With the emergence of the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus, the pandemic has resulted in a severe respiratory disease known as COVID-19. Data and literature are limited in the evaluation, treatment, and considerations for pediatric patients including special populations (e.g., neonates, children, immunocompromised patients, and those with sickle cell disease). There exists a need for a comprehensive review of pediatric proven and disproven treatments as therapies continue to emerge. This article evaluates the pharmacologic treatment and prevention therapies used in pediatric patients to date, including emergency use authorizations, as well as rationales for pharmacotherapies not routinely used to treat acute COVID-19 infection. It is important to note this review article is current as of January 25, 2021, given the rapid evolution of the pandemic.

**ABBREVIATIONS**

ACE2, angiotensin-converting enzyme 2; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; CDC, Centers for Disease Control and Prevention; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; EUA, emergency use authorization; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; ICU, intensive care unit; IFN, interferon; IDSA, Infectious Diseases Society of America; IgG, immunoglobulin G; IL, interleukin; IV, intravenous; JAK, Janus kinase; MIS-C, multisystem inflammatory syndrome in children; mRNA, messenger RNA; NAAT, nucleic acid amplification test; NIH, National Institutes of Health; NS, normal saline; PCR, polymerase chain reaction; QTc, corrected ECG interval from the QRS complex to the end of the T wave; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCD, sickle cell disease; TNF-β, tumor necrosis factor beta; WHO, World Health Organization

**KEYWORDS**

children; COVID-19; pandemic; pediatric; review; SARS-CoV-2

**Introduction**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly discovered coronavirus undergoing continued research; therefore, the following information is subject to change as new data emerge. COVID-19 is the clinical disease caused by SARS-CoV-2, an enveloped RNA coronavirus that emerged from Wuhan (Hubei Province, China) in December 2019. COVID-19 infection rapidly spread worldwide, resulting in cases in over 100 countries by early March. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. As of January 21, 2021, cases in the United States exceeded 24,800,000 resulting in over 416,000 deaths.

Viruses are typically transmitted via 3 routes: direct contact, droplet, or airborne. Contact transmission requires direct contact with the infectious individual. Droplet transmission occurs when an infectious individual exhales within a 6-feet diameter, secondary to a larger droplet size and time suspended in the air. Airborne transmission spreads via smaller respiratory droplets and particles, which can remain suspended...
for longer periods of time and travel far from the source, typically farther than 6 feet. Early in the pandemic, transmission of SARS-CoV-2 was thought to be airborne. However, upon further review, SARS-CoV-2 transmission is not considered airborne by definition, but rather occurring secondarily to an infectious person producing respiratory droplets for an extended time in an enclosed space (i.e., tent).

The incubation period of COVID-19 is approximately 14 days with most patients becoming symptomatic around day 5. However, confirmed COVID-19 infections have been documented in asymptomatic carriers and presymptomatic patients. Studies reveal that presymptomatic and asymptomatic patients often host large quantities of SARS-CoV-2 RNA, and though not showing symptoms, are highly likely to transmit the virus. Asymptomatic patients are often unaware and do not self-isolate, resulting in continued viral transmission. It is important to note that this review discussing the evaluation and management of COVID-19 in special populations is based on data as of January 25, 2021.

**Pathophysiology**

SARS-CoV-2 is transmitted via respiratory droplets. Once inside the body, using its spike protein S subunit, the virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in the lungs. The S subunit further facilitates the fusion of viral and host cell membranes, resulting in endocytosis, viral uncoating, and viral content release. Once released, the virus undergoes replication, transcription, translation, and exocytosis releasing the newly formed viral particles extracellularly, permitting continued transmission. Systemic inflammation is a known complication of COVID-19 infection. Patients significantly vary in the severity of their inflammatory response to COVID-19. Patients with severe inflammatory cascade (cytokine storm) often suffer from the most devastating consequences and worse outcomes. Though not yet fully described, possible genetic and independent risk factors responsible for these variations appear likely and are undergoing continued investigation.

The COVID-19 hyperinflammatory response is a unique and challenging feature necessitating more robust research to aid providers in early identification of patients with the greatest risks. Advanced age is a well-established independent risk factor associated with increased morbidity and mortality, while younger age is linked to milder disease and asymptomatic presentation. This age divide became evident early on and as the pandemic progressed, it became even more compelling. Acute COVID-19 infections in pediatric patients, with the exception of the rare post-viral multisystem inflammatory syndrome in children (MIS-C), are milder with a rapid recovery and minimal severe sequelae. Among the 18,455,050 cases reported in the United States, only 11% of the cases were reported in patients younger than 18 years. COVID-19 in pediatric patients is significantly less prevalent and severe. The age divide is believed to be secondary to multiple factors, including variations in the distribution of ACE2, T-cell and B-cell responses, and the balance of modulating and proinflammatory cytokines. The impact of COVID-19 infections in pediatric patients with known high-risk comorbidities, identified in adults (see below), and/or other specific high-risk conditions, is not fully understood. Much remains unknown in pediatric patients with COVID-19.

**SARS-CoV-2 Variants**

SARS-CoV-2 tracking and mutation cataloging began early in the pandemic. SARS-CoV-2 mutates frequently, acquiring a new mutation approximately every week. Many of these mutations are silent, incidental, and do not alter viral behavior. Toward the end of 2020, two specific variants gained substantial media coverage, sparking fear worldwide: the United Kingdom variant (B1.1.7) and the South Africa variant (501Y.V2). Evidence suggests both SARS-CoV-2 variants have the ability to spread more rapidly with unaltered viral behavior. Interestingly, neither SARS-CoV-2 variants have been associated with increased morbidity or mortality. Notably, none of the variants thus far possess the ability to evade vaccine-induced immunity, cause more severe disease, or evade detection by the currently used diagnostic tests.

As long as the SARS-CoV-2 virus continues to exist, the emergence of new strains is inevitable. The virologic, epidemiologic, and clinical characteristics of newly identified variants will be closely monitored. The National SARS-CoV-2 Strain Surveillance program was launched by the CDC to increase the number of viruses undergoing characterization. Data will be continuously analyzed, and genomic data rapidly uploaded to public databases. In addition, the CDC established the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance, a national genomics conglomerate to coordinate SARS-CoV-2 sequencing across the United States. As clinicians we must stay abreast of established and newly detected variants, specifically, any variant demonstrating diminished activity to our current vaccines.

**Clinical Presentation**

The spectrum of illness with COVID-19 varies vastly ranging from asymptotic presentation, to pneumonia with rapid progression, respiratory failure, and even death. Mild to moderate disease (mild symptoms to mild pneumonia) is the most common and accounts for approximately 80% of the reported cases. Clinical signs and symptoms may vary depending on the severity of illness and duration. The most common symptoms are fever, cough, sore throat, headache, diarrhea, and shortness of breath. Other common symptoms include...
myalgias, abdominal pain, rhinorrhea, dizziness, anosmia, and dysgeusia.\textsuperscript{2,5} Risk factors for severe COVID-19 include older age (>65 years) and specific comorbid conditions. These comorbid conditions include obesity, chronic kidney disease, diabetes, immunosuppression, sickle cell disease, heart disease, underlying respiratory diseases, and hypertension.\textsuperscript{12} This data is supported by strong and consistently published literature. COVID-19 infections typically follow 3 progressive stages that often overlap.\textsuperscript{13}

- **Stage 1**: Early phase, typically occurs within days 0 to 5, and involves viral infiltration and replication.
- **Stage 2**: Pulmonary phase, a progression of stage 1, occurring days 6 to 9, leads to subsequent collateral tissue injury and inflammation resulting in pulmonary damage and cardiovascular stress.
- **Stage 3**: Hyperinflammatory phase, a progression of stage 2, occurring days 10 to 14, involves an intensified host inflammatory response and progressive systemic inflammation. This is known to occur even in the presence of decreasing viral loads. A visual depiction of all 3 stages can be seen in Figure 1.

**SARS-CoV-2 Testing**

The diagnosis of COVID-19 requires a sample from the lower respiratory tract or nasopharynx to be evaluated by either a molecular or antigen-specific assay (Table 1).\textsuperscript{6,14}

**Nucleic Acid Amplification Test (NAAT).** NAAT is a reverse transcriptase-polymerase chain reaction–based diagnostic test that detects SARS-CoV-2 RNA.\textsuperscript{9,15} Often referred to as a molecular test, it is highly specific; however, sensitivity may vary owing to incorrect timing or poor sample collection. Poor quality specimen collection increases the likelihood of false negatives. To optimize sensitivity, sample collection should occur close to symptom onset as possible. Asymptomatic and recovering patients may have false-negative results.\textsuperscript{15}

**Antigen Test.** Antigen-based diagnostic tests detect specific SARS-CoV-2 viral proteins. In comparison to the nucleic acid amplification test, antigen tests remain highly specific but less sensitive.\textsuperscript{3} To optimize sensitivity, antigen testing should occur when nearing peak viral load, approximately day 5 of illness. If the initial antigen test result is negative, and exposure is highly suspected, consider confirming via the nucleic acid amplification test.
amplification test. Antigen tests are less expensive and results are rapid, making it an attractive option when quarantining is required and transmission control is critical.

**Antibody Test.** The SARS-CoV-2 antibody or serology test, specifically immunoglobulin G (IgG), detects an immune response as opposed to the actual virus itself. Antibody testing should only be used to identify patients previously infected with SARS-CoV-2 and should not be used to diagnose acute infections.

**Radiologic and Laboratory Findings**

Bilateral multifocal opacities or consolidations are the most common chest x-ray findings. Common computed tomography abnormalities in patients with severe COVID-19 include peripheral "ground-glass" opacities with or without areas of consolidation. The most common overall laboratory finding is lymphopenia, occurring in approximately 83% of patients. Additional findings include neutrophilia and elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer levels. Procalcitonin and specific inflammatory markers may or may not be elevated. An elevated D-dimer level and lymphopenia have been associated with higher mortality.

**Special Populations**

Most published data on the epidemiology, clinical course, prevention, and treatment of COVID-19 descend from studies conducted in adults. Special patient populations including neonates, children, pregnant individuals, and many others lack specific clinical considerations on the treatment and management of COVID-19 (see Table 2).

**Pregnancy.** Pregnant women, especially in their third trimester, are more likely to suffer from respiratory complications requiring mechanical ventilation and intensive care than non-pregnant patients. As of January 18, 2021, over 57,000 total COVID-19 cases in pregnant women have been reported to the CDC with 10,116 hospitalized cases and 71 deaths. To date, COVID-19 clinical trials have excluded, or included very few, pregnant and lactating patients. Therefore, specific therapy considerations are limited. Potentially effective treatment for COVID-19 should not be withheld from pregnant women secondary to hypothetical safety-related concerns. The decision to use any treatment should be a shared discussion between the clinical team and the patient and/or family. This discussion should be based on a risk versus benefit assessment and an extensive review of any available data on the use in pregnancy and lactation. Clinical management of pregnant COVID-19 patients should entail individualized regimens based on illness severity, underlying comorbidities, and clinical status. Maternal COVID-19 infections rarely necessitate an early delivery unless complications occur, preventing full maternal recovery. Breastfeeding considerations can be found under "Neonates."

**Neonates.** Vertical transmission via the transplacental route of SARS-CoV-2 is thought to be rare but possible. SARS-CoV-2 has been detected in the placenta, umbilical cord blood, vaginal mucosa, and expressed breast milk of symptomatic and asymptomatic women infected with COVID-19. Research is ongoing in an effort to provide recommendations on the best management of neonates born to a COVID-19–positive mother. The American Academy of Pediatrics recommends against physical separation of infants and mothers and suggests maternal and infant rooming-in with appropriate infection prevention. The neonatal registry, including 1500 infants, reported a 2% to 5% positivity rate, which suggested a low likelihood of mother-infant transmission. The role of SARS-CoV-2 detection in expressed milk is controversial. No documented cases of COVID-19 transmission via human milk have been reported to date. The protective role of maternal COVID-19 antibodies in human milk remains unknown. Diagnostic SARS-CoV-2 testing is recommended in hospitalized asymptomatic newborns of COVID-19–positive mothers at 24 and 48 hours of life. Testing is primarily used to facilitate inpatient isolation and provide epidemiologic information. Neonates are considered a low-risk population, based on cumulative evidence and experience. Special considerations for children will be discussed separately.

**Children.** The significant differences observed in the prevalence, severity, and mortality of pediatric patients with COVID-19 compared with adults depicts a compelling age divide. Among the US-reported cases, only 11% involve patients younger than 18 years. Pediatric

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**Table 1. Diagnostic SARS-CoV-2 Testing**

<table>
<thead>
<tr>
<th>Type</th>
<th>Detects</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular (NAAT)</td>
<td>Viral RNA</td>
<td>High</td>
<td>Good/variable</td>
<td>Potential false negatives due to inappropriate timing and/or inadequate samples.</td>
</tr>
<tr>
<td>Antigen</td>
<td>Viral proteins</td>
<td>High</td>
<td>Less</td>
<td>Less expensive and faster results. Often requires molecular confirmation.</td>
</tr>
<tr>
<td>Antibody (serology)</td>
<td>IgG</td>
<td>NA</td>
<td>NA</td>
<td>Not for acute diagnosis. Identifies previous infection.</td>
</tr>
</tbody>
</table>

*IgG, immunoglobulin G; NAAT, nucleic acid amplification test; NA, not applicable*
patients with COVID-19, with the exception of MIS-C, present with mild signs and symptoms and recover quickly without severe sequelae. This age divide is thought to be secondary to variations in the distribution of ACE2, T-cell and B-cell response, and/or the balance of modulating and proinflammatory cytokines. The impact of COVID-19 in pediatric patients with comorbidities, specifically high-risk comorbidities identified in adults, remains unknown. Evidence on the treatment of COVID-19 is especially lacking in children. Clinical trials should prioritize the enrollment of children whenever possible. The management and treatment of patients with MIS-C will be discussed separately.

Cancer. Patients with cancer are more prone to infections and poor outcomes, specifically those receiving chemotherapy, immunotherapy, and those who are post–stem cell transplant. Early on, the vast paucity of data on SARS-CoV-2 in patients with cancer raised great concern. Although clinical evidence is lacking, available data suggest higher all-cause mortality and increased risk of requiring intensive care in infected cancer patients. The risks for severe COVID-19 infection varies by cancer type, treatment regimens, stage of therapy, and overall level of immunosuppression. Patients in remission are reported to have a decreased risk of severe COVID-19 infections. Cancer survivors are thought to have decreased COVID-19 severity; however, much still remains unknown. Cancer and immunocompromised patients are known to have prolonged viral shedding. However, it is unclear how this impacts patient outcomes or the likelihood of ongoing viral transmission. Repeated COVID-19 testing is not recommended in cancer patients as it is unknown how to use the results. Literature suggests that pediatric cancer patients have milder disease than adult cancer patients.

A recent publication from Italy reported no significant difference in the outcomes of children with COVID-19 and cancer compared with COVID-19–positive children with and without other comorbidities. Current COVID-19 treatment recommendations for the general population should also apply to pediatric and adult cancer patients. No evidence exists recommending therapy modifications of ongoing chemotherapy regimens in patients with COVID-19. For children, evidence suggests continuing chemotherapy in mild or asymptomatic COVID-19 as it has not been associated with worsening COVID-19 severity. For adults, treatment should be based on a case-by-case evaluation. Especially with curable cancers, delays in treatment should be avoided if possible. If chemotherapy modifications are deemed necessary, the optimal time to reinitiate post–COVID-19 cancer therapy remains unknown.

Venous thromboembolism prophylaxis or treatment may need to be initiated, if not contraindicated. Methods should be implemented to minimize any potentially avoidable treatments, emergency room visits, and hospitalizations in an effort to decrease exposure risks. Potential methods include, but are not limited to, optimizing the use of granulocyte colony-stimulating factor to decrease risks of febrile neutropenia and radiation therapy rescheduling. For hospitalized patients admitted with febrile neutropenia, guidelines recommend molecular diagnostic testing for SARS-CoV-2 in addition to initiation of empiric antibiotics.

Transplant. This section focuses on treatment considerations for transplant recipients with acute COVID-19 and does not include potential donors or candidates. Solid organ transplant, hematopoietic cell transplant, and cellular immunotherapy recipients require close medical follow-up and frequent appointments within health care facilities, placing them at an increased risk for SARS-CoV-2 exposure. Transplant patients commonly require immunosuppression and have multiple comorbid conditions, which makes it

<table>
<thead>
<tr>
<th>Table 2. COVID-19–Specific Therapy</th>
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<tbody>
<tr>
<td><strong>Class</strong></td>
</tr>
<tr>
<td>Antiviral</td>
</tr>
<tr>
<td>JAK-1 inhibitor</td>
</tr>
<tr>
<td>IgG monoclonal antibody</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Convalescent plasma</td>
</tr>
</tbody>
</table>

EUA, emergency use authorization; IgG, immunoglobulin G; JAK, Janus kinase
exceedingly difficult to determine the true impact of COVID-19 in this population. Many of these concomitant conditions are independently associated with poor outcomes. Therefore, differentiating the risk of the transplant itself is near impossible. Depending on the organ transplanted, patients require varying degrees of immunosuppression and a case-by-case assessment to determine individual risk factors is recommended, and clinical outcomes vary owing to the heterogeneity of transplant recipients. Data published in adult kidney transplant recipients with COVID-19 reported higher prevalence and mortality than in the general population, while other analyses demonstrated no difference.20,21

A recent multicenter, multorgan cohort analysis in pediatric solid organ transplant patients reported full recovery of all patients within 7 days and none required supplemental oxygen.22 These findings mirror various other results suggesting milder symptomatology and better outcomes in children than adults, even in the presence of high-risk conditions. However, these results are limited by small sample size, and more robust studies are required before conclusions are made. Therapeutic management of the transplant patients with acute COVID-19 does not differ from treatment recommendations in the general population with the exception of a few caveats.23 Upon initiating COVID-19–specific antivirals, steroids, or immune modulators, it is critical to review medications for any potential drug-drug interaction(s), organ-specific side effects, drug-associated toxicities, specific dose modifications, and required medication-specific laboratory monitoring. Immunosuppression requirements should be reevaluated in patients presenting with moderate to severe COVID-19.20 Antiproliferative agents should be discontinued, and calcineurin inhibitors should be reduced or temporarily held depending on that patient’s clinical status and resumed once symptoms resolve. Venous thromboembolism prophylaxis or treatment should be initiated, if not contraindicated, based on anticoagulation risk factors. In the presence of acute kidney injury, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be suspended until resolution to baseline.

Human Immunodeficiency Virus. HIV affects approximately 1.2 million people in the United States.29 Most patients being treated with antiretroviral therapy are well controlled with CD4 counts of ≥500 cells/mm³ and considered clinically immunocompetent. Immunocompetent HIV patients present with similar clinical symptoms and severity as non-HIV COVID-19 patients. Multiple published case reports and cohort studies illustrate no significant difference in clinical outcomes in immunocompetent HIV COVID-19 patients compared with patients without HIV. The treatment of acute COVID-19 in HIV patients does not differ from the general population. Special attention is required to detect and anticipate potential drug-drug interactions and/or overlapping toxicities. Remdesivir and dexamethasone are generally considered safe to administer with antiretroviral therapy and have no known clinically relevant interactions.25–27 HIV patients with CD4 counts lower than 200 cells/mm³ are associated with worse outcomes, even when virologic suppression is adequate.28 Additional research encompassing HIV patients in all stages is required to accurately evaluate the true impact of COVID-19 in this population.

Other Comorbidities. Almost half (42%) of US pediatric COVID-19 hospitalizations were associated with 1 or more underlying medical conditions, suggesting the presence of underlying conditions places children at a higher risk for COVID-19–associated hospitalizations.24 Among those who were hospitalized, the most prevalent underlying condition was obesity (37.8%), followed by chronic lung disease (18%), neurological disorder (14%), and asthma (13.5%). Obesity was defined as BMI (kg/m²) ≥ 95th percentile for age and sex, based on CDC growth charts among children at least 2 years of age. According to the CDC, children with the following conditions may be at risk for severe illness: obesity, medical complexity, severe genetic disorders, severe neurological disorders, inherited metabolic disorders, sickle cell disease, congenital heart disease, diabetes, chronic kidney disease, asthma and other chronic lung disease, and immunosuppression due to malignancy or immune-weakening medications.25

Only a handful of case reports showed SARS-CoV-2 infection may trigger acute chest syndrome in patients with sickle cell disease (SCD) given COVID-19 is an acute infectious pneumonia.26 Although SCD cases comprised only 2.3% of pediatric hospitalized patients in 14 states from March 1–July 25, 2020, there were a total of 178 pediatric and adult patients with SCD in the United States who reported to the SCD–COVID-19 case registry from March 2021.24,27 Most (69%) SCD patients were hospitalized during their COVID-19 illness with 11% admitted to the ICU. Given the average age of 28.6 ± 14.5 years and concerning hospitalization rates, patients with SCD are encouraged to take extra precautions to prevent COVID-19.

Current evidence is limited on which underlying medical conditions in children are associated with increased risks. Many of these risk factors have been extrapolated from adult data and are subject to change as more evidence becomes available. Recall that there is much still unknown about this virus and how it may affect other disease states; therefore, it is best for patients with all underlying medical conditions and caregivers to take extra precautions when it comes to preventing COVID-19.

Pharmacologic Management of Acute COVID-19

There are numerous pharmacotherapy options worthy of discussion, proven and disproven, used in
the treatment of pediatric patients with COVID-19. If not already in place, we recommend the development of institution-specific guidelines or algorithms for both the inpatient and outpatient setting (see Figures 2 and 3). As these guidelines assist health care providers in the evaluation and management of COVID-19, they should be regularly updated as more evidence becomes available.

Emergency Use Authorization (EUA). Pandemics or any threats to public health necessitate alternative procedures to expedite the allocation of emergency medications, diagnostics, and resources as quickly and safely as possible. Under section 564 of the Federal Food, Drug, and Cosmetic Act, the FDA Commissioner may allow unapproved medical products or off-labeled uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions when there are no adequate, approved, and available alternatives. This approval is known as EUA. As of December 10, 2020, the FDA had approved EUAs for 9 drug and biological products for use during the COVID-19 pandemic. Most new and repurposed medications being used to treat COVID-19 required an EUA and will be discussed in more detail below.

Inpatient Therapies. Corticosteroids. Corticosteroids exhibit potent anti-inflammatory properties and are used to mitigate the COVID-19–specific systemic inflammatory response and minimize deleterious outcomes. Prior to the pandemic, corticosteroids were heavily used thanks to their low cost, availability, established efficacy, and well-described side effect profiles. Corticosteroid side effects, although far from benign, are often anticipated, which may alleviate the concern of prescribing. Studies evaluating corticosteroids for the treatment of non–SARS-CoV-2 coronavirus infections, such as influenza pneumonia and acute respiratory distress syndrome, reported slower viral clearance, worse outcomes, and conflicting results. Initially, the use of corticosteroids for the treatment of COVID-19 was highly controversial; however, with continued experience treating COVID-19–associated cytokine storm, corticosteroids are now recommended by the Infectious Disease Society of America (IDSA) and National Institutes of Health (NIH) in hospitalized COVID-19 patients requiring supplemental oxygen who have no known contraindications. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial is an
ongoing multicenter, randomized, adaptive, open-label study in hospitalized COVID-19 patients. Patients were randomly assigned to receive one of several potential COVID-19 treatments (including dexamethasone) plus the standard of care or the standard of care alone. Preliminary results revealed a 28-day mortality reduction in COVID-19 patients requiring supplemental oxygen who were receiving dexamethasone 6 mg daily for up to 10 days. The mortality reduction was most apparent in patients receiving mechanical ventilation. Benefits were not observed in patients who did not require supplemental oxygen. The initial RECOVERY protocol only included patients 18 years of age and older, excluding children and pregnant or breastfeeding women. Therefore, caution is warranted when extrapolating the results of the RECOVERY trial until a comprehensive evaluation of the safety and efficacy of corticosteroids for COVID-19 in pediatric and pregnant or breastfeeding patients is available. Despite this limitation, experience with dexamethasone is extensive across the entire pediatric age spectrum. To date, no evidence exists suggesting dexamethasone is any less efficacious in pediatric than in adult patients. Therefore, dexamethasone therapy should be considered in hospitalized COVID-19 pediatric patients requiring supplemental oxygen with no known contraindications.

The RECOVERY trial is actively recruiting patients for a revised protocol that includes children of all ages and pregnant or breastfeeding women. An adapted corticosteroid regimen is used in this revision for patients with any of the following (see Table 3): pediatric multisystem inflammatory syndrome—temporally associated with SARS-CoV-2 or MIS-C, neonates ≤ 44 weeks’ gestation with acute COVID-19, and pregnant or breastfeeding women. The use of corticosteroids for the treatment of COVID-19 should encompass a comprehensive individualized risk versus benefit assessment and appropriate dose modifications, if applicable. Corticosteroids are not recommended for patients with mild symptoms and low levels of oxygen support (i.e., nasal cannula only). Corticosteroids should be considered in patients with moderate-severe COVID-19 requiring supplemental oxygen and no known contraindications.

See COVID-19 VTE prophylaxis guideline
Additional testing to be done at the discretion of the provider
For moderate/severe disease
Recommended for patients who are mechanistically ventilated or requiring oxygen \( \geq 2 \text{ L/min for age} \leq 12 \text{ years OR} \geq 6 \text{ L/min for age} > 12 \text{ years}) to maintain oxygenation saturations \geq 94%.

- Use of corticosteroids
- Dexamethasone 0.15 mg/kg (max 6 mg/day) QD x 5-10 days. No more than 10 days.
- Use of corticosteroids
- Dexamethasone 0.15 mg/kg (max 6 mg/day) IV once daily days 2-5
- Emergency use authorization (EUA) or compassionate use in pediatrics (age < 12 years or weight < 40 kg) in only considered for hospitalized patients
- Criteria for use include ALL of the following:
  1. PCR-confirmed SARS-CoV-2
  2. Hospitalized for 7 days or fewer (in disease thought to provide more benefit)
  3. Requiring oxygen \( \geq 2 \text{ L/min (age < 12 years OR} \geq 6 \text{ L/min (age > 12 years)}) to maintain oxygenation saturations \geq 94% or invasive mechanical ventilation OR ECMO
  4. ALTs less than 10X upper normal limit
  5. Remdesivir only: ALTs less than 10X upper normal limit.
- EUA requiring ID approval.
- Do not use if on dialysis, end-stage renal disease, have active kidney disease (eGFR <30), or known active tuberculosis
- Requires renal/hematopoietic adjustment
- Dose: Age < 9 years: 4 mg PO once daily; Age 2-8 years: 2 mg PO once daily
- Duration: 14 days or until hospital discharge, whichever is first.
- Tocilizumab requires ID approval.

ALT, alanine aminotransferase; BCX, blood culture; BNP, B-type natriuretic peptide; CMP, comprehensive metabolic panel; CrCl, creatinine clearance; CRP, C-reactive protein; CVVH, continuous veno-venous hemofiltration; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; ID, infectious diseases; PO, orally; QD, daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VTE, venous thromboembolism

**Figure 3. Example of inpatient pediatric treatment algorithm.**

**Pediatric Inpatient Treatment Algorithm**

<table>
<thead>
<tr>
<th>Home Bound</th>
<th>ED Assessment</th>
<th>Suspect for COVID-19</th>
<th>PICU Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID testing only&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Well Appearing: COVID testing only&lt;sup&gt;2&lt;/sup&gt;</td>
<td>II Appearing: CBC, CMP, BCX, CRP/ESR, CVR&lt;sup&gt;2&lt;/sup&gt;</td>
<td>III Appearing: CBC, CMP, BCX, CRP, CRP/ESR, BNP, troponin, procalcitonin, ferritin, fibrinogen, D-dimer</td>
</tr>
<tr>
<td>Continue with current management</td>
<td>Evaluate for corticosteroids and/or (remdesivir&lt;sup&gt;2&lt;/sup&gt; + baricitinib&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>Repeat aforementioned labs &amp; review</td>
<td>If worsening clinically consult Pediatric Infectious Disease&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Disease severity:**
- Mild/uncomplicated disease: SpO2 >95% on room air (RA) at rest (child < 12 years of age not requiring oxygen or admitted for non-respiratory issues) with no other complications of COVID-19
- Moderate disease: fever, SpO2 > 94% on RA, radiographic evidence of pulmonary infiltrates
- Severe disease: fever, SpO2 < 94% on RA, radiographic evidence of pulmonary infiltrates
symptoms requiring additional respiratory support. Until more information becomes available, patients on chronic systemic or inhaled steroid therapy should not discontinue treatment or surpass recommended studied doses of corticosteroids.

**Remdesivir.** Remdesivir is an antiviral drug originally evaluated in clinical trials to treat Ebola during the 2014 outbreak. It is an IV nucleotide prodrug that binds to viral RNA-dependent RNA polymerase, inhibiting viral replication via premature termination of RNA transcription. Remdesivir is widely distributed, hepatically metabolized (~80%) via CYP3A4, 2C8, and 2D6, and renally excreted. Remdesivir was initially strictly available through Gilead’s compassionate use program. In March 2020, secondary to overwhelming demand, the compassionate use program was suspended and restricted to include only children and pregnant women. This expedited the initiation of remdesivir clinical trials to establish a basis for expanded access treatment protocols. On May 1, 2020, the FDA approved an EUA on the basis of results from a Gilead-sponsored open-label trial demonstrating the safe and effective use of remdesivir in hospitalized COVID-19 infected adults and children. On October 22, remdesivir gained FDA approval for the treatment of COVID-19 in patients at least 12 years of age and weighing at least 40 kg. Remdesivir remains the only FDA-approved antiviral for the treatment of COVID-19. Post approval, the existing EUA was revised to include hospitalized patients with suspected or laboratory-confirmed COVID-19 who are <12 years of age and weighing between 3.5 kg to 40 kg, or all pediatric patients weighing less than 40 kg. It is important to recognize that initial remdesivir studies were rushed, poorly designed, underpowered, and unbalanced, resulting in skewed results (see below).

Antiviral drugs should be initiated early within the viral life cycle to maintain low overall viral loads in order to optimize clinical outcomes. Remdesivir has primarily only been studied in severely ill patients with high viral loads secondary to severe drug shortages and compassionate use requirements. As expected, many of these poorly designed studies failed to identify a clinical benefit. The NIH-sponsored Adaptive COVID-19 Treatment Trial (ACTT-1) in adult patients revealed a reduction in time to recovery of 10 days in the treatment group versus 15 days in the placebo, and suggested a mortality benefit in patients receiving remdesivir. A Chinese trial that evaluated adults with severe COVID-19 failed to demonstrate a difference in time to improvement or 28-day mortality rate; however, the study did not meet power. Remdesivir is recommended by the IDSA and NIH in hospitalized COVID-19 patients with supplemental oxygen requirement who are not receiving mechanical ventilation. Remdesivir therapy should be considered in patients requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Studies evaluating the use of remdesivir in COVID-19 remain controversial owing to conflicting results.

The SOLIDARITY trial was a randomized, controlled, and significantly larger study than its predecessors. Results revealed little or no effect on overall mortality, initiation of ventilation, or length of hospitalization in adult COVID-19 patients, generating doubt on recommendations for its use. The interim results of the SOLIDARITY trial and a systematic review led to the WHO issuance of recommendations against the use of remdesivir regardless of disease severity. When evaluating and interpreting the remdesivir trials, it is critical to establish a timeline noting the actual day of illness, not day of hospitalization, in relation to the initiation of remdesivir therapy. Remdesivir initiated on day 7 of illness, well into the viral life cycle and after primary replication, may have skewed results. Therefore, it is unclear if therapy initiated earlier would have revealed clinical improvement. The SOLIDARITY trial also excluded children, pregnant or breastfeeding women, and immunocompromised patients. Nevertheless, most clinicians continue to use remdesivir therapy despite the controversial reported results and recom-

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**Table 3. Corticosteroids**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Agent</th>
<th>Dosing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Dexamethasone</td>
<td>0.15 mg/kg once daily (max: 6 mg)</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Prednisolone</td>
<td>1 mg/kg once daily (max: 40 mg)</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>0.8 mg/kg once daily (max: 32 mg)</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>0.5 mg/kg every 12 hr × 7 days, followed by 0.5 mg/kg daily × 3 days</td>
</tr>
<tr>
<td>Other</td>
<td>Breastfeeding/pregnant</td>
<td>Prednisolone or methylprednisolone (in doses above)</td>
</tr>
<tr>
<td></td>
<td>Corrected gestational age &lt; 40 wk</td>
<td>Hydrocortisone (in doses above)</td>
</tr>
</tbody>
</table>

* Duration of therapy up to 10 days.
mendations. This decision is likely based on individual experience or observed positive outcomes in patients who received remdesivir. With ongoing rapid publications, it is critical to recognize study limitations and use caution when interpreting reported outcomes. The emergency use of remdesivir was approved by the European Medicines Agency (EMA) in July 2020, for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen. As of January 2021, the EMA continues to support the use of remdesivir despite the change in recommendations from the WHO. The EMA has requested full SOLIDITY results for review and will assess the evidence, together with relevant data, to evaluate if the current recommendations and/or authorizations require change.

Laboratory studies to evaluate baseline renal function, hepatic function, and coagulation should be obtained prior to initiating remdesivir. Required laboratory test results include serum creatinine, blood urea nitrogen, prothrombin time, total and direct bilirubin, alkaline phosphatase, aspartate transaminase, and ALT. An estimated glomerular filtration rate (eGFR) must be calculated to ensure remdesivir eligibility and safety. Remdesivir contains sulfobutylether-β-cyclodextrin, which is known to accumulate in renal dysfunction and increasing risks of liver necrosis and renal tubule obstruction. Remdesivir should not be administered in neonates with a serum creatinine ≥ 1 mg/dL or in patients at least 29 days old with an eGFR < 30 mL/min. Overall, remdesivir is generally well tolerated with a reassuring side effect profile. The most common documented side effect of remdesivir is an increase in ALT. This ALT increase typically does not require intervention or therapy modification and fully resolves upon completion of therapy. It is challenging to determine if the ALT elevation is secondary to remdesivir, the underlying disease, or a combination of both. Remdesivir is contraindicated in patients with an ALT ≥ 10 times the baseline upper normal limit. Remdesivir should be discontinued if the ALT becomes elevated ≥10 times the upper limit of normal or if the ALT is elevated in addition to signs or symptoms of liver inflammation. Hepatic function should be monitored for the duration of therapy as clinically appropriate. Mild infusion reactions are rare but have been reported during remdesivir therapy.

There are currently no data available on the presence of remdesivir in human milk or its effect on the nursing infant. Animal studies have detected remdesivir and its metabolites in the plasma of rat pups, estimating 1% of maternal exposure. However, remdesivir is not a novel therapy to neonates as it has been used to treat Ebola, with the most common reported side effects including elevated liver enzymes, elevated bilirubin levels, diarrhea, rash, renal impairment, and hypotension. Additionally, remdesivir has poor oral bioavailability, indicating infants are unlikely to absorb significant amounts from breast milk. Thus, mothers receiving remdesivir do not need to avoid breastfeeding, but given the limited information, infants should be carefully monitored while receiving breast milk until more data are available. It may be appropriate to avoid breast milk in babies who are more prone to develop previously mentioned remdesivir-induced side effects (i.e., infants prone to hyperbilirurinemia or with cardiac or hepatic dysfunction). If complete avoidance of remdesivir exposure from breast milk is desired, the pharmacokinetics of the drug will need to be carefully evaluated. A drug is typically considered eliminated from the body after 4 to 5 half-lives. The half-life of remdesivir and its metabolite (GS-441524) is 1 hour and 27 hours, respectively; thus, remdesivir is estimated to be completely eliminated from the body after approximately 5 days.

Remdesivir should be considered in all symptomatic and eligible hospitalized patients with COVID-19 within the first 7 days of symptom onset. Eligible patients must weigh at least 3.5 kg, require supplemental oxygen, should not be receiving mechanical ventilation, should have an eGFR of at least 30 mL/min for non-neonates or serum creatinine < 1 mg/dL for full-term neonates, and should have normal baseline hepatic function. Remdesivir therapy should be considered in patients requiring mechanical ventilation or ECMO. The standard duration of therapy is 5 days and may be extended to 10 days if symptoms fail to improve (see Table 4).

Convalescent Plasma. This form of therapy is composed of harvested antibodies from plasma of COVID-19–recovered patients and given to the acutely ill. This is known as an adaptive immunity transfer resulting in passive immunity. COVID-19 convalescent plasma with high antibody titers may be effective in reducing mortality in hospitalized patients with COVID-19. From these data, the FDA issued an EUA for convalescent plasma on August 23, 2020. To optimize clinical benefits, therapy should be administered early in the course of disease. Additional research evaluating the efficacy of COVID-19 convalescent plasma is required to ultimately determine the potential benefits, if any, of such therapy. The use of convalescent plasma in the general population has been severely limited owing to lack of availability. The neutralizing antibodies in COVID-19 convalescent plasma may have diminished effects or be rendered completely ineffective with the emergence of new SARS-CoV-2 variants and is subject to change as more information becomes available. Per the NIH and IDSA guidelines, convalescent plasma should only be used in patients younger than 18 years in the context of a clinical trial.

Baricitinib. Baricitinib is a Janus kinase inhibitor. These are intracellular enzymes that transmit signals arising from cytokine- or growth factor–receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell func-
Baricitinib (Olumiant) is approved by the FDA for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to 1 or more tumor necrosis factor antagonist therapies. The proposed benefits of baricitinib in the management of COVID-19 are a combination of known anti-inflammatory properties and potential antiviral activity. On November 19, 2020, the FDA issued an EUA for the use of baricitinib in combination with remdesivir in hospitalized adults and children at least 2 years of age with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or ECMO. The Adaptive COVID-19 Treatment Trial (ACTT-2) included hospitalized adults with COVID-19 who received a combination of baricitinib and remdesivir compared with remdesivir alone. Results described a faster time to recovery for the baricitinib group by 1 day (7 days versus 8 days; 95% CI: 6–8), better clinical outcomes at day 15 (OR 1.3; 95% CI: 1.0–1.6), and lower 28-day mortality rates (5.1 versus 7.8%) (HR 0.65; 95% CI: 0.39–1.09). The true clinical significance of these results remains debatable. Many questions remain regarding the use of this drug, most notably if the potential risks of therapy are worth the proposed benefit. These risks include serious infections, thrombosis, hypersensitivity reactions, increased ALT and AST levels, anemia, and lymphocytopenia. Potentially, the most concerning is the warning of serious venous thrombosis including pulmonary embolism, which has been observed in COVID-19 patients. In addition, baricitinib use has the possibility of significant drug-drug interactions requiring dose adjustments when given concomitantly with strong organic anion transporter inhibitors. Baricitinib also requires dose adjustments based on eGFR, absolute lymphocyte count, and absolute neutrophil count. Use is not recommended in patients with severe hepatic impairment (Table 5). Baricitinib is an oral medication available as 1-mg and 2-mg immediate release tablets that may be dispersed in water and are compatible with gastric or nasogastric tube administration. Baricitinib should not be used routinely unless there is a contraindication to corticosteroids, and the benefits of baricitinib in combination with remdesivir outweigh the risks.

**Outpatient Therapies. Bamlanivimab.** In late 2020, the FDA issued an EUA approval for the investigational monoclonal antibody therapy bamlanivimab to treat mild to moderate COVID-19 in adult and pediatric patients at least 12 years of age and older, and weighing at least 40 kg. Bamlanivimab is a recombinant neutralizing human IgG1K monoclonal antibody that binds to the spike protein on SARS-CoV-2 and blocks attachment to the human ACE2 receptor. Bamlanivimab is a 1-time dose of 700 mg administered via IV infusion over 1 hour followed by clinical observation for at least 1 hour after completion of the infusion. Bamlanivimab is authorized for non-hospitalized individuals with positive test results of direct SARS-CoV-2 who are at high risk for progressing to severe COVID-19 and/or hospitalization. Ideally, bamlanivimab should be initiated as soon as possible after a positive viral test and within 10 days of symptom onset. High risk is defined as patients who meet at least 1 of the following: 1) BMI ≥ 35 kg/m²; 2) chronic kidney disease and/or diabetes; 3) immunosuppressive...
disease or currently receiving immunosuppressive therapy; 4) age 12 to 17 years AND with BMI > 85th percentile, sickle cell disease, congenital/acquired heart disease, neurodevelopmental disorders, a medically related technologic dependence, asthma or reactive airway or other chronic respiratory disease that requires daily medication for control; 5) age 55 years or older AND with cardiovascular disease or hypertension or chronic obstructive pulmonary disease or other chronic respiratory disease; and 6) age ≥ 65 years.

The EUA was approved on the basis of interim analysis of the BLAZE-1 trial showing non-hospitalized adult patients with mild or moderate COVID-19 with median time to symptom improvement of 6 days for those treated compared with 8 days for those who received placebo (NCT04427501).45 The most common side effect was nausea, although infusion site reactions have been documented. In the initial trial, rare infusion reactions occurred in 2.3% of the bamlanivimab group compared with 1.4% in the placebo group. These events occurring during the infusion were considered mild and consisted of pruritus, flushing, rash, and facial swelling. There were no observed changes in vital signs during these reactions, and the infusions were completed in all cases.45 If an infusion-related reaction occurs, consider slowing or stopping the infusion. Antihistamines may be used to relieve symptoms if required. Although rare, severe reaction could occur; therefore, bamlanivimab must be administered in a setting with immediate access to emergency medications, and the ability to activate an emergency medical system to ensure patient safety.44

Bamlanivimab was not authorized for hospitalized COVID-19 patients because there was no benefit shown in this specific population.44 In addition, like other monoclonal antibodies, bamlanivimab may also be associated with worse clinical outcomes when administered to hospitalized patients requiring high-flow oxygen or mechanical ventilation. The safety and effectiveness of bamlanivimab in pediatric patients were not assessed in any clinical trials. Recommended dosing in the EUA was expected to result in comparable serum exposures in patients at least 12 years of age and weighing at least 40 kg, as observed in adults. The benefit of bamlanivimab use in the pediatric population should be a case-by-case basis where benefits outweigh the risk.

Casirivimab-Imdevimab. Casirivimab and imdevimab are both recombinant human monoclonal antibodies, given together concurrently, with unmodified Fc regions that bind the SARS-CoV-2 spike protein receptor and block binding to the human ACE2 receptors.46 Based on viral load and clinical outcomes, a flat dose-response relationship was identified for casirivimab and imdevimab with a 1 to 1 ratio. The 1-time dose includes 1200 mg of casirivimab and 1200 mg of imdevimab given together as a single (2400 mg) intravenous infusion over at least 60 minutes followed by clinical observation for at least 1 hour after completion of the infusion. The EUA was ap-

<table>
<thead>
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<th>Table 5. Baricitinib</th>
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<tbody>
<tr>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td>2–8 yr of age</td>
</tr>
<tr>
<td>≥9 yr of age</td>
</tr>
<tr>
<td><strong>Dose adjustments</strong></td>
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<tr>
<td>Renal dysfunction, eGFR, mL/min/1.73 m²</td>
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<tr>
<td>≥60</td>
</tr>
<tr>
<td>30 to &lt;60</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>15 to &lt;30</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate

Acute COVID-19 in the Pediatric Populations

Parsons, S et al

Baricitinib

Hepatic dysfunction

Absolute lymphocyte count, cells/μL

≥200  No change

<200  Consider holding until counts are ≥200

Absolute neutrophil count, cells/μL

≥500  No change

<500  Consider holding until counts are ≥500

ALT, alanine aminotransferase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate
proved for the treatment of mild to moderate COVID-19 in non-hospitalized adult and pediatric patients at least 12 years of age and weighing at least 40 kg, positive for SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19 and/or hospitalization. High risk is defined above in the “Bamlanivimab” section. The REGN-COV2 trial compared 2 doses of casirivimab and imdevimab—2.4 g and 8 g—versus placebo and reported a 2% rate of infusion reactions in the larger-dose 8-g group with 1% observed in the lower-dose 2.4-g group.47 One infusion was stopped secondarily to an infusion reaction in the 8-g group. Casirivimab and imdevimab must be administered in a setting with immediate access to medications to treat a severe infusion reaction, and ability to activate an emergency medical system to ensure patient safety. Should an infusion-related reaction occur, consider slowing or stopping the infusion. Antihistamines may be used to relieve symptoms if required.46

This monoclonal antibody combination may also be associated with worse clinical outcomes with hospitalized patients requiring high-flow oxygen or mechanical ventilation as well as eliciting an infusion reaction.46 The safety and effectiveness in pediatric patients have not been assessed for casirivimab-imdevimab for the same reason as above. Thus, the benefit of casirivimab-imdevimab use in the pediatric population should be a case-by-case basis where benefits outweigh the risk.

Pharmacotherapies Not Routinely Recommended. Chloroquine or Hydroxychloroquine With or Without Azithromycin. Chloroquine, an antimalarial drug, along with its analog, hydroxychloroquine, was widely used at the beginning of the SARS-CoV-2 pandemic. The use of chloroquine or hydroxychloroquine, with or without azithromycin, has been evaluated in randomized control trials and observational studies mainly in adult patients. Despite demonstrating in vitro antiviral activity, hydroxychloroquine with or without azithromycin did not reduce respiratory tract viral loads or demonstrate clinical efficacy in a monkey model.48 Studies of hydroxychloroquine use, with or without azithromycin, in hospitalized COVID-19 patients did not show association in reducing risk of death or mechanical ventilation.5,35,49,50 Interestingly, the use of these agents was associated with more harm (i.e., prolonged QTc and ventricular tachycardia) than benefit, leading to their dereferent for the treatment of COVID-19 by the NIH and IDSA.9,29,51 Shortly after, the SOLIDARITY trial revealed that the hydroxychloroquine treatment arm showed little to no reduction in the mortality of hospitalized COVID-19 patients, when compared with standard of care.38 Inappropriate use and dosing can also lead to, usually fatal, acute poisoning.52 Additionally, it is unclear if the benefits truly outweigh the risk given there is no well-established safe and effective dose for the treatment of COVID-19, especially for the pediatric population. Thus, this medication has no place in current treatment regimens.

Famotidine. Hospitalized patients, especially ICU patients, often require stress ulcer prophylaxis therapies. In the case of COVID-19, it was thought that famotidine may serve a dual purpose. To date, 2 studies compared outcomes in hospitalized adult patients with COVID-19 who received famotidine therapy to those who did not.53,54 Both studies found famotidine use was associated with improved clinical outcomes in hospitalized patients with COVID-19, including lower inpatient mortality (OR 0.37; 95% CI, 0.16–0.86; p = 0.021), a lower composite of death and/or intubation (OR 0.47; 95% CI, 0.23–0.96; p = 0.04), and lower levels of serum markers for serious disease (peak C-reactive protein, procalcitonin, and ferritin levels). However, these findings should be interpreted with caution because both studies were conducted at a single center, were retrospective as well as observational in nature, and did not assess the possible effects of other H2 receptor antagonists. A multivariable logistic regression showed no correlation between inpatient famotidine use and 30-day mortality (OR 1.59; 95% CI, 0.94–2.71) after adjusting for WHO severity, smoking status, and listed medications.55 A secondary analysis, accounting for interaction between inpatient use of famotidine in patients not using prior to admission, showed a higher risk of 30-day mortality (OR 1.77; 95% CI, 1.03–3.03). Famotidine should not be used primarily for the treatment of COVID-19, especially in pediatric patients, outside the setting of clinical trials. Stress ulcer prophylaxis and/or treatment should be used per routine clinical practice until further data become available. We identified only 1 current trial evaluating famotidine use in patients at least 16 years of age with COVID-19 (NCT04504240).

Interferons (Alfa, Beta). Interferons are a family of cytokines with antiviral properties in vitro and in vivo, suggestive as a potential treatment for COVID-19.9 A systematic review of 66 studies reported 41% (n = 252) of pediatric patients with COVID-19, mostly in China, treated with interferon.55 However, this systematic review did not elaborate on ICU placement, clinical improvement, or the relative safety and efficacy of use in pediatric patients.52 Side effects are not benign as they include low-grade fever, flu-like symptoms, and suicidal ideations, which occur more commonly in children than adults. Interferon use is contraindicated in patients with abnormal liver function, those with creatinine clearance below 50 mL/min, and those with histories of mental illness, severe or unstable heart disease, or aplastic anemia. Similar to hydroxychloroquine and lopinavir-ritonavir (see below), the NIH and IDSA recommend against the use of interferon as the SOLIDARITY trial did not show any reduction in overall mortality, initiation of ventilation, and duration of hospital stay in hospitalized adult patients.5,29,35

Ivermectin. The use of ivermectin, an antiparasitic, has shown antiviral activity in vitro, leading to its off-label
use. Countries with routine mass drug administration of prophylactic chemotherapy, including ivermectin, have significantly lower incidence of COVID-19, suggesting there may be a causal connection. Studies have reported use of this therapy for pediatric patients. The pharmacodynamics of lopinavir-ritonavir, a protease inhibitor widely used for HIV, raises concerns of whether it is possible to achieve adequate drug concentrations that can inhibit the SARS-CoV-2 proteases. Randomized controlled trials, including the SOLIDARITY trial, did not show any statistically significant clinical improvement or reduction in mortality in adult patients who received lopinavir-ritonavir compared with standard of care alone. Owing to unclear benefit and significant rates of adverse effects associated with lopinavir-ritonavir (i.e., hepatotoxicity, QTc prolongation), the NIH and IDSA strongly recommend against the use of lopinavir-ritonavir or other HIV protease inhibitors for the treatment of any hospitalized patients with COVID-19, regardless of age. There is no literature available for the use of lopinavir-ritonavir for post-prophylaxis use in non-hospitalized pediatric patients. From available data, pediatric patients should not receive lopinavir-ritonavir therapy in the inpatient or outpatient setting for the treatment or prevention of COVID-19.

**Tocilizumab.** Early in the pandemic, off-label use of tocilizumab became standard of care for patients with COVID-19 with evidence of hyperinflammation, even with limited literature to support its use in pediatrics. Tocilizumab was thought to be useful in cytokine storm, but published trials and preliminary, unpublished data (NCT04320615, NCT04315298) failed to demonstrate efficacy. As such, the NIH and IDSA recommend against the use of anti-IL-6-receptor monoclonal antibodies in patients with COVID-19 outside of clinical trials. Until tocilizumab’s positive effects can be more easily predicted in pediatric patients, its use for COVID-19 should be limited to clinical trials, especially considering associated side effects (i.e., secondary infections).

**Other.** In addition to pharmacotherapies discussed above, the following currently do not contain enough evidence to recommend their use outside of clinical trials: ACE inhibitors and angiotensin II receptor blockers, ascorbic acid (vitamin C), bacillus Calmette-Guerin vaccine, maraviroc, melatonin, montelukast, and zinc. Based on the lack of safety regulations for over-the-counter products and lack of evidence for use, the use of these agents should be avoided in the pediatric population. Additional therapies are being investigated and information is subject to change as this pandemic continues to evolve.

**Prevention**

**Non-Pharmacologic Strategies.** Strategies to reduce transmission of SARS-CoV-2 include scrupulous handwashing, appropriate mask wearing, eye protection, physical distancing, and avoidance of crowds. To prevent the transmission of SARS-CoV-2, as it is predominantly transmitted by respiratory droplets, the CDC recommends community use of masks, specifically non-valve multilayer cloth masks, for everyone who is able. Multilayer masks, when appropriately worn covering the nose and mouth, can help reduce the emission of virus-laden droplets (“source control”) by up to 80%. A meta-analysis found masks had a protective effect against influenza virus (OR 0.55; 95% CI: 0.39–0.76), SARS-CoV (OR 0.26; 95% CI, 0.18–0.37), and SARS-CoV-2 (OR 0.4; 95% CI: 0.00–0.60). Avoidance of touching one’s face with unwashed hands should also be regularly practiced. In addition to face masks, limiting close face-to-face contact with others is another strategy to reduce the spread of SARS-CoV-2. The practice of physical distancing, also known as social distancing, entails staying at least 6 feet from other people who are not within the same household, in both indoor and outdoor settings. A meta-analysis reported transmission of viruses was lower with a physical distancing of 1 m or more, compared with a distance of less than 1 m (OR 0.18; 95% CI: 0.09–0.39), with increasing protection as distance was lengthened. Eye protection was also associated with less infection (OR 0.22; 95% CI: 0.12–0.39).

**SARS-CoV-2 Vaccine.** Among all vaccine approaches, a messenger RNA (mRNA)–based vaccine has emerged as a versatile and rapid option to meet the urgency of a COVID-19 vaccine amongst the ongoing SARS-CoV-2 pandemic. Unlike conventional vaccines grown in eggs or cells, these vaccines are simply chemicals catalyzed in test tubes or a tank, allowing a rapid and inexpensive method for mass production. Unlike many vaccines with a weakened or inactivated viral strain, mRNA vaccines trigger an immune response by teaching the body to manufacture a protein, or a piece of protein (CDV vaccines). Specifically, the COVID-19 mRNA vaccine instructs the body to create a “spike protein,” found on the SARS-CoV-2 virus. The body’s cell then displays the protein piece on its surface, eliciting
antibodies against this “foreign matter.”

Companies began mass production of the COVID-19 vaccine well before studies even suggested efficacy. This project known as operation “Warp Speed” was highly publicized producing widespread skepticism surrounding vaccine safety. Operation Warp Speed was initiated to rapidly drive manufacturing and avoid manufacturing delays, which are critical to avoid during a pandemic. Operation Warp Speed was never intended to unsafely rush clinical testing and/or approval. The general safety and effectiveness of RNA platforms have been demonstrated in oncologic clinical trials with different administration routes (NCT02410733, NCT03871348).

As mRNA vaccines do not use live virus, they cannot cause COVID-19 or interact with human body DNA. In terms of SARS-CoV-2 infection may be offered to those who have fully received the vaccine. Recommendations may change as more information becomes available or other vaccine types are authorized. Inactivated ingredients for the Pfizer-BioNTech vaccine include lipids (polyethylene glycol; dimyristoyl glycerol; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose. Neither vaccine contains any preservatives or adjuvants but do contain polyethylene glycol within the lipid nanoparticle. For patients with a history of anaphylaxis to any other vaccine, the CDC recommends they can still receive the mRNA vaccine with counseling regarding the unknown risks of developing a severe allergic reaction and be monitored longer than someone without a history of anaphylaxis (i.e., 30 minutes versus 15 minutes). COVID-19 vaccine products are currently not interchangeable as the safety and efficacy of a mixed-product series have not been evaluated. Vaccination using the same mRNA product for the series is recommended; however, if different mRNA products are inadvertently administered, no additional doses of either mRNA product are recommended. COVID-19 vaccines should be administered alone, with a minimum interval of 14 days before or after administration with other non-COVID vaccines. If the vaccine is inadvertently administered within 14 days of another vaccine, doses do not need to be repeated for either vaccine. Additionally, until further information becomes available, vaccination should be deferred for 90 days in individuals who have received monoclonal antibodies or convalescent plasma. This separation is a precautionary effort to avoid interference of the recent antibody treatment with the vaccine-induced immune response. With no data on the optimal period to receive COVID-19 vaccination, the CDC states there is no minimum wait interval for those receiving antibody therapy (i.e., IV immunoglobulin for immune deficiency) and an mRNA COVID-19 vaccine. Those who are on anticoagulants may take a little longer to stop bleeding or bruise much easier but should not be excluded from receiving the vaccine. Immunocompromised patients, inclusive of those on large doses of corticosteroids (>2 mg/kg/day or 20 mg/dose prednisone or equivalent), may have an attenuated immune response to the vaccine. However, an attenuated response may still offer protection and therefore immunosuppressive patients should receive the COVID-19 vaccination. Recommendations may change as more information becomes available or other vaccine types are authorized.

COVID-19 vaccination of persons with known SARS-CoV-2 infection may be offered to those who have fully recovered from the acute illness, as it is considered safe and likely efficacious. In terms of SARS-CoV-2 variants, it is important to note as of date, none of the variants possess the ability to evade vaccine-induced immunity. There are no data from persons who have received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment. COVID-19 vaccines may be administered to those with underlying medical conditions as long as there are no contrain-
dications, with the understanding that there is limited data available on the safety and efficacy of COVID-19 vaccines for those who are pregnant, breastfeeding, or immunocompromised (secondary to disease state or medication).\textsuperscript{72–78} Important considerations to discuss include the current level of community transmission; the potential efficacy of the vaccine; the potential risk and severity of maternal disease, including the effects of disease on the fetus and newborn; and the safety of the vaccine for the pregnant patient and the fetus.\textsuperscript{83} The American College of Obstetricians and Gynecologists recommends vaccines not be withheld from pregnant and lactating individuals who meet criteria outlined by the Advisory Committee on Immunization Practices, as there are also no data to indicate that the vaccine should be contraindicated.

It is vital that the COVID-19 vaccine be universally adopted and accepted. To reach herd immunity, the vaccine must be effective and adequate vaccination rates must be achieved. Herd immunity is an important defense against outbreaks and has been shown to be successful in previous pandemics such as smallpox.\textsuperscript{84} Assuming no population immunity exists and all individuals are equally susceptible and equally infectious—with the WHO’s estimated infection fatality rate at 0.5%—about 198 million individuals in the United States are required to be immune in order to reach a herd immunity threshold of approximately 60%. Given a large vulnerable pediatric population still at risk, all qualifying individuals should consider receiving the SARS-CoV-2 vaccine to achieve herd immunity.

**Influenza Vaccine.** Influenza and COVID-19 can present with similar symptoms, and coinfections may be associated with a more severe and complicated, or possibly even fatal, outcome.\textsuperscript{85} The 2020–2021 influenza season will coincide with the continued circulation of SARS-CoV-2. It is imperative to elicit herd immunity and protect those for whom the vaccine may not be effective.\textsuperscript{86} A retrospective, single study of 2000 adult patients revealed that COVID-19–positive patients who had not received the influenza vaccination within the last year were 2.5 times more likely to be hospitalized and more than 3 times more likely to be admitted to an ICU than those who were vaccinated.\textsuperscript{86} The CDC recommends influenza vaccination of all persons at least 6 months of age to reduce the prevalence of illness caused by influenza in order to reduce symptoms that may be confused with those of COVID-19.\textsuperscript{87} The influenza vaccine should be administered at least 14 days before or after the COVID-19 vaccine.\textsuperscript{87} Prevention of and reduction in the severity of influenza illness and reduction of hospitalization and ICU admission through influenza vaccination could also alleviate the stress on the US health care system.\textsuperscript{84,85}

**MIS-C.** Increased surveillance of a hyperinflammatory syndrome associated with SARS-CoV-2, known as pediatric multisystem inflammatory syndrome—temporally associated with SARS-CoV-2 or MIS-C, was observed after the peak of COVID-19 infections. The rising cases of MIS-C triggered a national health advisory by the CDC.\textsuperscript{87} Please refer to Part 2 of our trilogy series for further detail on the evaluation and management of MIS-C.

**Antiplatelet and Anticoagulation Considerations.** As mentioned above, SARS-CoV-2 infection incorporates a hyperinflammatory phase resulting in a prothrombotic state. Thus, prophylactic or even therapeutic anticoagulation therapies may need to be considered.\textsuperscript{88} Please refer to Part 3 of our trilogy series for further detail on antiplatelet and anticoagulation considerations in acute COVID-19 and MIS-C pediatric patients.

**Conclusion**

SARS-CoV-2 continues to wreak havoc worldwide, filling hospitals with COVID-19 adult and pediatric patients, overwhelming health care systems. The epidemiology and pathophysiology of the virus, as well as pharmacotherapies for COVID-19, continue to evolve. While published data provide a basis for clinical decisions, it is critical to review the details of each study and evaluate clinical application, especially when applying to pediatric patients. Pediatric populations continue to be underrepresented in clinical trials. Larger clinical trials, as well as trials including pediatric patients, are required to evaluate the safety and efficacy of these specific pharmacotherapies in this population. Lastly, to battle the pandemic and protect our most vulnerable populations, health care providers are strongly encouraged to continue to support the ongoing public health effort of vaccinating the public against SARS-CoV-2.

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