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Evidence-based approach to early outpatient treatment of SARS-CoV-2 (COVID-19) infection

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ABSTRACT
Misinformation and promotion of well-intended but disproved therapies for COVID-19 have plagued evidence-based shared decision-making throughout the COVID-19 pandemic. In times of crisis, clinicians may feel that their strong inclination to prescribe potentially harmful, unproven therapies on behalf of their patients is supported by beneficence. Clinicians should mindfully identify and avoid commission bias during this pandemic, especially as more data have accumulated to assist with clinically sound decision-making. We describe a more evidence-based approach to treatment of early outpatient COVID-19, stressing the availability of Food and Drug Administration emergency use authorization therapies and considering plausibly beneficial, nonprescription supplements that are generally regarded as safe.

CME

Target audience: All physicians

Learning objectives: After completing the article, the learner should be able to

1. Identify evidence-based therapy for outpatient SARS-CoV-2 (COVID-19) infection
2. Identify nonprescription supplements generally regarded as safe for therapy of SARS-CoV-2 (COVID-19) infection.
3. Define commission bias.

Faculty credentials/disclosure: Dr. J. Drew Payne is a general internist and assistant professor at Texas Tech Health Science Center, where he serves as internal medicine residency program director. Kimberly Sims, MD, is a general internist with the Houston Methodist Primary Care Group and oversees residents in a community continuity clinic. Cynthia Peacock, MD, is associate professor, internal medicine, at Baylor College of Medicine. Tanis Welch, PharmD, is an infectious disease pharmacist and co-chair of the antimicrobial stewardship program at University Medical Center in Lubbock, Texas. Ruth E. Berggren, MD, is director of the Center for Medical Humanities and Ethics and professor of medicine at UT Health San Antonio. None of the planners/authors for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing health care products used by or on patients.

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With the continued stream of patients suffering from COVID-19, hospitalization rates remain concerning, depleting health care resources. Primary care clinics and emergency departments are under increasing pressure to find interventions to keep patients out of the hospital, reduce suffering, and prevent deaths. Many off-label therapies recommended in opinion articles are not supported by high-quality evidence or professional organizational guidelines.[1-3] Misinformation and promotion of these well-intended but disproven therapies may result in potential harm. In times of crisis, clinicians may feel that their strong inclination to prescribe potentially harmful, unproven therapies for their patients is supported by beneficence, a tendency that has been described as commission bias. We suggest that initial evidence-based management start with education of the patient and his or her close contacts about disease progression, isolation, and the definition of quarantine. The approach should then focus on four main categories: contagion control, evidence-based outpatient therapeutics that can prevent progression, mitigation of secondary infections/complications, and supportive measures.

CONTAGION CONTROL

Facial covering is foundational to infection control for respiratory pathogens. Mask wearing protects both the mask wearer as well as potential contacts of persons infected with SARS-CoV-2. Additional recommendations from the Centers for Disease Control and Prevention (CDC) include hand hygiene and social distancing.[4,5] After diagnosis, CDC guidelines recommend isolation of infectious persons for a minimum of 10 days with a requirement for a final 24-hour (minimum) period without fever, without the use of antipyretics. During the isolation of a documented case, unvaccinated household members of the patient and his or her close contacts (unvaccinated persons who were unmasked and within 6 feet of an infectious person for a cumulative time totaling 15 minutes) should be quarantined according to public health guidelines. Fourteen days of quarantine has been standard, although a shortened quarantine option of 10 days, or 7 days with a recent negative COVID-19 test, was posted recently by the CDC.[4] Exposed vaccinated persons are required to self-monitor for symptoms and isolate themselves if they develop fever or other COVID-19 symptoms, highlighting the excellent efficacy and importance of primary prevention through vaccination.[4]

EVIDENCE-BASED OUTPATIENT THERAPEUTICS

Therapy for COVID-19 should be guided by principles of evidence-based medicine and current science. While

Table 1. Evidence-based therapeutics for early COVID-19 infection

Drug	Dose	Comment	Available evidence
Outpatient therapeutics with emergency use authorization			
Casirivimab/ imdevimab	2400 mg/ 800 mg IV *one time*	Hospitalizations or ER visits occurred in 3% of patients treated with combined monoclonal antibody therapy vs 9% of placebo group (NNT = 16.7).	Weinreich et al[7]
Bamlanivimab/ etesevimab	700 mg/ 1400 mg IV *one time*	Hospitalization or death occurred in 36 (7%) patients who received placebo compared to 11 (2%) patients treated with combination; all 10 deaths occurred in the placebo group.	Chen et al[6]
		Treatment with combination compared to placebo was associated with a statistically significant reduction in SAR-CoV-2 viral load at day 11; no significance was observed with bamlanivimab monotherapy.	Gottlieb et al[8]
Supportive measures with possible benefit available over the counter			
Zinc gluconicum	13.4 mg PO every 6 h	Documented antiviral activity; high doses can cause GI side effects or copper deficiency.	Arentz et al[12]
Melatonin	3 mg PO nightly	Antioxidant and antiinflammatory; decreased production found in the elderly.	Zhang et al[13] Andersen et al[9]
Vitamin D	2000 IU PO daily	Important immune modulator; consider especially for those at high risk for vitamin D deficiency.	Jain et al[10] Entrenas Castillo et al[11]

ER indicates emergency room; GI, gastrointestinal; IV, intravenous; NNT, number needed to treat; PO, oral.

currently no therapy for outpatient COVID-19 infection has been approved by the US Food and Drug Administration (FDA), two regimens were recently approved under emergency use authorization (EUA) in the United States (see *Table 1*[6-13]). However, because these monoclonal antibodies are in short supply and challenging to administer, the mainstay of outpatient management remains supportive care with education about warning signs and symptom management. Clear communication about optimal management of fever, hydration, nonprescription therapies, and prone positioning may all decrease utilization of emergency services.[4–6] Home use of pulse oximetry and thermometers should be initiated immediately, with twice daily monitoring of oxygen saturation and temperature, once a COVID-19 diagnosis is made. Patients should be taught to recognize warning symptoms and signs that warrant urgent medical attention, including acute oxygen desaturation (oxygen saturation <94% at rest), breathlessness, persistent high fever despite antipyretics, postural dizziness from dehydration, strokelike symptoms, and altered mental status.[4,5]

Symptomatic patients who meet the EUA criteria for monoclonal antibodies *(see Table 2)* may be referred to pre-identified regional infusion centers that must be prepared with the protective equipment, intravenous infusion capacity, and qualifications necessary to administer treatments that rarely cause anaphylaxis or transfusion-like reactions. Bamlanivimab received EUA from the FDA on November 9, 2020, for the treatment of nonhospitalized patients with mild or moderate confirmed cases of COVID-19. Shortly

thereafter, on November 21, 2020, similar monoclonal antibodies casirivimab and imdevimab, administered together, were also awarded EUA because placebo-controlled trials showed reduced rates of emergency room visits and hospitalization in high-risk patients.[6,7] A similar EUA was issued on February 9, 2021, for bamlanivimab and etesevimab when administered together.[8] The monoclonal antibodies bind to viral spike proteins, reducing infection of human cells.[6] The BLAZE 1 trial (bamlanivimab) showed a reduction in emergency room visitation to 1.6% (5/309) compared with 6.3% (9/143) for placebo.[6] Hospitalizations or emergency room visits occurred in 3% of patients treated with casirivimab/imdevimab vs 9% of the placebo group (number needed to treat = 16.7).[7] Neither product is indicated for hospitalized or hypoxemic individuals. More recently, based on the FDA's ongoing analysis of increase in SARS-CoV-2 viral variants that are resistant to bamlanivimab alone, the FDA has determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use and thus revoked the EUA on April 16, 2021.

Monoclonal antibodies should be given within 10 days of symptom onset to COVID-19–positive patients at high risk for disease progression. The criteria for utilization, logistical difficulty, and limited supply restrict this intervention's possible impact. However, with a number needed to treat of approximately 16 to 20, these medications may well reduce hospitalizations and lower the strain on medical facilities in areas that need relief.[6,7] The Infectious Diseases Society of America has recommended against routine use of bamlanivimab or casirivimab/imdevimab, but has suggested the use of bamlanivimab and etesevimab based on an interim analysis of the BLAZE-1 clinical trial, which announced via press release a 70% risk reduction of hospitalization or death (*P* = 0.0004).[8] The National Institutes of Health (NIH) recommends either bamlanivimab/etesevimab or casirivimab/imdevimab, yet recommends against bamlanivimab monotherapy.[4]

Hydroxychloroquine or chloroquine alone or in combination with azithromycin is not recommended outside of a clinical trial by the NIH, the Infectious Diseases Society of America, or the American College of Physicians for treatment of COVID-19. Hydroxychloroquine was studied in adults with early COVID-19, patients with mild to moderate COVID-19, and as postexposure prophylaxis in randomized controlled trials and was ineffective in all cases.[14–16] Additionally, although QT prolongation is a potential concern from hydroxychloroquine, there are no clear guidelines for monitoring cardiac status in outpatients.

Corticosteroid therapy is not currently recommended for use in the early outpatient setting. Current NIH guidelines list not using corticosteroid or dexamethasone as an AIII recommendation.[4] Hypoxemic inpatients are typically treated with dexamethasone for a duration of 5 to 10 days. If patients are discharged prior to completion of corticosteroids, they may be sent home with oral corticosteroids.

Table 2. High-risk criteria required for bamlanivimab/etesevimab or casirivimab/imdevimab infusion*

Group	Criteria
General population	• Has a BMI ≥35 kg/m^2 • Has chronic kidney disease • Has diabetes • Has immunosuppressive disease • Is currently receiving immunosuppressive treatment • Is ≥65 years of age
≥55 years	• Has cardiovascular disease • Has hypertension • Has chronic obstructive pulmonary disease/other chronic respiratory disease
12–17 years	• Has a BMI ≥85th percentile for age and gender based on growth charts† • Has sickle cell disease • Has congenital or acquired heart disease • Has a neurodevelopmental disorder, e.g., cerebral palsy • Has a medical-related technological dependence, e.g., tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19) • Has asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control

*Meeting a single criterion for the group qualifies as high risk.
†https://www.cdc.gov/growthcharts/clinical_charts.htm.
BMI indicates body mass index.

Ivermectin has gained popularity as a possible early outpatient therapy. To date, the therapy has not been listed as recommended by the NIH.[4] Ivermectin was found to have effect on reducing or stopping viral replication in vivo, but concentrations needed to obtain the in vitro IC50 are considerably higher than those achieved in human plasma and lung tissue.[17] The medication has been highly publicized as useful and effective in prevention and treatment of COVID-19 by the group Front Line COVID-19 Critical Care Alliance.[18] However, a recent double-blind randomized trial including 478 patients showed no significant difference in time to resolution of symptoms in the ivermectin group vs placebo.[19] A few small trials in the United States and Europe compared ivermectin plus doxycycline to "standard" care. Standard care varied in each study and involved vitamin B6, vitamin C, and hydroxychloroquine or a combination of these medications. Elgazzar et al and Hashim et al reported decreased mortality with ivermectin-containing regimens.[20,21]

Colchicine was recently studied by the COLOCORONA investigative group.[22] Encouraged by the medication's antiinflammatory role, the studied enrolled 4488 patients, 4159 of whom were polymerase chain reaction (PCR) positive for COVID-19 and 329 of whom were assumed to be positive due to clinical conditions. When taken in total, there was a nonsignificant reduction in hospitalization or death in patients receiving colchicine vs placebo, yet there was a significantly higher incidence of pulmonary embolism (0.5%) in colchicine-treated vs placebo patients (0.1%). However, a subgroup analysis of patients with PCR-confirmed COVID-19 vs those taking placebo showed a risk reduction in hospitalization and death (4.6% vs 6.0%, 95% confidence interval, 0.57 to 0.99; $P = 0.04$).[22]

Early promising results are being investigated in the selective serotonin reuptake inhibitor and σ-1 receptor agonist fluvoxamine. This is an area of evolving evidence, with at least five ongoing clinical trials listed at www.clinical-trials.gov.

MITIGATION OF SECONDARY INFECTIONS AND THROMBOTIC COMPLICATIONS

Although the risk of venous thromboembolism is markedly increased in COVID-19, the NIH does not recommend routine venous thromboembolism prophylaxis for patients with COVID-19.[4] A recently published study found that "aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19" but concluded that randomized, controlled, prospective trial data are needed to confirm a causal relationship between reduced mortality and aspirin use in SARS-CoV-2 infection.[23] The International Society of Thrombosis and Haemostasis discusses the importance of considering venous thromboembolism prophylaxis in hospitalized COVID-19 patients but does not recommend for or against this in the early outpatient setting.[24] This is also an area of evolving evidence, with at least nine ongoing clinical trials listed at www.clinical-trials.gov.

Secondary bacterial infections are a common concern in SARS-CoV-2–positive patients. However, antimicrobials have not been shown to be effective in early COVID-19 disease. Suggesting that antibacterial agents be given to prevent secondary infection is contrary to antibiotic stewardship principles and may lead to possible harm, such as antimicrobial resistance, adverse drug reactions (for example, azithromycin-related QT prolongation), and antimicrobial-related infections, such as *Clostridium difficile*. If a patient does develop a secondary infection, local antibacterial guidelines related to microbial susceptibility should be followed.

SUPPORTIVE MEASURES REGARDED AS SAFE

While evidence-based outpatient therapies are few, some clinicians recommend therapies that have biological plausibility for benefit, with minimal risks of harm. We describe several supplements in this category, acknowledging that to date, they lack sufficient randomized clinical trial evidence for benefit in COVID-19. Symptom management for cough suppression, nausea, diarrhea, and fever should be no different than those commonly offered for non-COVID patients.

Oral zinc (especially zinc lozenges) is widely available without a prescription and is considered relatively safe. Several studies, including human trials for other coronavirus infections, have demonstrated that zinc may reduce viral replication and symptom duration.[25] There is ample indirect evidence that zinc reduces COVID-19 duration and severity, especially in zinc-deficient populations, people with comorbidities, and older adults. Prospective, randomized trials for zinc in preventing or treating SARS-CoV-2 are under way.[12] Currently, the NIH recommends against taking more zinc than the daily required amount.[4]

Melatonin is a naturally occurring sleep hormone with antiinflammatory and antioxidative effects, whose production wanes with aging.[9] Melatonin has long been available as a nonprescription sleep aid and has previously been studied for its anti-lung injury effects in viral illnesses. A large observational study from the Cleveland Clinic (N = 26,779 individuals from a COVID-19 registry) indicated that those taking melatonin had a 28% reduced risk in infection from SARS-CoV-2.[26] Melatonin doses of 3 to 10 mg at bedtime are generally regarded as safe in adults, and melatonin is well tolerated with few reported side effects.[10] At a minimum, this intervention may improve the quality of sleep, which can support recovery and provide comfort for people who are suffering with COVID-19 symptoms at home.

Finally, vitamin D deficiency appears to be associated with worse outcomes in COVID-19.[10] A 6-week prospective observational study showed significantly higher mean vitamin D levels in asymptomatic than in severely ill COVID-19 patients (27.89 ± 6.21 vs 14.35 ± 5.8 ng/mL). Moreover, the prevalence of vitamin D deficiency was 33% in

asymptomatic patients vs 97% in critically ill COVID-19 patients. A small pilot randomized clinical trial from Spain showed that 25-hydroxyvitamin D supplementation can significantly reduce the need for ICU care in hospitalized COVID-19 patients.[11] While some authors advise widespread supplementation of vitamin D in at-risk populations, we would consider safe supplementation (2000–4000 IU daily) for COVID-19 patients at risk for both vitamin D deficiency and adverse outcomes.

CONCLUSION

Medical professionalism mandates our continued effort to balance avoiding harm (nonmaleficence) with the duty to treat (beneficence). Nonhypoxemic patients who do not need imminent life support but are at high risk for COVID-19 morbidity should be informed of the risks and benefits of targeted therapeutics, such as specific monoclonal antibodies. For non–high-risk patients with COVID-19 symptoms, several safe nonprescription options are readily available and provide plausibility and/or retrospective observational evidence of potential benefit. Physician-led patient education, compassionate listening, and frequent reassessment are essential to our approach. Continued awareness of equipoise and avoidance of commission bias are essential to minimize harm and to lessen the erosion of public trust in our professional practice of evidence-based medicine.

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