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COVID-19 Pandemic and Children: A Review

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The severe respiratory disease COVID-19 (coronavirus disease 2019) was first reported in late December 2019 in Wuhan City, China. Soon thereafter, the World Health Organization (WHO) officially declared it a pandemic. The adult population is highly affected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); however, infants and children are also not spared. Transmission in the pediatric population appears to be primarily from COVID-19–positive adults, largely from family contacts through droplets, direct contacts, and aerosols. There is also evidence of fecal-oral route of transmission. The incubation period of COVID-19 in children ranges from 2 to 10 days. Most children are asymptomatic. The most common symptoms amongst symptomatic children are fever and cough. Shortness of breath, sore throat, rhinorrhea, conjunctivitis, fatigue, and headache are other common symptoms. Diarrhea, vomiting, and abdominal pain are the common gastrointestinal symptoms that may be present with or without respiratory symptoms. Very few children are likely to develop severe disease.Supportive care is the mainstay of treatment. Though data are limited, antiviral therapies such as remdesivir, favipiravir, lopinavir/ritonavir, and other drugs like hydroxychloroquine/chloroquine have been used for severe COVID-19 cases, with remdesivir showing the greatest promise. A few children may develop an exaggerated immune response, characterized by exaggerated cytokine release and manifests with features similar to Kawasaki disease. The syndrome has been referred to by many names including *pediatric inflammatory multisystem syndrome* (PIMS) and more recently, as *multisystem inflammatory syndrome in children* (MIS-C); this life-threatening condition often requires a multidisciplinary team effort and use of immunomodulators.

ABBREVIATIONS ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; CBC, complete blood count; CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; CT, computed tomography; EC, effective concentration; FDA, US Food and Drug Administration; HIV, human immunodeficiency virus; IV, intravenous; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; MERS, Middle East respiratory syndrome; MIS-C, multisystem inflammatory syndrome in children; NIH, National Institutes of Health; PCR, polymerase chain reaction; PIMS, pediatric inflammatory multisystem syndrome; PIM-TS, pediatric multisystem inflammatory syndrome temporally associated with severe acute respiratory syndrome coronavirus-2; QTc, ECG interval from the QRS complex to the end of the T wave (corrected); RT-PCR, reverse transcription–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WHO, World Health Organization

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

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Editor's Note *Reflective of the nature of COVID-19, data from basic/clinical research and experiential evidence regarding all aspects of this infectious disease in humans across the entire age spectrum become available multiple times each day. Reports of the newest advances are often announced via the lay press and university-directed press releases with great fanfare though virtually all of these announcements opine prior to rigorous peer-review underscoring the large amount of unscientific "hysteria" continuing to surround this pandemic disease. This review succinctly summarizes the broad landscape of COVID-19 in pediatrics as of early August 2020. Our understanding of this disease, its effects on children and in better defining specific treatment regimens are very likely better understood now at the time of your reading this review than when it was written. We are reminded by this experience to continue to stay current, inquisitive, and critical in assessing the available data each time we provide care for a COVID-19–infected patient. To stay current with the most up-to-date, scientific-based information we recommend, at a minimum, the COVID-19 websites for the United States National Institutes of Health and the American Academy of Pediatrics.*

Introduction

New to our lexicon, coronavirus disease 2019 (COVID-19) is a zoonotic infection caused by a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] As of June 24, 2020, SARS-CoV-2 has spread to more than 200 countries worldwide and infected over 9 million people. On March 11, 2020, the

World Health Organization (WHO) officially declared COVID-19 a pandemic disease.[2] Current experience suggests adults are much more prone to SARS-CoV-2 than children.[3] Data from China's Centers for Disease Control and Prevention have shown that children aged less than 10 years account for 1% of COVID-19.[3] As of June 24, 2020, among the 2,336,615 laboratory-confirmed cases reported to the United States Centers for Disease Control and Prevention (CDC), 4.5% were in children <18 years.[4,5]

There are many unknowns about this disease, but ever since the emergence of SARS-CoV-2, several studies have been published on the epidemiology, treatment, and management of this disease. Most studies have targeted the adult population. Because it is a novel disease, there is neither a vaccine nor a specific treatment available, with treatment regimens constantly evolving as clinical experience and clinical research data become available. In this review, we discuss the epidemiology and management of COVID-19 in children, based upon available data as of June 28, 2020. This date qualification for our review is extremely important in considering the data we present because new data regarding this highly contagious infectious disease become available on a daily basis.

Origin and Evolution of Coronavirus

Coronavirus is an enveloped plus-strand RNA virus that belongs to the order Nidovirales in the subfamily Coronavirinae (family Coronaviridae) and is classified into 4 primary genera: 1) *Alphacoronavirus*, 2) *Betacoronavirus*, 3) *Gammacoronavirus*, and 4) *Deltacoronavirus*. The coronaviruses of the α and β genera generally infect mammals and humans, while the γ and δ genera infect birds. Coronaviruses are known to circulate in animals and have been associated with human infections and diseases. As per available literature, the bat is considered as one of the main reservoirs of the coronavirus.[6] Coronaviruses are known for their rapid mutation and recombination leading to the development of a novel virus.[7] In the recent past this phenomenon has led to the development of 2 novel coronaviruses that caused human disease in epidemic proportion: SARS-CoV virus responsible for the epidemic of severe acute respiratory syndrome (SARS) in China in 2002 and the MERS-CoV virus responsible for the epidemic of Middle East respiratory syndrome (MERS) in Saudi Arabia in 2012.

SARS-CoV-2 is a novel coronavirus of the β genus; morphologically, it is round or oval, with a diameter of approximately 60 to140 nm with a crown-shaped appearance under electron microscopy.[8] SARS-CoV-2 represents the seventh member of the coronavirus family that infects humans. The virus is phylogenetically related to SARS-CoV as well as to several other bat coronaviruses. Bats appear to be the primary source of SARS-CoV-2; whether it is transmitted directly from bats to humans or through some other mechanism (e.g., through an intermediate host) is yet unknown.[9]

Pathogenesis. The pathogenesis of the SARS-CoV-2 infection involves binding to a human cell receptor that expresses angiotensin-converting enzyme 2 (ACE2), internalization, replication, and the release of new virions from the infected cell.[10,11] The structure of coronaviruses includes 4 structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). The spike protein binds to ACE2 and results in membrane fusion via conformational changes in the cell membrane. This process affects target organs (lungs, digestive tract, heart, blood vessels, and kidneys) where ACE2 expression is very high and induces local and systemic inflammatory responses involving the affected organ.[12,13]

The basis of the lesser severity of SARS CoV-2 infection in children as compared to adults is unknown. This favorable difference may be due to differences in the distribution, maturation, and functioning of viral receptors such as ACE2.[14] ACE2 expression has been found to be much higher in well-differentiated ciliated epithelial cells. In mice, ACE2 expression is reduced till postnatal day 10, then increases[15] until postnatal day 56. In addition, dysregulation/dysfunction of both adaptive and innate immune responses and greater incidence of important comorbidities in adults may also contribute to the more severe manifestations observed in adults vs children.

Contagion Potential. Transmission capacity is variable across the globe and depends on multiple factors. Each patient transmits the infection to an additional 1.5 to 6.68 individuals.[16] A characteristic of this virus, resulting in its high contagiousness, is that the virus can be transmitted by an individual prior to their development of symptoms as well as throughout their course of illness. Most data on communicability are from studies evaluating viral RNA detection from respiratory specimens. It is important to note that the detection of viral RNA does not necessarily indicate the presence of infectious virus. Thus, prolonged viral RNA detection following the resolution of illness does not necessarily indicate infectiousness.

It appears that infected individuals are more likely to be infectious in the earlier stages of infection. Viral RNA levels from upper respiratory tract specimens appear to be in higher concentrations soon after symptom onset than in later stages of the illness.[17–21] Additionally, in a study of 9 patients with mild COVID-19, SARS-CoV-2 virus was isolated from nasopharyngeal/oropharyngeal and sputum specimens during the first 8 days of illness, but not after this interval, despite continued high viral RNA levels at these sites.[19] One modeling study on the timing of infection suggested that infectiousness started 2.3 days prior to symptom onset, peaked 0.7 days before symptom onset, and declined within 7 days.[20]

Characteristics of COVID-19 in Children

Transmission in the Pediatric Population. Most children appear to acquire infection from COVID-19–posi-

tive adults, mainly from the family contacts. In fact, the first pediatric case was reported in a 10-year-old male as part of a family screening.[22] Fang and Luo,[23] in their study, reported transmission through family members in 56% of children with COVID-19 infection. As noted above, both symptomatic patients and asymptomatic carriers can transmit disease.[24–27] It is probable that as schools and other locations where many children congregate start to reopen, acquisition patterns will expand from child to child and child to adult.

As with adults, the main route of infection in children is from respiratory droplets, direct contact, and aerosol transmission. The fecal-oral transmission has also been studied as a potential route of transmission, particularly in the pediatric population.[28] Some literature data suggest gastrointestinal tropism of the SARS-CoV-2 virus.[29] Studies have shown that as much as 36% to 53% of infected patients have stool samples positive for the SARS-CoV-2 virus.[30,31] A few studies on the adult population have even reported a positive stool polymerase chain reaction (PCR) finding, while at the same time the respiratory sample was negative in as many as 82% of patients.[29,32] This phenomenon has also been observed in children. In one study,[28] 8 of 10 children tested positive by reverse transcription–PCR (RT-PCR) on rectal swabs after their nasopharyngeal testing had become negative. Whether the fecal positivity by RT-PCR represents residual viral genomic material or active viral replication capable of causing infection is at present unclear. However, the isolation of SARS-CoV-2 from fecal samples of COVID-19 patients and the demonstration of viral nucleocapsid protein in gastric, duodenal, and rectal epithelia indicate that the virus actively infects these gastrointestinal glandular epithelial cells and a fecal-oral route of transmission is possible.[33]

Evidence for vertical transmission of the SARS-CoV-2 virus through the placenta is unclear. Published case series[34–36] have found no laboratory evidence of vertical transmission in women infected in the third trimester of pregnancy with SARS-CoV-2. Further, viral transmission through the birth canal is also not clear.[37,38] Amniotic fluid, cord blood, and neonatal throat swab samples from 6 patients tested negative for SARS-CoV-2 in a recent study by Chen et al.[34] Therefore, so far, it is recommended that obstetric and clinical indications should direct the mode of delivery.[39] Isolating an infant born to a woman with suspected or confirmed COVID-19 is a difficult decision to make. The well-documented benefits of keeping the mother with her newborn must be weighed against the risk of neonatal infection. Evidence is limited on this topic; therefore, decisions should be made on a case-by-case basis along with critical discussion with the parents. Until further data are available, temporary separation should be strongly considered in higher-risk infants, that is, preterm infants and infants with medical conditions. For others, coisolation with respiratory and contact precautions, such as use of maternal mask and hand hygiene, could be an option.

Transmission of SARS-CoV-2 through breast milk is unknown. Chen et al[34] reported negative breast milk samples by RT-PCR from 9 mothers with COVID-19 pneumonia. Most neonatal guidelines do not recommend against breastfeeding for mothers with COVID-19. However, contact precautions such as the use of maternal masks, appropriate social distancing from other individuals, severely limiting all contacts, and hand hygiene (e.g., washing hands with soap and water for 20 seconds before and after touching the baby) must be followed meticulously during breastfeeding. Communicability of infection amongst children has been tracked and, as expected, infected children shed virus although, as noted above, they are frequently asymptomatic or only mildly symptomatic. Children are likely to be the primary case in less than 10% of SARS-CoV-2 familial clusters.[40,41] The secondary attack rate ranges between 4% and 7% amongst pediatric contacts.[42,43] Even outside of household settings, SARS CoV-2 transmission by children seems less.[44,45] However, the data from the studies reported to date should be interpreted with caution, because these studies have been performed during lockdowns, strict physical distancing, school closure, and other measures.[42,43]

Incubation Period. The best data to date suggest the incubation period of COVID-19 for adults is 5 to 6 days (range, 2–14 days),[46,47] whereas the incubation period for children may be shorter, possibly 2 days (range, 2–10 days).[48] However a few reports have described a longer incubation period for children than adults.[25,49] Only with further experience will we be able to determine if a true difference exists in the incubation period between adults and children by age group.

Clinical Presentation. The clinical features of COVID-19 infection in children, like in adults, vary from asymptomatic to critical illness, including acute respiratory distress syndrome (ARDS) and multiorgan dysfunction. Children of all ages can be infected with COVID-19, and there appears to be no age or sex preponderance.[50]

Current cases suggest that the median age appears to be 11 years (range, 0–17 years) in the United States and 7 years (range, 1–18 years) in China.[51,52] As based on one of the reports,[53] children can be divided into 5 categories depending upon disease severity: 1) asymptomatic infection (silent infection); 2) acute upper respiratory tract infection; 3) mild pneumonia; 4) severe pneumonia; and 5) critical cases.

As noted previously, the disease is more likely to be mild in children than adults. Between 9% and 15% of virologically positive children remain asymptomatic and those that are symptomatic most often exhibit symptoms that are mild to moderate in severity and can be cared for in the home.[54,55]

The most common finding amongst symptomatic children are fever (50%) and cough (38%).[54] Shortness of breath, sore throat, rhinorrhea, conjunctivitis, fatigue,

and headache are other commonly reported symptoms. Diarrhea, vomiting, and abdominal pain are common gastrointestinal symptoms that may be present with or without respiratory symptoms.[56] Loss of smell and taste sensation are also reported as an additional symptom in adults. Dermatologic lesions may be seen in up to 20% of patients.[57] The common manifestations are maculopapular, urticarial, and vesicular eruptions and transient livedo reticularis and pernio (chilblain)–like acral lesion.

Symptomatic children seem to have more upper respiratory symptom occurrences, whereas lower respiratory involvement is observed more frequently in adults.[50] Approximately 19% of children infected with the virus had upper respiratory infections in one study.[55] A retrospective study of 2141 pediatric patients (median age, 7 years; IQR, 2–13 years) with confirmed COVID-19 disease found mild disease in 43.1%; moderate disease in 41.0%; severe disease in 2.5%; and critical disease in 0.6%.[50] A recent review involving 2228 children also reports severe disease in only 6% of infected patients.[58]

While increasingly the chronologic course of COVID-19 infection in adults is better characterized, similar data for pediatric patients are extremely limited owing to the much smaller number of affected, symptomatic pediatric patients to date, but it would appear near certain that our understanding of the time course in children by age will be better defined as experience expands. In adults, the median time to develop dyspnea and ARDS from symptom onset appears to be 5 and 8 days, respectively.[59] Others have reported the development of ARDS in 20% of COVID-19 cases, with 12% to 24% of patients requiring mechanical ventilation.[59–61] In children, a recent review involving 2228 children reported ARDS in only 0.6% of patients.[58] Cardiac arrhythmias, shock, and acute cardiac injury were reported in 17%, 9%, and 7% of hospitalized adults, respectively.[59] Thromboembolic complications, acute kidney injury, and secondary bacterial or fungal infection were other complications described.

Mortality in hospitalized adults ranges from 4% to 11%, while the overall death rate in adults appears to be 2% to 3%.[62] In contrast, only 2 deaths (0.09%) were reported in the recent review of 2228 children.[58] In children, full recovery is anticipated in the second to third week of illness but may take up to 6 weeks.[63]

High-Risk Groups. In adults, the presence of certain comorbidities like diabetes, hypertension, chronic respiratory disease, chronic kidney disease, pregnancy, cancer, immunocompromised status, and cardiac disease have all been clearly identified as important risk factor for poor prognosis.[64–66] However, in children, the data regarding the predictors of poor outcomes are insufficient. Limited data suggest infants younger than 1 year are likely to have more severe disease. Forty of 48 children (83%) requiring pediatric intensive care support had underlying conditions, the most common being developmental delay/genetic anomalies (40%), immune suppression/malignancy (23%), obesity (15%), with others including diabetes, seizure disorders, and congenital heart disease.[67] The other conditions that may affect severity appear to be chronic pulmonary disease (including asthma), chronic kidney disease, chronic liver diseases, and malnutrition. Patient with hematologic conditions like sickle cell disease are particularly prone to develop vaso-occlusive crisis and acute chest syndrome secondary to COVID-19 pneumonia.[68]

Laboratory Findings. Routine laboratory investigations are usually non-specific. In adults, CBC is dominated by lymphopenia.[69] Limited data in children describe relatively lower rates of lymphopenia.[48] A summary of studies on 66 children reported normal leukocyte counts in 69.2%, neutropenia in 6.0%, neutrophilia in 4.6%, and lymphopenia only in 3.0%. Similarly, inflammatory markers like C-reactive protein and procalcitonin were elevated only in 13.6% and 10.6% of patients.[70]

An elevated procalcitonin level should point toward the possibility of a secondary bacterial infection.[71] An elevated marker of inflammation (i.e., elevated C-reactive protein, erythrocyte sedimentation rate, D-dimer, fibrinogen, ferritin, procalcitonin, interleukin-6) should point toward more severe disease and/or the possibility of pediatric inflammatory multisystem syndrome (PIMS)/multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2. Further, elevated blood levels of liver enzymes, D-dimer, lactate dehydrogenase, and a prolonged prothrombin time may be indicative of more severe disease.[72]

Radiologic Findings. Chest x-ray findings are usually non-specific and show bilateral infiltrates but may be normal in the early phases of the disease.[73,74] Although computed tomography (CT) of the chest should not be used routinely because of radiation risk, it is more sensitive. In the early stages of the disease, chest CT shows peripheral multiple small plaques and interstitial changes. With disease progression, bilateral multiple ground-glass opacities and/or infiltrating shadows appear, which may progress to lung consolidation with a surrounding halo, which is a typical finding in the pediatric patient. Pleural effusion seems to be an uncommon finding.[53] Peripheral distribution of lung lesions with multilobed involvement is also common.[75] The chest CT findings can be abnormal even in asymptomatic patients and may be useful in an early diagnosis.[76,77] On the other hand, radiologic abnormalities may continue to persist even after the resolution of clinical symptoms.[78]

Virologic Tests. Real-time RT-PCR–based testing to detect SARS-CoV-2 RNA from nose and throat swabs is the recommended diagnostic method for COVID-19. RT-PCR can also be used for other samples like bronchoalveolar lavage or endotracheal aspirate. Criteria for testing vary from country to country, and local guidelines should be followed. The tests are considered to be

highly specific.[79,80] Ideally they are also very sensitive, although in the real-world sensitivity depends upon multiple variables including the site and quality of the specimen obtained, the duration of illness at the time of testing, and laboratory quality control measures.[81,82] In the pediatric-specific clinical COVID-19 PIMS-TS (PIMS temporally associated with severe acute respiratory syndrome coronavirus-2)/MIS-C, the test result may be negative. Unfortunately, and based upon numerous variables, the false-negative rates have been reported to range from 10% to 40%.[83,84] Hence when the clinical suspicion is high, the test may be repeated with patient management based on clinical judgment.

Antigen Tests. Most available antigen tests probe for the nucleocapsid (N) or spike (S) proteins of SARS-CoV-2 by using enzyme-linked immunosorbent assay. These test systems can be performed on respiratory samples and are easy to use and above all less time-consuming. However, their sensitivity is typically less than that of nucleic acid amplification tests.[85]

Serologic Test. Serologic tests detect antibodies to SARS-CoV-2 primarily in blood directed against the viral protein (nucleocapsid or spike protein). These tests are used to determine previous viral exposure for retrospective diagnosis and epidemiologic purposes.

Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

Riphagen et al[86] reported a cluster of 8 previously healthy children from South East London with hyperinflammatory shock, a syndrome exhibiting features similar to atypical Kawasaki disease (KD). These children did not have any significant respiratory issues. Most of the children tested negative for SARS-CoV-2 but had exposure to SARS-CoV-2 subjects.[87] Similar presentations were reported from other areas as well.[88–92]

The syndrome has been referred to as *pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2* (PIMS-TS). As noted above, this syndrome is referred to as MIS-C in current National Institutes of Health (NIH) management guideline recommendations. This is a rare complication of COVID-19 in children. In contrast to typical KD, which affects infants and young children, PIMS-TS seems to also affect the previously healthy older children and adolescents.

PIMS-TS seems to be triggered by an abnormal immune response after the acute infection has passed (as highlighted by the fact that many children have positive serology findings but negative PCR test results for SARS-CoV2), leading to exaggerated cytokine release. The exact mechanism(s) of this exaggerated immune response and why it develops in a small number of children at present, is very poorly understood.

These children typically present with persistent fever, gastrointestinal symptoms (abdominal pain, vomiting, diarrhea), a skin rash, conjunctivitis, mucositis, swollen hands, and/or feet. Some patients develop vasodilatory shock requiring volume resuscitation and vasopressors, all occurring usually within 3 to 5 days of onset of fever. Most of these children will meet the standard criteria for the diagnosis of KD.

Laboratory findings in these children are characterized by lymphocytopenia, thrombocytopenia, mild anemia, and elevated inflammatory markers (e.g., C-reactive protein, erythrocyte sedimentation rate, D-dimer, fibrinogen, ferritin, procalcitonin–interleukin-6, and elevated cardiac markers [troponin, brain natriuretic peptide, or N-terminal prohormone of brain natriuretic peptide]). Markers of inflammation usually correlate with the severity of the diseases.[91] Echocardiography typically demonstrates a coronary artery abnormality, including dilation or aneurysm, depressed Left Ventricular function, and/or pericardial effusion. The diagnosis typically relies on CDC or WHO case definition criteria.[88–93]

A multidisciplinary team involving specialists in pediatric infectious disease, rheumatology, cardiology, and critical care should ideally all be involved in the management of these patients. Management involves supportive care, management of shock with volume expansion and vasopressors, dobutamine, and milrinone for left ventricular dysfunction, antibiotics for suspected or confirmed concurrent bacterial infection, and other critical care support. The role of antiviral therapy like remdesivir is not clear given most pediatric patients are PCR negative for SARS-CoV-2. In children who meet the criteria for KD, treatment should be consistent with standard KD therapy, IVIG and aspirin. Glucocorticoids may be used in patients having persistent symptoms after IVIG. Other drugs that could be considered include tocilizumab and anakinra, which are used in the management of other cytokine release syndromes,[94] although no controlled data supporting their use for this syndrome are currently available.

Management

Fortunately, the data to date suggest few children are likely to develop severe disease although as noted above, the incidence and severity in children may change dramatically as children increasingly engage in school and other group activities. At present clinical management is guided by the severity of the disease and the presence of comorbidities. As COVID-19 is a new disease, the current evidence to guide treatment is sparse.[95,96] The understanding of the management of patients with hematologic diseases like blood cancers and of transplant recipients during the COVID-19 pandemic is even more limited.[97,98] The results of ongoing clinical trials and experiential databases hopefully will provide evidence-based guidelines.[99] Clearly this fast-moving dynamic process underscores our need to closely monitor the rapidly evolving database with a sense of healthy cynicism in our continued critical assessment of all newly published communications,

recognizing that much of the data may be reported/published before critical peer review.

Most cases involving children of all ages are mild and can be managed symptomatically (e.g., acetaminophen for fever). All patients should be monitored for clinical deterioration (e.g., difficulty breathing, chest pain, cyanosis, difficulty arousing, confusion, poor feeding, decreased urine out). Those children with underlying medical conditions and definitely those few who present with severe and life-threatening COVID-19 require hospital admission. Supportive care is the mainstay of treatment in these patients. Supportive care includes the provision of respiratory support (e.g., supplemental oxygen, non-invasive and invasive ventilation), fluid and electrolyte management, adequate nutrition, prevention of complications such as secondary infection, and in more severe cases, extracorporeal membrane oxygenation. Renal replacement therapy may be needed in the setting of acute kidney injury, difficult to manage/life-threatening electrolyte imbalance, fluid overload, and acidosis. In children receiving immunosuppression therapy, the risk and benefit of reducing immune suppression must be considered.[100]

Antiviral Therapy. The following antiviral therapies have been studied for their clinical efficacy and safety in COVID-19. It is important to recognize that the data addressing the use of any of the drugs discussed below are extremely limited to date, derived under conditions of variable control (i.e., clinical observation, case reports/series, retrospective analysis), and are continuingly evolving. Clinicians are strongly encouraged to access the increasing data/clinical experiences with these and other therapies from reputable, trusted resources such as the websites/guideline recommendations from the NIH, CDC, FDA, and WHO.

***Remdesivir*.** Remdesivir is a prodrug nucleotide analog that inhibits RNA-dependent RNA polymerase and has been found to have in vitro activity against SARS-CoV-2.[101] The drug appears to be well tolerated and has received emergency authorization by the FDA for emergency use in both children and adults with severe COVID-19 disease.[102] It should be avoided in liver injury (Alanine transaminase >5 times upper limit of normal) and when the estimated glomerular filtration rate is <30 mL/min/1.73 m^2. The current dose in pediatrics is 5 mg/kg (maximum dose 200 mg) IV loading dose on day 1, followed by 2.5 mg/kg (maximum dose 100 mg) IV every 24 hours for 5 to 10 days.[103]

Data from a randomized control trial have suggested some benefit from the drug in adults. Remdesivir resulted in a faster recovery time and a trend toward lower 14-day mortality in a large multinational trial, including 1059 adult patients.[104] However, another trial involving 237 adult patients did not find any significant clinical benefit,[105] underscoring the continued non-specific, cursory nature of the evolving data/experience.

Favipiravir. Favipiravir is a guanine analog that inhibits RNA polymerase, approved for the treatment of patients with influenza virus infection in Japan.[106] A non-randomized study in adults described better therapeutic responses in COVID-19 (improvement in chest imaging, 91.43% vs 62.22%) and viral clearance (median 4 days; IQR, 2.5–9 days vs 11 days; IQR, 8–13 days) in patients treated with favipiravir plus Interferon alpha by aerosol inhalation vs lopinavir and ritonavir.[107] The role, if any, these drugs may have for the treatment of COVID-19 requires additional critical study before any recommendations can be offered.

***Hydroxychloroquine/Chloroquine*.** Both chloroquine and hydroxychloroquine, used for the treatment of malaria and certain autoimmune disorders like systemic lupus erythematosus and rheumatoid arthritis, have been reported to inhibit SARS-CoV-2.[108] Chloroquine increases endosomal pH, which prevents virus/cell fusion. It also interferes with the glycosylation of cellular receptors of SARS-CoV-2. Wang et al[101] demonstrated the in vitro effectiveness of chloroquine in reducing viral replication, with an EC90 of 6.90 μM, which may be achievable in target tissues like lungs with standard doses. In combination with azithromycin, these drugs have been described as having good efficiency for viral clearance.[109,110] Large clinical trials are underway to assess the clinical use of these drugs.[99] Preliminary data suggest that these drugs did not appear to have clinical benefits in hospitalized patients.[111] Most importantly, concerns regarding the safety of these drugs, particularly QTc prolongation and arrhythmias, have arisen.[112] Reflective of the tenuous nature of our pre-publication/publication system pertaining to COVID-19, and in particular as it pertains to chloroquine-based therapy, is the recent retractions of one paper in the *New England Journal of Medicine*[113] and one paper in the *Lancet*.[114] Thus, based on the most recent adult experience, the use of hydroxychloroquine/chloroquine should be discouraged, outside of a sanctioned, controlled clinical trial in the management of COVID-19 patients.

***Lopinavir/Ritonavir*.** These protease inhibitors are used in the management of HIV infection and possess in vitro activity against SARS-CoV-2. Nevertheless, and despite the initial preliminary promise, the drug combination appears to offer no benefit beyond standard care for treating these patients. Other drugs that have also been tried in the management are interferon-beta and interferon-alpha and ribavirin.[115–118]

***Convalescent Plasma*.** Convalescent plasma contains antibodies in the plasma of patients recovering from viral infection and might suppress viremia.[119] It is generally well tolerated but may be associated with transfusion-related reactions. A randomized control trial in patients with severe or life-threatening COVID-19 given convalescent plasma therapy did not result in a statistically significant improvement in time to clinical improvement within 28 days.[120,121] Despite these disappointing overall results, a subset of patients who had

severe but not life-threatening disease did show benefit from this therapy.[122] The time to clinical improvement was shorter by 4.94 days (95% CI, −9.33 to −0.54 days) in patients with severe disease receiving convalescent plasma as compared to controls. However, in patients with life-threatening diseases there were no significant differences. A large multicenter, multinational controlled comparative trial of the value, if any, of donated convalescent plasma infusion in the treatment of COVID-19 patients representing a spectrum of the disease is ongoing.

Immunomodulators and Adjunctive Therapy. The role of glucocorticoid steroids in the treatment of COVID-19–infected patients is receiving increased attention, although their exact role and for which patients is uncertain. The use of steroid has been reported to increase mortality and secondary infection rates and impair clearance of SARS-CoV-2.[123] In contrast, the preliminary report of Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, a large well-designed, controlled multicenter clinical trial involving a large number of adult patients, shows a reduction in 28-day mortality in patients with severe COVID-19 infection receiving respiratory support (supplemental oxygen support and/or mechanical ventilation) who were treated with dexamethasone, as compared to controls.[124]

A pilot study has described some benefit in hospitalized adult patients with severe COVID-19 by blocking interleukin-6 pathway by tocilizumab where the drug seems to be particularly helpful in patients with cytokine release syndrome. Other immunomodulatory therapies that are being evaluated in patients with cytokine release syndrome associated with COVID-19 are anakinra, ibrutinib, barcitinib, eculizumab, and monoclonal antibodies against SARS CoV-2.[125–130.] Clearly more data from randomized controlled clinical trials are needed, describing the value if any of these agents, as well as the regimen(s) for the treatment of these patients across the disease spectrum, before any recommendations can be offered.

Antibiotics and antifungal agents should be used when a bacterial or fungal infection is suspected/confirmed. Continued use of these anti-infective agents should be guided by clinical and laboratory assessments with the goal of limiting the duration, if at all, their use. The role of dietary and vitamin supplements such as vitamin A, vitamin C, vitamin D, and zinc in the management of COVID-19 remains controversial and until more data become available should be avoided in the absence of any documented deficiency.[131]

Vaccine

The WHO is actively involved with numerous agencies to monitor the progress of vaccine discovery and development. The Coalition for Epidemic Preparedness Innovations is working with global health authorities and vaccine developers to support the development of vaccines against COVID-19.[132] At least 16 candidate vaccines are currently in the pipeline.[133] The vaccines developed by Moderna and the collaboration of the University of Oxford with AstraZeneca (and others) have entered phase III trials and if demonstrated both safe and effective are expected to be available for use in early 2021.[134]

Based upon our current experience and given the relative benign nature of COVID-19 disease in children, the use of the vaccine when it is available in healthy children will remain questionable, requiring considerable personal and clinical consideration. The role of a vaccine in children with important comorbidities may initially be more straightforward.

Conclusions

SARS-CoV-2 is mainly spread by the respiratory route. The available data suggest that infected children are usually asymptomatic or develop only mild symptoms that can be managed symptomatically, usually at home. Nevertheless, there is a risk of more severe disease in high-risk children (immunocompromised children, long-term steroid use, nephrotic syndrome, etc.). The treatment of severe disease is essentially supportive. Few children mount an exaggerated immune response to the virus, leading to PIMS. The treatment of this rare syndrome involves the use of immunomodulators along with supportive care.

The treatment regimens for use in children continue to be guided by the experience gleaned from previous coronavirus diseases like SARS and MERS, and the continuously evolving experience in adults with SARS CoV-2 infection. Evidence-based diagnostic and treatment guidelines for use in children still await dedicated pediatric studies.

ARTICLE INFORMATION

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