoral traction and pedal pump.<sup>80,81</sup> Although the OMT technique of rib raising is used by osteopathic physicians to help loosen thick mucus, stimulate the nerves to the lungs and facilitate breathing, we feel the close contact needed to deliver this treatment may also increase the risk of virus transmission. The fundamentals of osteopathic medicine believe in the utility of the above mentioned OMT techniques in maintaining a healthy immune system or improving it to an extent where it is successfully able to fight disease.<sup>81</sup> Mobilizing the osteopathic workforce to train allopathic physicians or caregivers living at home with patients who have or are at risk of COVID-19 would be fulfilling the founding beliefs of osteopathic medicine, including looking at the person as a unit that is capable of homeostasis, self-healing and health maintenance.<sup>76</sup>

## CONCLUSION

The COVID-19 pandemic is highly fluid and there is still much to be learned. Once the pandemic stabilizes, it will be important to conduct a thorough analysis to fill in the current gaps in knowledge. At this point, many questions remain. How long is a person contagious? How long and through which means can the virus persist in the human body? Are there any genetic signatures that tilt the immune reaction in favor of CSR? Why are minorities more vulnerable to increased morbidity and mortality due to COVID-19? Can some drugs be used as pre- or post-exposure prophylaxis? Which platforms and surveillance technologies can be implemented to more quickly prevent the next infectious disease threat? Will these strategies be effective in preventing fatality? Experiments conducted at the United States Army's high-level biosecurity laboratory at Fort Detrick, Maryland, show that an increase in heat, humidity and sunlight reduces the survival of the virus. These experiments have not been published and were reported in a press briefing of the White House coronavirus task force. However, even if the approaching summer months may show a decrease in cases and severity of cases due to lower infectious dose with transmission outdoors, we may still need to contend with the very real problem of superspreaders.<sup>82</sup>

## AUTHOR DISCLOSURES:

The author(s) declare no relevant financial affiliations or conflicts of interest.

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